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VIA ELECTRONIC MAIL

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

Re: Food and Drug Administration Amendments Act of 2007
Prohibition Against Food to Which Drugs or Biological Products Have Been Added
Docket No. FDA-2008-N-0389

These comments are submitted on behalf of the Council for Responsible Nutrition (CRN) and the Consumer Healthcare Products Association (CHPA) in response to the Food and Drug Administration (FDA) Notice and Request for Comments on the implementation of new section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FDCA or Act), which was added by section 912 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). 73 Fed. Reg. 43937 (July 29, 2008). Founded in 1973, CRN is the leading trade association representing the dietary supplement industry, including ingredient suppliers and manufacturers. CHPA is the trade association representing the leading manufacturers of over-the-counter, nonprescription medicines and dietary supplements.

FDA seeks comments on section 301(ll) which prohibits the interstate shipment of certain foods to which has been added an approved drug or a licensed biologic product, or to which has been added a drug or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations have been made public. While lengthy, section 301(ll) is straightforward, codifying in the Prohibited Acts section of the FDCA provisions and concepts that have long been established elsewhere in the Act and FDA's subsequent regulations. Indeed, if the intended use of a substance is for the "diagnosis, cure, mitigation, treatment, or prevention of disease," the Act has long held that intended use to constitute a drug use of the substance regardless of how the marketers attempt to position the product. In addition, the agency's food additives regulations and generally recognized as safe (GRAS) requirements have long required food ingredients to be safe. And finally, section 201(ff) of the Act was added in 1994 as a provision of the Dietary Supplement Health and Education Act (DSHEA) and established limitations on the marketing of dietary supplements containing an approved drug, a provision that is dramatically similar (although not identical) to the one now being applied to all food by 301(ll). Section 301(ll) must therefore be interpreted and applied according to the plain meaning of its terms, with an appreciation for the context in which it must exist and the ways in which it is identical to and distinct from section 201(ff).

The plain meaning of the language of section 301(ll) along with a comparison to section 201(ff) and the application of well-recognized canons of statutory construction establish the proper interpretation and implementation of this provision. Where it

invokes terms of art defined elsewhere in the Act, section 301(ll) must be interpreted similarly, and where it is different, the provision must reflect the substantive changes from section 201(ff). In the end, it is apparent that section 301(ll) is largely an extension of the concepts of section 201(ff) to *all* foods, along with some deliberate changes and exceptions to the provision as applied to food generally that were not applicable to dietary supplements in 1994.

When section 301(ll) is applied in this fashion, as is appropriate, CRN is not aware of any substance that would be prohibited from use in a dietary supplement under section 301(ll) that is not already disallowed by section 201(ff)(3)(B). To be clear, section 201(ff) may already prohibit the use of some substances as a dietary supplement that would still be permissible for use "in food" under section 301(ll), but any substance that would be permitted for use as a dietary supplement under 201(ff) would also be permitted "in food" under the correct reading of section 301(ll). In fact, the new provision, because of its differences from section 201(ff), may allow the marketing of certain substances in food generally, even if they would be prohibited under section 201(ff) from being marketed as dietary supplements.

Moreover, to interpret section 301(ll) in any other manner would discourage innovation and new product development for the full range of products considered to be "food" under the FDCA. It would create the opportunity for almost anyone to conduct a few clinical trials for a supposedly "drug" purpose on any ingredient under development for inclusion in food and effectively thwart the ability of food manufacturers to market a product containing that ingredient. To discourage rigorous examination and study of new

food and dietary ingredients certainly could not have been the intent of Congress in enacting this provision. Indeed, Congress has enacted laws that require or encourage research on food and food components, including, but not limited to the Nutrition Labeling and Education Act (NLEA) of 1990, which authorized FDA to establish regulations for health claims,[1] and DSHEA, which established the Office of Dietary Supplements[2] (ODS) at the National Institutes of Health (NIH). Both of these are examples of Congress' unequivocal intent to allow for and encourage research, including human clinical trials, on food, food components, dietary supplements and dietary ingredients, even if such trials have disease or disease-surrogate endpoints. If Congress had intended to dissuade research on food, food components and dietary supplements for product development and label claim substantiation by enacting 301(ll), it would have expressly stated so, and would have amended or repealed the relevant provisions of the aforementioned legislation. The absence of such action by Congress indicates that this was not its intent.

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[1] 21 CFR Part 101 Subpart E § 101.70 includes specific requirements for health claims, including meeting the significant scientific agreement (SSA) standard. FDA has expanded on this in § 101.14 emphasizing the need for randomized, controlled clinical trials involving a food, food component or dietary supplement in order to meet the SSA standard.

[2] 42 U.S.C. § 287c-11(b) called for the establishment of an Office of Dietary Supplements, whose purpose is to "explore more fully the potential role of dietary supplements as a significant part of the efforts of the United States to improve health care" and to "promote scientific study of the benefits of dietary supplements."

I. Section 201(ff): The Context for Understanding Section 301(ll)

To begin, one must appreciate the substantial similarity of 201(ff), an existing provision in the FDCA, to section 301(ll).

