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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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[Docket No. FDA-2008-N-0389]

Food and Drug Administration Amendments Act of 2007; Prohibition Against Food to Which Drugs or Biological Products Have Been Added; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is requesting comments relevant to the implementation of section 912 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Section 912 of FDAAA establishes section 301(II) in the Federal Food, Drug, and Cosmetic Act (the act), which prohibits the interstate shipment of certain foods to which an approved drug or a licensed biological product has been added. Section 301(II) also prohibits the interstate shipment of foods containing an added drug or a biological product that has been the subject of substantial clinical investigations, the existence of which has been made public. FDA requests that interested persons submit data, information, and comments that will help provide a context for the agency's decisions on implementation of this provision. To encourage responsive comments, FDA is including a series of questions for interested persons to consider in preparing comments.

DATES: Submit written or electronic comments by [*insert date 90 days after date of publication in the Federal Register*].

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4

ADDRESSES: Submit written comments, data, and other information to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *www.regulations.gov*.

FOR FURTHER INFORMATION CONTACT: Catherine L. Copp, Center for Food Safety and Applied Nutrition (HFS-4), Food and Drug Administration, 301-436-1589, e-mail: *catherine.copp@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background

On September 27, 2007, the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85) (FDAAA) was enacted. Section 912 of FDAAA establishes section 301(ll) in the Federal Food, Drug, and Cosmetic Act (the act), 21 U.S.C. 331(ll), which adds the following prohibited act to section 301.21 U.S.C. 331: The introduction or delivery for introduction into interstate commerce of any food to which has been added a drug approved under section 505, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, unless--

(1) such drug or such biological product was marketed in food before any approval of the drug under section 505, before licensure of the biological product under such section 351, and before any substantial clinical investigations involving the drug or the biological product have been instituted;(2) the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, approving the use of such drug or such biological product in the food;(3) the use of the drug or the biological product in the food is to enhance the safety of the food to which

the drug or the biological product is added or applied and not to have independent biological or therapeutic effects on humans, and the use is in conformity with--

(A) a regulation issued under section 409 prescribing conditions of safe use in food; (B) a regulation listing or affirming conditions under which the use of the drug or the biological product in food is generally recognized as safe; (C) the conditions of use identified in a notification to the Secretary of a claim of exemption from the premarket approval requirements for food additives based on the notifier's determination that the use of the drug or the biological product in food is generally recognized as safe, provided that the Secretary has not questioned the general recognition of safety determination in a letter to the notifier; (D) a food contact substance notification that is effective under section 409(h); or (E) such drug or biological product had been marketed for smoking cessation prior to the date of the enactment of the Food and Drug Administration Amendments Act of 2007; or

(4) the drug is a new animal drug whose use is not unsafe under section 512.

Section 301(ll) makes it a prohibited act to ship in interstate commerce certain foods to which an approved drug or a licensed biological product has been added. Section 301(ll) also prohibits the interstate shipment of certain foods containing an added drug or a biological product that has been the subject of substantial clinical investigations, the existence of which has been made public. Under the act, persons who commit a prohibited act may be enjoined, 21 U.S.C. 332, or prosecuted criminally, 21 U.S.C. 333. In addition, a food which may not, under the provisions of section 301(ll), be introduced or delivered for introduction into interstate commerce, is subject to seizure and forfeiture, 21 U.S.C. 334, and under 21 U.S.C. 381, a food offered for import into the United States that appears to be prohibited from introduction or delivery for introduction into interstate commerce under section 301(ll) is subject to refusal of admission.

The language of section 301(ll) has a number of parallels to, as well as significant differences from, the language of a similar provision in section 201(ff)(3)(B) (21 U.S.C. 321(ff)(3)(B)), which is part of the act's definition of "dietary supplement." Although there is legislative history of FDAAA, including a report from the House committee with jurisdiction (H. Rep. No. 225, 110th Cong., 2d Sess. (2007)), section 301(ll) is not addressed in that legislative history.

The Secretary of Health and Human Services has delegated to the Commissioner of Food and Drugs the principal responsibility for administering the act. As the administering agency, it is FDA's responsibility generally to implement amendments to the act, including the amendments made by section 912 of FDAAA.

Section 301(ll) presents a number of questions of statutory interpretation for FDA to consider. The scope of the agency's discretion to interpret section 301(ll) is defined by the Supreme Court's decision in *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). Under *Chevron*, if the language of a statute makes Congressional intent on a particular question clear and unambiguous, the agency charged with administering the statute must give effect to that intent. *Chevron*, 467 U.S. at 842–43. If the statute is silent or ambiguous on the question, however, the agency is permitted to give the statute a reasonable construction, *Chevron*, 467 U.S. at 844–845, and that construction is entitled to deference. *Chevron*, 467 U.S. at 844.

II. Questions Presented

FDA believes that a fuller understanding of the impact of various interpretations of section 301(ll) would be beneficial as the agency considers how to implement this new provision. Accordingly, FDA is requesting that

interested persons submit data, information, and other comments regarding possible approaches to implementation. To guide those submissions and responses, the agency has prepared the following questions. FDA suggests that, in preparing responses to this request for comments, interested persons consider the following:

A. Food

Section 301(l) prohibits the introduction or delivery for introduction into interstate commerce of certain “food.” Under section 201(f), “food” means articles used for food or drink for man or other animals, chewing gum, and articles used for components of such articles. Food includes human food, including infant formula, medical foods, and dietary supplements; food contact substances, including food packaging; and animal feed, including pet food and feed ingredients. Consistent with the broad definition of “food” in section 201(f), FDA seeks information about the impact of section 301(l) on food in all its forms, including food ingredients, categories of food, and finished food products.

1. What types or categories of food would likely be subject to the prohibition of section 301(l)? What types or categories are likely to be unaffected by section 301(l)? If possible, please provide specific examples of these foods.

2. What is the likely impact of applying section 301(l) to infant formula? Are there substances used or potentially used in infant formula that would be prohibited from such use by section 301(l)?

3. What is the likely impact of applying section 301(l) to dietary supplements? Are there substances used or potentially used in or as dietary supplements that would be prohibited from such use by section 301(l)? What

would be the advantages and disadvantages of applying both section 301(ll) and section 201(ff)(3)(B) to dietary supplements? Would such an approach lead to more effective regulation or less effective regulation of these products, and why?

4. What is the likely impact of applying section 301(ll) to animal feed? Are there substances used or potentially used in animal feed, including pet food and feed ingredients, that would be prohibited from such use by section 301(ll)?

5. What is the likely impact of interpreting “food” in section 301(ll) to include food contact substances, including packaging components that meet the definition of a food additive? Are there substances used or potentially used in food packaging or other food contact substances that would be prohibited from such use by section 301(ll)?

B. Previously Marketed Foods Now Barred from Interstate Commerce

Section 301(ll) identifies a category of foods that can no longer be introduced or delivered for introduction into interstate commerce although these foods were allowed in interstate commerce before the enactment of FDAAA. Specifically, if a food contains a substance that is an approved drug, that is a licensed biological product, or that has been the subject of substantial clinical investigations that have been made public, and if the substance was added to the food to have an independent biological or therapeutic effect on the person consuming it, rather than to enhance the safety of the food, the food is now barred from interstate commerce if any substantial clinical investigations of the substance were instituted, or the drug was approved or the biologic was licensed, prior to the first marketing of the substance in food. FDA seeks information on foods in this category that were legally marketed

prior to the enactment of FDAAA but that are now barred from interstate commerce.

1. How many and what types of foods would be affected? What would be the impact on businesses that produce and sell these foods?
2. What would be the impact on consumers who currently use the products?
3. If possible, please provide specific examples of affected foods.

C. Drug

Section 301(ll) prohibits the introduction or delivery for introduction into interstate commerce of food to which has been added a “drug approved under section 505.”

Implementing section 301(ll)’s restrictions on adding approved drugs to food will require FDA to consider how the identity of a “drug” is to be determined for purposes of section 301(ll).

1. What would be the impact of deeming two substances to be identical if they are chemically identical?
2. Are there approved drugs that cannot be identified by their chemical structure? If so, what would be a scientifically accurate and technically feasible way for FDA to determine the identity of the “drug approved under section 505” or “drug * * * for which substantial clinical investigations have been instituted” and consider whether that drug was marketed in food before the drug’s approval by FDA or before the initiation of the substantial clinical investigations? Which drugs or classes of drugs cannot be identified by their chemical structure?

D. Biological Product

Section 301(ll) prohibits the introduction or delivery for introduction into interstate commerce of food to which has been added a “biological product licensed under section 351 of the Public Health Service Act.” Under section 351(i) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(i)), a “biological product” means “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”

- What are the special concerns, if any, related to determining whether a biological product that is added to food has previously been licensed under section 351 of the PHS Act?

E. Clinical Investigations

Section 301(ll) prohibits the introduction or delivery for introduction into interstate commerce of food to which has been added a “drug” or a “biological product” for which “substantial clinical investigations have been instituted” and for which “the existence of such investigations has been made public,” unless the drug or the biological product was “marketed in food * * * before any substantial clinical investigations involving the drug or the biological product have been instituted.”

1. What is the likely impact of interpreting “clinical investigations” to refer exclusively to studies in humans?

2. What is the likely impact of interpreting the existence of substantial clinical investigations of a substance in humans to prevent the addition of such substance to animal feed, including pet food and feed ingredients?