Section 201(ff) was added to the FDCA by DSHEA in 1994 and limits the definition of a dietary supplement to exclude:	Section 301(ll), added to the FDCA by FDAAA in 2007, created a new section to the prohibited acts:
	The introduction or delivery for introduction into interstate commerce of **any food** to which has been added
i) an article that is	
approved as a new drug under section 355 of this title, certified as an antibiotic under section 357 of this title,	**a drug approved under section 505 [21 USC §355]**,
or **licensed as a biologic under section 262 of title 42**,	**a biologic product licensed under section 351 of the Public Health Service Act [42 USC §262]**,
or (ii) an article **authorized for investigation as a new drug**, antibiotic, or **biological**	or **a drug** or **biologic product**
for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public,	**for which substantial clinical investigations have been instituted and for which the existence of such investigations have been made public**,
which **was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food** unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter.	unless – (1) **such drug or biologic 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 biological product have been instituted**; …

The similarities between the two provisions are significant, and where there are differences, they can be either be explained by changing circumstances since 1994, or justified by the treatment of the broader category of food as opposed to only dietary supplements. For instance, the omission of the word "antibiotic" in section 301(ll) that appeared in section 201(ff) is simply a result of amendments to the Act in 1997 that transferred the regulation of antibiotics from a separate section of the Act to section 505 (which regulates all new drugs).

Section 201(ff) became the subject of judicial review in *Pharmanex v. Shalala*, 221 F.3d 1151 (10th Cir. 2000), in which the court invoked this provision to prohibit the marketing of red yeast rice containing the drug lovastatin, which was previously an approved drug, in a dietary supplement making claims to reduce cholesterol. The similarities between the two provisions makes clear that Congress intended to extend that existing limitation on marketing a dietary supplement containing a drug, which was invoked in the *Pharmanex* case, to apply to all foods. Dietary supplements are, of course, treated as a category of "food" under the Act[3] but Section 201(ff) is specific only to supplements. There is no evidence that Congress intended to expand the scope of ingredients prohibited from use in food beyond the scope of ingredients covered under section 201(ff). However, to better understand how the two provisions interact, it is essential to examine the meaning of particular aspects of this new section.

[3] 21 U.S.C. 321(ff)(3)(B).

II. The Plain Meaning of Section 301(ll)

As described below, a plain reading of section 301(ll) prohibits a drug from being added to food only if the substance:

- is intended to diagnose, cure, mitigate, treat, or prevent disease through its use in the food, as shown objectively by marketing and labeling representations; and

- is the exact same moiety or mixture as the active ingredient in a drug currently approved under section 505 and is added to the food in the same dosage range as authorized by the new drug approval; or

- if not an approved drug or mixture, is the identical moiety or mixture that is the subject of at least two post-phase I clinical investigations listed in ClinicalTrials.gov and is subject to an active clinical development program in accordance with 21 C.F.R. part 312.

An overbroad interpretation, inconsistent with the above, would discourage research into new food ingredients, frustrate the research goals of ODS/NIH, and implicitly repeal the health claim provisions of the FDCA.

A. <u>The Prohibition Against the Addition to Food of an Approved Drug or Licensed Biologic</u>

1. "Food"

"Food" in section 301(ll) simply means food as defined under section 201(f) of the FDCA, *i.e.*, articles used for food or drink for man or other animals, chewing gum, and articles used for components of such articles. It thus includes every form of food,

such as conventional food, medical food, food for special dietary use, "functional food," and food contact articles. "Food" also includes dietary supplements, as section 201(ff) of the FDCA plainly states. Section 301(ll) imposes no different impact on dietary supplements than on conventional food, and throughout these comments, the term "food" is used (as it is in the FDCA) to encompass dietary supplements.

As we demonstrate that section 201(ll) imposes a substantially similar limitation on "food" as is already imposed on dietary supplements by section 201(ff), there is no need to ask whether "food" in section 201(ll) includes dietary supplements or not. However, should the agency decide to interpret 301(ll) in any regard differently from its implementation of 201(ff), dietary supplements should not be subject to that treatment because of the existence of section 201(ff). It is a well-recognized canon of statutory construction that Congress must be assumed to have reason for its enactments.[4] There is also a strong presumption that if Congress intends one statute to repeal an earlier statute or section of a statute, it would say so directly in the repealing act.[5] In fact, repeals by implication are not favored, and will not be found "unless an intent to repeal is clear and manifest."[6] If Congress had intended with the enactment of FDAAA for section 301(ll) to subsume the requirements of section 201(ff) – given that dietary supplements are a

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[4] *See, e.g., Chapman v. Houston Welfare Rights Organization*, 441 U.S. 600, 608, 99 S.Ct. 1905, 1911 ("As in all cases of statutory construction, our task is to interpret the words of these statutes in light of the purposes Congress sought to serve.").

[5] *See, e.g., United States v. Fausto*, 484 U.S. 439, 453 (1988); CRS Report 97-589, *Statutory Interpretation: General Principles and Recent Trends* (March 30, 2006).

[6] *See, e.g., Rodriguez v. United States*, 480 U.S. 522, 524 (1987); *Morton v. Mancari*, 417 U.S. 535, 550-51 (1974).

category of food – it could easily have repealed the relevant portion of 201(ff); but Congress did not. Other rules of statutory construction applicable here require that every word of the statute be given meaning[7] and that a more specific pronouncement shall have precedence, even when it demands unique treatment of the specific instance over a general requirement.[8] Accordingly, the new section 301(ll) does not change the regulation of dietary supplements, and even if it was interpreted as more restrictive in some respect than the prohibition in 201(ff), dietary supplements must be excluded from that treatment given the continuation of 201(ff) in the Act.

2. "Added"

Section 301(ll) applies to food "to which has been added" a drug. The prohibition therefore does not apply to any substances or constituents inherent in food, even where the substance is identical to a drug substance or drug product approved under section 505 or under investigation. If drug claims are made for natural substances that are inherently included in food, they may be prohibited under other sections of the FDCA, but not by section 301(ll).

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[7] *See, e.g., Bailey v. United States*, 516 U.S. 137, 145, 116 S. Ct. 501, 506-07 (1995) ("judges should hesitate . . . to treat [as surplusage] statutory terms," citing *Ratzlaf v. United States*, 510 U.S. 135 (1994); *Solid Waste Agency v. United States Army Corps of Eng'rs*, 531 U.S. 159, 171, 121 S. Ct. 675, 682 (2001) ("one thing to give a word limited effect and quite another to give it no effect whatever.").

[8] *See, e.g., United Ass'n, Plumbing & Pipe Fitting v. Reno*, 73 F.3d 1134, 1140 (D.C. Cir. 1996) (referencing the "canon of statutory construction dictating that specific statutory provisions govern general ones").

Also of importance is the fact that section 301(ll) permits the marketing of a substance "*in* food" where it has been marketed "*in* food" before the advent of substantial clinical trials for the substance's drug purposes. By contrast, the substance can only continue to be marketed as a dietary supplement if it has been marketed "as a dietary supplement or *as a food*" prior to the substantial clinical investigations. It is quite conceivable that substances have been marketed somewhere in the world "in food" but not marketed "as a food" and thus could still be marketed in food under section 301(ll) but not as a dietary supplement under section 201(ff).

3. "Drug"

The term "drug" is used in the FDCA to refer at times to drug substances (i.e., drug active ingredients) and at other times to finished drug products (including inactive ingredients). In the context of section 301(ll), it is clear that the term is intended to refer to drug active ingredients.[9]

The FDCA defines "drug" to mean, in relevant part, "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." For over 70 years, "intended use" has been FDA's touchstone for determining whether a substance is a drug. FDA emphasized that product categorization turns on intended use in the preamble to its regulation on structure/function claims that may be

[9] Section 301(ll) also prohibits the addition to food of a biological product licensed under section 351 of the Public Health Service Act (PHSA). The discussion in these comments relating to drugs applies equally to biological products, which will not be addressed separately.

made for dietary supplements. There, the agency explained that "Because the act classifies products on the basis of intended uses, dietary supplements that make disease claims are drugs, unless the disease claim is also an authorized health claim for which the product qualifies."[10] Similarly, in numerous warning letters, FDA has asserted that a food or dietary supplement bearing unlawful disease claims is, in fact, a drug because the claims establish that the product is intended for use in the cure, mitigation, treatment, or prevention of disease.[11] Courts have historically and consistently interpreted the FDCA to classify substances and products as drugs based on their intended use.[12] Accordingly, in order for a substance to be a "drug" that cannot be added to food under section 301(ll), the substance added to the food must be intended to diagnose, cure, mitigate, treat, or prevent disease. Of course, the inclusion in food of a substance that is the subject of an FDA-authorized health claim does not render the product prohibited under 301(ll).

As the FDA Chief Counsel has stated, it is well settled that intended use is determined with reference to marketing claims.[13] Courts have consistently held that

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[10] 65 Fed Reg. 1000, 1040 (January 6, 2000).

[11] For a recent example, *see* Warning Letter from Barbara Cassens, Director, San Francisco District, to Renewal Research, September 25, 2008 ("The therapeutic claims on your website establish that the products are drugs because they are intended for use in the cure, mitigation, treatment, or prevention of disease. The marketing of these products with these claims violates the Act.")

[12] *E.g.*, *Whitaker v. Thompson*, 239 F. Supp. 2d 43, 51 (D.D.C. 2003) ("Courts have long upheld FDA decisions to classify products as drugs based on their intended use."), *aff'd*, 353 F.3d 947 (D.C. Cir. 2004); *National Nutritional Foods Assoc. v. Matthews*, 557 F.2d 325, 333 (2d Cir. 1977) (The "vendor's intent in selling the product to the public is the key element" in the FDCA drug definition.).

[13] Letter from Daniel Troy, FDA Chief Counsel, to Jeffrey N. Gibbs, October 17, 2002, at 3.

claims or other marketing representations are what reveal an "intended use" that makes a substance or product a drug.[14] The United States Court of Appeals for the Fourth Circuit found in 1998 that "no court has ever found that a product is 'intended for use' or 'intended to affect' within the meaning of the [FDCA] absent manufacturer claims as to that product's use."[15] We are aware of no courts that have reached a different conclusion since that time. To the contrary, in no case has FDA prevailed in regulating a substance or product as a drug in the absence of disease claims or other relevant representations by the product's manufacturer or distributor.[16]

There is nothing inherent in a substance that makes it a drug. FDA has agreed that "it is not membership in a given class of compounds that makes a product a drug, but rather the intended use of the product."[17] For example, FDA approval of a new drug application for an antimicrobial labeled to prevent infection would not preclude use of the

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[14] *E.g.*, *United States v. Undetermined Quantities . . . "Pets Smellfree,"* 22 F.3d 235, 240 (10th Cir. 1994) ("PSF's claims [in labeling and promotional materials] . . . bring Smellfree within the scope of § 321(g)(1)(C)."); *United States v. Storage Spaces Designated Nos. "8" and "49,"* 77 F.2d 1363, 1367 n. 6 (9th Cir. 1985) (relying on "the manner in which the products [were] promoted and advertised in finding that the products were drugs under Section 321(g)(1)(C)).