3. What factors should FDA consider in deciding whether clinical investigations of a substance are “substantial?”

4. What factors should FDA consider in determining whether substantial clinical investigations “involv[ed] the drug or the biological product?”

5. Could this provision operate as a disincentive to conduct clinical studies of substances intended for use in products to be marketed as conventional foods or dietary supplements? If so, is there an approach to implementation that could minimize or eliminate this disincentive?

6. To the extent that this provision discourages clinical investigations of substances added to food and the public disclosure of such investigations, what is the likely impact of this provision on so-called self-determinations of the general recognition of safety (GRAS) of substances added to food?

F. Marketed

Under section 301(ll)(1), a food containing an approved drug or a licensed biological product may be shipped in interstate commerce if the drug or the biological product was “marketed in food” prior to the approval of the drug, the licensing of the biological product, or the initiation of substantial clinical investigations of the drug or biological product. Section 201(ff) contains a similar provision. Section 201(ff) uses the phrase “marketed as a dietary supplement or as a food,” however, while section 301(ll) uses the phrase “marketed in food.” In the context of section 201(ff), FDA has evaluated whether a substance has been “marketed” within the meaning of that provision by considering: (1) Whether the substance itself has been sold or offered for sale, either as a finished product or as an ingredient; (2) for substances that are not sold separately but are components present in a marketed product, whether the component itself was marketed to prospective purchasers through,

e.g., labeling or advertising for the product that made claims about the component or otherwise highlighted its presence. *See Pharmanex v. Shalala*, 2001 WL 741419, at *4 & n.5 (D. Utah March 30, 2001).

1. What would be the likely impact of interpreting the term “marketed” the same way in section 301(ll) as in section 201(ff)? What could be the regulatory significance, if any, of the differing phrases “marketed in food” (section 301(ll)) and “marketed as a dietary supplement or as a food” (section 201(ff))?

2. What could be the significance, if any, of the marketing in food of an approved drug or a licensed biological product outside the United States?

3. What factors should be considered the indicia of being “marketed in food?” What types of evidence should FDA consider in deciding whether a substance has been “marketed in food?”

G. Enhance The Safety of The Food Supply

Section 301(ll)(3) provides an exception to the prohibition of adding a drug or biological product to a food if use of the drug or biological product is “to enhance the safety of the food * * * and not to have independent biological or therapeutic effects on humans.”

1. What factors should FDA consider in determining whether the use of a substance in food is to “enhance the safety of the food” within the meaning of section 301(ll)?

2. What would be the likely impact of each of the following possible interpretations of what kinds of uses “enhance the safety of the food?”

- The addition of a substance to a food enhances the safety of the food only if such addition reduces a risk not inherent in the food itself, such as the risk of microbial or other contamination.

- The addition of a substance to a food enhances the safety of the food if such addition reduces either a risk inherent to the food itself, such as inherent toxicity or a risk that derives from the nutritional content of the food (e.g., high saturated fat content), or a risk not inherent in the food itself, such as the risk of microbial or other contamination.

H. Independent biological or therapeutic effects on humans

As noted, section 301(l)(3) provides an exception to the prohibition of adding a drug or biological product to a food if use of the drug or biological product is “to enhance the safety of the food * * * and not to have independent biological or therapeutic effects on humans.”

1. What factors should FDA consider in determining whether the use of a substance in food is to have a “biological” effect on humans?

2. What factors should FDA consider in determining whether the use of a substance in food is to have a biological effect on humans that is “independent?”

3. What factors should FDA consider in determining whether the use of a substance in food is to have a “therapeutic” effect on humans?

4. What factors should FDA consider in determining whether the use of a substance in food is to have a therapeutic impact on humans that is “independent?”

I. In the Secretary’s Discretion

Section 301(l)(2) permits the addition of a drug or biological product to a food “if the Secretary, in the Secretary’s discretion, has issued a regulation after notice and comment, approving the use * * * in food.” As noted, the Secretary has delegated his authority under the act to the Commissioner of Food and Drugs.

1. What factors should the Commissioner consider in exercising his discretion under section 301(l)(2)?

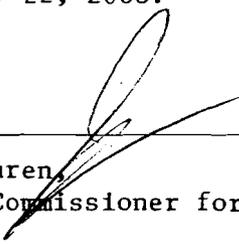
2. What should be the impact, if any, on the exercise of the Commissioner's discretion where use of the drug or biological product in food has been the subject of another statutory or administrative process (e.g., a food contact substance notification that is effective under section 409(h))?

III. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Please note that on January 15, 2008, the FDA Division of Dockets Management Web site transitioned to the Federal Dockets Management System (FDMS). FDMS is a Government-wide, electronic docket management system. Electronic comments or submissions will be accepted by FDA only through FDMS at <http://www.regulations.gov>.

Dated: 7/22/08
July 22, 2008.



Jeffrey Shuren,
Associate Commissioner for Policy and Planning.

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