[15] *Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. 1998) (internal quotation marks omitted) (citing *Coyne Beahm, Inc. v. FDA*, 966 F. Supp. 1374, 1390 (M.D.N.C. 1997), *aff'd*, 529 U.S. 120 (2000).

[16] *E.g.*, *National Nutritional Foods Assn' v. Mathews*, 557 F.2d 325 (2d Cir. 1977) (rejecting FDA's attempt to regulate high-dose vitamin supplements as drugs in the absence of objective evidence indicating therapeutic intent).

[17] 65 Fed. Reg. at 1026. It is only *claims* of membership in certain product classes strongly associated with use to treat or prevent disease that constitute evidence that a product is intended to treat or prevent disease. *Id.* (emphasis in original).

same moiety as a food preservative. Moreover, a substance deemed a drug due to marketing claims would no longer be deemed a drug once such claims have ceased.[18]

In light of the foregoing history and context, it is clear that section 301(ll) is triggered only when a manufacturer or distributor makes drug claims for a substance added to food, *i.e.*, claims that the added substance is intended to diagnose, cure, mitigate, treat, or prevent disease. Because the statutory definition of "drug" turns on intended use, rather than chemical identity, section 301(ll) does not prohibit the addition of drugs approved under section 505 or under investigation, or substances that are chemically identical to such drugs, in the absence of marketing claims suggesting that the substance is intended for use as a drug when added to the food. Other provisions of the FDCA prohibit the addition of a drug substance to food where the substance is unsafe and would thus adulterate the food.[19]

4. "Approved Under Section 505"

Section 301(ll) prohibits the addition of a "drug approved under section 505" of the FDCA. Section 301(ll) therefore does not extend to over-the-counter (OTC)

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[18] *United States v. Articles of Drug . . . Neptone*, Food Drug Cosm. L. Rep. (CCH) ¶ 38,240 (N.D. Cal. 1983) ("The Court finds that the claimant's promotional claims clearly show that it intended Neptone to be used 'in the diagnosis, cure, mitigation, treatment, or prevention of disease in man.' . . . The Court does not view this opinion as establishing for all time that Neptone is a drug. The determination that Neptone is a drug rests entirely on the pattern of promotion used by claimant in the several years immediately preceding the instant seizure. Should Neptone again be marketed after some hiatus and a change in labeling, this order will not necessarily work an estoppel on whether that batch of Neptone is a drug.")

[19] FDCA §§ 402(a), 301(a).

monograph drugs which, by definition, are not "new drugs" approved under section 505. Nor does section 301(ll) apply to new animal drugs, which are approved under section 512 of the FDCA. The prohibition extends only to those drugs currently approved under section 505. A drug that previously had been approved but for which approval has been withdrawn is no longer a "drug approved under section 505," and therefore cannot be the subject of enforcement action under section 301(ll).

A drug "approved under section 505" is a very narrow, precise entity, for NDA approval encompasses only a specific moiety. It does not include, for example, a salt, ester, analogue, or metabolite of the approved moiety, unless that salt, ester, analogue, or metabolite is also approved under an NDA. If it is a mixture that has been approved as the active ingredient under section 505, then section 301(ll) applies only to the identical mixture when added to food. Different forms of the substance or mixture are not the drug "approved under section 505."

It is common practice for pharmaceutical patents to cover every possible form of a moiety, including different salts, esters, analogues, metabolites, and mixtures. Patents are, however, completely irrelevant under section 301(ll). It is only the specific active ingredient approved under section 505 (or, as discussed below, under substantial clinical investigation) that is protected under section 301(ll).

Only the active ingredient is the approved drug. Inactive ingredients in a finished drug product are not drugs "approved under section 505" that are excluded from addition to food. A drug approved under section 505 also has a specific FDA-approved dosage

level or range. Thus, a substance must be added to food in the same dosage range as is encompassed by the new drug approval for that substance to be deemed a "drug approved under section 505." For example, FDA has approved folic acid as a new drug at 1 mg, but less than 1 mg folic acid as a food additive.[20]

Section 301(ll) therefore prohibits the addition to food only the exact same active ingredient (same moiety or mixture) at the dosage range approved under section 505. And as discussed in the preceding section, the prohibition is triggered only where the substance added to food is a "drug" because of marketing representations that the added substance is intended to diagnose, cure, mitigate, treat, or prevent disease. Mere chemical identity with a drug approved under section 505 does not render a substance a "drug" in the absence of such marketing claims.

Thus, it is apparent that section 301(ll) to this point is straightforward. "Food" must be given the same meaning it is given throughout the FDCA. The prohibition on marketing a drug in food applies only to a substance that is added to, but not naturally inherent in food. And "drug" likewise must have the same meaning as it is given elsewhere in the Act. Thus section 301(ll) applies only where the food manufacturer evidences an intent to market a constituent of food for a drug purpose. Finally the prohibition applies only to the exact same moiety or mixture as the one approved in the new drug application at issue.

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[20] FDA Orange Book; 21 C.F.R. 172.345.

5. Biological Product

Section 301(ll) prohibits the marketing of food to which has been added a biological product licensed under section 351 of the Public Health Service Act (PHS Act) [21] or a biological product for which substantial clinical investigations have been instituted and their existence made public. In light of rapid advances being made in the field of biotechnology (and with respect to research and development of probiotics specifically), FDA should avoid any interpretations of section 301(ll) that are broader than necessary to give effect to its limited objectives. Otherwise, there is a risk that whole classes of products that have the potential to benefit human health will unnecessarily be kept off the market.

The Public Health Service Act defines a biological product as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings."[22] In turn, the term "virus" is broadly defined in FDA regulations to include a wide range of microorganisms such as bacteria and fungi.[23] However, microorganisms such as bacteria and fungi are not biological products per se. As the language of the PHS Act makes clear, a bacterium or fungus is a biological product only if it is "applicable to the prevention, treatment, or cure of a

[21] As with the phrase "drug approved for use under section 355," the phrase "biological product licensed under section 351" has a clear, specific, and narrow meaning. To be licensed, a biological product must be demonstrated to be safe and effective for its intended use.

[22] 42 U.S.C. 262(i). Biological products are approved under the PHS Act, but are also subject to regulation as drugs under FDC Act.

[23] 21 C.F.R. § 600.3(h)(1).

disease or condition of human beings." Microorganisms currently used in food (including dietary supplements) or under development for use in food would not meet this definition when they are used for food (e.g., to provide nutrients and/or serve some other permissible function such as to support the immune system).[24]

FDA has been encouraged to interpret the term "biological product" as used in section 301(ll) by reference to FDA's regulatory definition of "same drug"[25] for purposes of implementing the exclusivity provisions of the Orphan Drug Act.[26] The definition of "same drug" should not control FDA's interpretation of "biological product" for purposes of section 301(ll), for several reasons. First, this view reflects an unduly narrow perspective on the wide range of products that are added to food and that are potentially subject to the definition of "biological product." As noted above, the definition of "biological product" encompasses microorganisms, which give rise to considerations not explicitly addressed by the definition of "same drug." Second, the definition of "same drug" was intended to apply only in the context of orphan drug exclusivity, and not in any other context. The definition of "same drug" does not apply in the context of new drug approval, nor should it apply in the context of section 301(ll). Third, the regulatory

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[24] FDA has recognized that a number of microorganisms are approved or GRAS for use in food. See, http://www.cfsan.fda.gov/~dms/opa-micr.html. As FDA made clear in its final rule on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, a claim that a substance supports the immune system is an acceptable structure/function claim. 65 Fed. Reg. 999, 1029 (January 6, 2000).

[25] 21 C.F.R. § 316.3(b)(13).

[26] See comment submitted by Rick Barsky, Chief Executive Officer, Agennix Inc., October 27, 2008.

definition of "same drug" is limited to "a drug that . . . is intended for the same use as the previously approved drug." Therefore, a substance would not fall within the definition of "same drug" if it is intended for a different use.

B. Prohibition Against the Addition to Food of a Drug or Biological Product For Which "Substantial Clinical Investigations Have Been Instituted and . . . Made Public"

Once again, straightforward analysis of the terms leads to but one conclusion for implementing the provision.

1. "Drug"

Section 301(ll) prohibits the addition to food of "a drug . . . for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public." In implementing this provision, it is important to take into consideration the intended use provisions of existing law, and the definition of "drug" discussed above. First, section 301(ll) only applies to the identical moiety or mixture for which there have been substantial clinical investigations. Second, even where a clinical investigation is being conducted under an investigational new drug application (IND), there are instances in which the substance under investigation may not be for a "drug" use, *i.e.*, intended to be marketed for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.[27]

[27] As discussed below, foods and dietary ingredients are sometimes studied under INDs in order to meet certain grant or Institutional Review Board (IRB) requirements. The (continued…)

The scope of the "substantial" and "public" nature of clinical investigations encompassed by section 301(ll) must be defined with reference to the provisions of the FDAAA relating to the registration of clinical trials. Those provisions set clear parameters for what clinical trials are "substantial" and how they are made "public." As part of the same legislation that established section 301(ll), those provisions of FDAAA appropriately inform the criteria for investigational drugs captured by section 301(ll) of the same law.

2. "Substantial Clinical Investigation" and "The Existence of Such Investigations Have Been Made Public"

Through the passage of FDAAA, Congress amended the Public Health Service Act (PHSA) to expand the public registry previously established by the National Library of Medicine of the National Institutes of Health and available at www.ClinicalTrials.gov.[28] ClinicalTrials.gov includes federally and privately sponsored clinical trials conducted in the United States and abroad. ClinicalTrials.gov provides information about the active ingredient, the trial's purpose, who may participate, locations, and contact information for further details. The FDAAA expanded the registry to require that all "applicable drug clinical trials" be listed.[29] An "applicable drug clinical

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mere study of such food substances, even when the studies have disease or disease-surrogate endpoints, should not subject them to regulation as drugs.

[28] PHSA § 402(j)(2).

[29] Previously, the registry included only clinical trials for drugs for serious or life threatening diseases or conditions

trial" means a controlled clinical investigation, other than a phase I investigation, of a new drug or a biological product that is a drug, conducted anywhere in the world.[30]

FDA regulations define "clinical investigation" broadly as "an experiment that involves a test article [(defined to include "any drug, medical device, . . . human food additive, . . . or any other article subject to regulation under the [FDCA] or the [PHSA]")[31]] and one or more human subjects . . . ."[32] However, for purpose of section 301(ll), the phrase "clinical investigation" must be assigned the meaning given the phrase in FDA's investigational new drug regulations – *i.e.*, an experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.[33] Such clinical investigations must be under an IND to be lawfully conducted in the United States,[34] and must meet the requirements of 21 C.F.R. 312.120 and 314.106 to be accepted by FDA as "substantial" if conducted abroad.

In that connection, these clinical investigations must be distinguished from those studies that are intended or are "likely to yield generalizable knowledge about the subjects' disorder or condition . . . ." 21 C.F.R. § 50.53(c). Clinical studies conducted for general knowledge about a condition or disease do not equate to clinical studies

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[30] PHSA § 402(j)(1)(A)(iii).

[31] 21 C.F.R. § 50.3(j).

[32] Id. § 50.3(c). A broader interpretation of "clinical investigation" would discourage research on safety of new food ingredients.

[33] 21 C.F.R. 312.3. The phrase "phase I" has the meaning given the phrase in FDA's IND regulations at 21 C.F.R. 312.21(a).

[34] 21 C.F.R. part 312.

conducted for use of a new drug to treat, cure, mitigate or prevent disease. Such studies clearly do not meet the literal requirements, or intent, of the provision on "substantial clinical investigations."

"Substantial clinical investigations" in section 301(ll) simply means those human investigations conducted under an IND or 21 C.F.R. 312.120 and substantial enough to be required to be listed in the public registry at ClinicalTrials.gov. Accordingly, only a drug moiety or identical mixture that is under investigation in accordance with an IND or 21 C.F.R. 312.120 in at least two[35] phase II or later human clinical trials would potentially be precluded from addition to food, and only as of the time that the trials are publicly identified in the registry at ClinicalTrials.gov. Substances that are the subject of laboratory or animal studies, or phase I trials, or that have not been publicly disclosed through the ClinicalTrials.gov registry, are not included within the scope of 301(ll). Investigations become publicly disclosed at the time of listing in the NIH registry, not when they commence.

The fact that section 201(ff) requires that the clinical investigations must have been "authorized" and section 301(ll) does not merely reflect the understanding by Congress that a clinical investigation may not lawfully be conducted in the United States except under an IND. Thus, Congress dropped the requirement for authorization under

[35] FDA has since 1962 interpreted the term "investigations" in section 505(d) to require at least two investigations of the identical moiety or mixture.

section 301(ll) because it would be redundant. Thus, there is no substantive difference between the two provisions in this regard.

3. "Have Been Instituted"

The requirement that substantial clinical investigations "have been instituted" means that the clinical development program is ongoing and not discontinued. Section 301(ll) does not allow someone to submit an IND for post-phase I trials of a substance, list the trials in Clinical Trials.gov, and then abandon clinical development of the substance and contend that the substance is nonetheless forever blocked from use as a dietary supplement. Section 301(ll) applies only as long as there is an ongoing active clinical development program leading to submission of an NDA and FDA approval of that application. Inactivity at any stage effectively terminates application of section 301(ll) to the substance.[36]

4. Investigated As a Drug

Before taking enforcement action under section 301(ll), FDA must make an independent inquiry into whether the substance is being investigated as a drug. Some Institutional Review Boards (IRBs) demand INDs even for trials involving substances intended for use as food. Accordingly, the existence of an IND and listing in ClinicalTrials.gov is not determinative of whether the substance is under investigation as

[36] See 21 C.F.R. 312.45.

a drug, and other factors must be considered. An IND is necessary but not sufficient to deny the use of the substance in food.

a. Additional Factors for Consideration

For a substance under investigation to fall under section 301(ll), there must be evidence that the investigation is being conducted as part of a clinical development program leading to the submission of an NDA. This could potentially be shown, for example, by: (1) evidence documenting that a clinical investigation is being conducted on behalf of a pharmaceutical manufacturer that would be expected to commercialize it as a drug, rather than a food company or an academic researcher who would not be expected to pursue an approved NDA; and (2) representations made by sponsors during pre-market meetings with FDA that the substance is being studied to support an NDA or BLA. On the other hand, if the study sponsor has been marketing the substance in a food or dietary supplement, or has submitted a food additive petition, food contact substance notification, new dietary ingredient notification, or GRAS notification for the substance, it is clear that the study sponsor intends to market the substance as a food – not a drug.

It is imperative that FDA look beyond the protocol and endpoints evaluated in a study when assessing whether it was conducted to support an NDA or BLA. While in some cases the protocol for the investigation will show plainly that the substance is intended to be used as a drug and that the investigation is intended to support an NDA, in other cases a protocol may be less clear or more generic – particularly since clinical trials for food and dietary ingredients often properly consider disease or disease-surrogate

endpoints. There are extensive studies, for example, that evaluate the relationship between foods and dietary ingredients and the risk of diseases such as coronary heart disease and osteoarthritis, among others. Although these studies may appear similar to studies conducted on drug ingredients, they are not conducted for purposes of obtaining an NDA or BLA, but rather, are typically conducted: (1) by the food and dietary supplement industry to support health claims or structure/function claims that are expressly permitted by FDA for use on food labeling; and (2) by NIH/ODS to meet research goals authorized by Congress.

b. FDA Must Interpret Section 301(ll) in a Manner that Does Not Conflict with Statutes Expressly Authorizing or Contemplating Research on Foods and Dietary Ingredients

There are a number of congressional mandates and statutory provisions authorizing the clinical study of foods to assess their impact on human health. For example, the NLEA amended the FDCA to authorize health claims for foods and dietary supplements. Health claims describe a relationship between a food, food component, or dietary supplement ingredient, and disease risk reduction or health-related condition. Companies can petition for new health claims by submitting a health claim petition containing data showing there is significant scientific agreement ("SSA") in support of the claim.[37] Clinical trials are often required to meet the SSA standard, and such trials are likely to have disease or disease-surrogate endpoints. Clinical studies are also

[37] FDCA § 403(r)(3)(B)(i).

necessary to substantiate many structure/function claims that are made for foods and dietary ingredients.[38]

Congress has also expressly authorized the NIH and various NIH institutes to engage in nutritional research, including research on foods and dietary ingredients. The ODS is authorized, for example, to "conduct and coordinate scientific research within the National Institutes of Health relating to dietary supplements and the extent to which the use of dietary supplements can limit or reduce the risk of diseases such as heart disease, cancer, birth defects, osteoporosis, cataracts, or prostatism."[39]

A clinical trial designed to examine the health benefits of a food component in anticipation of lawful structure/function claims or the submission of a health claim petition to FDA, must not be characterized as a drug investigation that would preclude use of the substance in food – the very purpose for which the substance is being investigated. Likewise, more general investigations by government researchers of the potential health benefits of food substances cannot be deemed drug investigations that would preclude the use of those components in food.

Such an overbroad reading of section 301(ll)'s substantial clinical investigations clause would clearly interfere with congressionally authorized research conducted by the NIH and ODS, and conflict with and effectively repeal the FDCA's health claim and structure/function regime. Congress clearly did not intend such a result.

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[38] FDCA §§ 403(a), 403(r)(6)(B).
[39] 42 U.S.C.A.§ 287c-11(c)(1).

Under principles of statutory construction, repeals by implication are not favored and will not be found unless an intent to repeal existing statutory language by Congress is clear and manifest.[40] Courts strongly presume that Congress does not alter the fundamental details of a regulatory scheme in "vague terms or ancillary provisions,"[41] and that "Congress will specifically address language on the statute books that it wishes to change."[42] Moreover, a court must make "every effort not to interpret a provision in a manner that renders other provisions of the same statute inconsistent, meaningless, or superfluous."[43]

Based upon the above, FDA must conclude that section 301(ll) simply prohibits the use in food of substances that are on track toward NDA approval as drugs. An overbroad interpretation by FDA, inconsistent with the above, would discourage research into new food ingredients, conflict with the congressionally authorized research goals of ODS/NIH, and implicitly repeal the health claim provisions of the FDCA.

C. Relevant Exceptions from the Prohibition

Section 301(ll) contains a number of exceptions from the prohibition against adding drugs to food. The exceptions most relevant to the food industry are addressed below.

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[40] *Rodriguez v. United States*, 480 U.S. at 524; *Morton v. Mancari*, 417 U.S. at 550-51.

[41] *Whitman v. American Trucking Ass'ns, Inc*., 531 U.S. 457, 468 (2001).

[42] *United States v. Fausto*, 484 U.S. at 453.

[43] *Boise Cascade Corp. v. EPA*, 942 F.2d 1427, 1432 (9th Cir. 1991).

1. "Marketed in Food"

Section 301(ll)(1) excepts from the prohibition a drug that was "marketed in food before any approval of the drug under section 505" or before substantial clinical investigations involving the drug were instituted. "Marketed in food" means simply that the substance has been "in food" that has been marketed, whether the substance was intrinsic or extrinsic to the food and whether or not it has been separately promoted. Once a substance has been marketed in food, for example, as an inherent natural constituent of a food, it remains within the "marketed in food" exemption even if that constituent is isolated or replicated and then added to other food. FDA's only inquiry, therefore, is whether the substance has been a part of food that has been marketed. As noted above, the term "food" has its statutory meaning, and plainly includes dietary supplements.

The phrase "marketed in food" differs from the language at section 201(ff) of the FDCA relating to substances "marketed as a dietary supplement or as a food," which may be included in dietary supplements even if they were subsequently approved as drugs. FDA's implementation of the "marketed in food" exception to the section 301(ll) prohibition must not be constrained by any prior interpretations of "marketed as food," from section 201(ff) because Congress plainly chose different language for this exception. This distinction is necessary because the section 301(ll) prohibition extends to conventional food as well as dietary supplements. If the "marketed in food" exception were interpreted to apply only to substances for which distinct marketing claims were made before the substances were investigated as drugs, then 301(ll) would prohibit the

addition to food of substances that were not the subject of prior marketing claims, but plainly would permit such substances to remain in foods in which they are naturally inherent. Foods in which such substances are inherent could lawfully make non-disease claims for such substances, while the very same substances could not even be included in other foods. Such a distinction makes no sense and advances no public health goal.

The "marketed in food" exception applies if the food has been marketed anywhere in the world, not just in the United States. Congress knows how to write legislation that relates only to United States marketing, e.g., in the definition of a new dietary ingredient in section 413(c) of the FDCA. Where there is no limitation to United States marketing, e.g., in the GRAS exception to the definition of a food additive in section 201(s) of the FDCA, the courts have held that the proper reference is to marketing anywhere in the world. *Fmali Herb, Inc. v. Heckler*, 715 F.2d 1385 (9th Cir. 1983). Accordingly, any food marketed in any part of the world qualifies for this exception from section 301(ll).

2. To "Enhance the Safety of the Food" But Not to Have an "Independent Biological or Therapeutic Effect"

Section 301(ll)(3) exempts from the prohibition a drug added to food where "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." This exception captures drugs added to food both to enhance the toxicological safety of food and to enhance the nutritional profile of food.

Toxicological safety may be enhanced by adding to food preservatives or antimicrobials that may also be approved as drugs, or by using other approved drugs as novel food ingredients or as part of formulations or processes that enhance food safety by preventing microorganisms from being propagated.

Given the now-widespread recognition of the role of nutrition in health promotion and in decreasing human disease, public health considerations favor a broad reading of the "safety" exception to include substances that promote wellness. Under section 403(r)(1)(B) of the FDCA, no unapproved disease claims may be made for such substances in food.

In this context, "biological" means acting like a biological product. That is, a licensed biological product must not be added to food for the same therapeutic purposes for which it is licensed, but may be added for other purposes if the remaining criteria in the exemption are met.

"Therapeutic" here is used in accordance with the dictionary definition of the term, *i.e.*, "of or pertaining to the treating or curing of disease or disorders; curative; rehabilitative."[44] This interpretation is in harmony with the balance of section 301(ll), which prohibits the addition of substances intended to diagnose, cure, mitigate, treat, or prevent disease, but acknowledges that the same substances may be added to food for other lawful purposes.

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[44] Webster's College Dictionary (1991).

III. The Retroactive Application of Section 301(ll) Would Result in a Taking

Finally, FDA must not interpret section 301(ll) in a manner that would have an adverse retroactive impact on currently marketed ingredients - particularly, but not limited to, those that have already been reviewed and authorized for use by FDA. As FDA is aware, many food manufacturers have obtained FDA authorization to market certain foods and food ingredients (or make certain claims) under the food additive, GRAS, new dietary ingredient, food contact substance, health claim, and other provisions of the FDCA. The application of section 301(ll) in a manner that would prohibit the continued marketing of such foods and ingredients would rise to a taking without just compensation in violation of the Fifth Amendment.

There is ample precedent for takings in the regulatory context. The Supreme Court has explicitly distinguished between two branches of Takings Clause cases - physical takings and regulatory takings.[45] A regulatory taking transpires when some significant restriction is placed upon an owner's use of property for which justice and fairness require that compensation be given.[46] The Supreme Court has found a number of intangible interests to be property for purposes of the Fifth Amendment's Takings

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[45] *Tahoe-Sierra Pres. Council, Inc. v. Taho Reg'l Planning Agency*, 535 U.S. 302 (2002) (distinguishing between acquisitions of property for public uses and regulations prohibiting private uses).

[46] *Philip Morris Inc. v. Reilly*, 312 F.3d 24, 33 (1st Cir. 2002).

Clause. Such intangible interests include, for example, trade secrets,[47] valid contracts,[48] and a lien provided for under state law.[49]

In order to evaluate whether a regulatory taking has occurred, courts generally apply a three-part "ad hoc, factual inquiry": (1) what is the economic impact of the regulation and does it impair the value or use of the property; (2) whether the government action interferes with reasonable investment-backed expectations; and (3) what is the character of the government action.[50]

Companies have a vested property interest in their FDA-authorized food ingredients. A retroactive application of section 301(ll) that prohibits the continued use of such ingredients in food would not only impair, but destroy, that property value. Moreover, a successful food additive, GRAS, or new dietary ingredient review by FDA results in reasonable investment-backed expectations. Companies invest significant amounts of time and money in their regulatory submissions to FDA and rely upon FDA's favorable review when making future business investment decisions related to the product/ingredient.

Based upon the above, FDA should interpret section 301(ll) such that the provision does not apply to currently marketed foods and ingredients - particularly those

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[47] *Ruckelshaus v. Monsanto*, 467 U.S. 986, 1003 (1984).

[48] *Lynch v. United States*, 292 U.S. 571, 579 (1934).

[49] *Armstrong v. United States*, 364 U.S. 40, 44 (1960).

[50] *Penn Central Transp. Co. v. New York City*, 438 U.S. 104, 124 (1978); *Phillip Morris, Inc. v. Reilly*, 312 F.3d at 33.

that received a favorable FDA review via a food additive, GRAS, new dietary ingredient, health claim, or nutrient content claim submission prior to the enactment of FDAAA.

CRN would be pleased to answer any questions FDA may have about these comments or provide additional information based upon our experience with the interpretation and implementation of section 201(ff)(3)(B).

Sincerely yours,

Steve Mister
President & CEO
Council for Responsible Nutrition