

GENELABS TECHNOLOGIES, INC.

August 1, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: FDA Docket No. 00P-1263

Dear Sir or Madam:

SUPPLEMENT TO CITIZEN PETITION

This submission supplements the citizen petition by Genelabs Technologies, Inc. ("Genelabs") dated April 19, 2000. As explained below, the recent appellate court decision in *Pharmanex v. Shalala* clarifies and strengthens FDA's legal authority to apply the section 201(ff)(3)(B) exclusion from the definition of "dietary supplement" in appropriate cases. Consequently, there is no reason for the Agency to delay the initiation of a process intended to gather data for purposes of deciding whether to apply the exclusion to DHEA-containing products, as requested in Genelabs' April 19 petition. For the reasons stated below, and for the reasons stated in the original petition, we request that the Agency take immediate action to initiate a procedure to determine whether DHEA is excluded from the definition of "dietary supplement."

I. The *Pharmanex* decision clarifies FDA's legal authority to apply the section 201(ff)(3)(B) exclusion from the definition of "dietary supplement."

On Friday, July 21, 2000, the United States Court of Appeals for the 10th Circuit decided the case of *Pharmanex v. Shalala* (No. 99-4087)(opinion enclosed). The court reversed a lower court ruling setting aside FDA's interpretation of section 201(ff)(3)(B) of the Federal Food, Drug, and Cosmetic Act (the "Act") as excluding a product

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containing the active ingredient of an approved new drug from the statutory definition of "dietary supplement," where the product was not marketed as a dietary supplement or a food before the approval of the prescription drug. In so doing, the appellate court resolved an important legal controversy regarding the scope of section 201(ff)(3)(B).

The plaintiff in *Pharmanex* sought to invalidate FDA's interpretation of section 201(ff)(3)(B) and to limit the application of that exclusion to entire drug products, rather than to components or ingredients of drug products. The district court agreed with the plaintiff's position and set aside FDA's determination that the product "Cholestin," which contained the same active ingredient as the cholesterol-lowering prescription drug Mevacor, could not be marketed as a "dietary supplement." The 10th Circuit reversed the district court on appeal, holding that:

- (1) Although the Dietary Supplement Health and Education Act of 1994 ("DSHEA") was primarily intended to relax regulatory burdens on the dietary supplement industry, section 201(ff)(3)(B) represents the limiting principle on that statute's relaxation of regulation burdens;
- (2) Section 201(ff)(3)(B) balances the goals of DSHEA with other policies of the Act, in effect carving out breathing room for dietary supplements while ensuring that drug manufacturers will not exploit this flexibility to make an "end-run" around the requirements of the new drug approval process;
- (3) Congress did not specify the exact contours of the section 201(ff)(3)(B) exclusion, but instead used broad language in crafting the provision;
- (4) Given the ambiguous statutory language and the overall statutory context, FDA was entitled to deference in interpreting section 201(ff)(3)(B) under *Chevron, U.S.A v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984);
- (5) While the plaintiff's argument was linguistically possible, the court was not compelled to adopt the conclusion that Congress clearly intended to limit section 201(ff)(3)(B)'s application to finished drug products, in light of the statutory context and the surrounding provisions;

- (6) Deference to FDA's interpretation was particularly appropriate in this case, which involved important questions of public health and safety; and
- (7) FDA's interpretation was not arbitrary, capricious, or manifestly contrary to the statute.

Thus, the *Pharmanex* decision clarifies FDA's authority to apply the section 201(ff)(3)(B) exclusion not only to prevent the marketing of "dietary supplement" products with the exact same composition as approved or investigational drug products, but also to prevent the marketing of "dietary supplement" products that contain the same active ingredient as approved or investigational drug products.

Moreover, the decision provides substantial support for the policy rationale underlying FDA's broad application of the section 201(ff)(3)(B) exclusion -- that the DSHEA was not intended to provide a loophole for avoiding the requirements of the new drug provisions of the Act. The court sustained as reasonable FDA's view that the plaintiff's narrow reading of the statute would undercut the broad purposes of the Act, including incentives for development of orphan and pioneer drugs, and would leave a gap in protection for the public.

II. The *Pharmanex* decision clarifies FDA's authority to grant the relief requested in Genelabs' citizen petition.

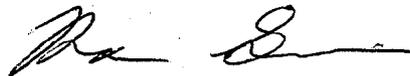
Although *Pharmanex* arose in a factual context involving the marketing of a product containing the active ingredient of an *approved* prescription drug, the ruling is equally applicable to the prohibition against marketing products containing ingredients of *investigational* drugs as "dietary supplements." The court's analysis centered on the meaning of the word "article" in section 201(ff)(3)(B). That statutory section contains two parallel subsections -- subsections 201(ff)(3)(B)(i) and 201(ff)(3)(B)(ii) -- which exclude from the definition of "dietary supplement" an "an article that is approved as a new drug..." and an "article authorized for investigation as a new drug," respectively.

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Because the operative language construed in the *Pharmanex* case is the same in both subsections, would be interpreted based on the same textual, legislative history, and policy bases, and because the court itself characterized its holding as interpreting section 201(ff)(3)(B) generally, it is clear that the case applies equally to approved drugs and investigational drugs. Indeed, as pointed out in Genelabs April 19, 2000 citizen petition (at pages 10-11), the rationale for interpreting section 201(ff)(3)(B) as applying to ingredients as well as finished products is even stronger in the case of investigational drugs than it is for approved drugs.

FDA, therefore, has the clear legal authority to interpret section 201(ff)(3)(B)(ii) as excluding from the definition of "dietary supplement" any product containing DHEA, the active ingredient in Genelabs' investigational new drug GL701, so long as the other requirements of section 201(ff)(3)(B)(ii) are satisfied. Genelabs' citizen petition sets forth a fair and efficient process by which FDA will be able to gather the information necessary to determine whether the requirements of section 201(ff)(3)(B)(ii) are satisfied with respect to DHEA. In view of FDA's strengthened legal authority to apply the section 201(ff)(3)(B) exclusion in appropriate cases, there is no reason for the Agency to delay the initiation of a process intended to gather data for purposes of deciding whether to apply the exclusion to DHEA-containing products. FDA should grant Genelabs' petition without further delay.

Sincerely,



Marc Gurwith, M.D.
Vice President of Drug Development and
Chief Medical Officer

Enclosure (Opinion of the U.S. Court of Appeals for the 10th Circuit in *Pharmanex v. Shalala*)

PUBLISH

FILED
United States Court of Appeals
Tenth Circuit

UNITED STATES COURT OF APPEALS
TENTH CIRCUIT

JUL 21 2000

PATRICK FISHER

Clerk

PHARMANEX, a Delaware corporation
authorized to do business in the State of
Utah,

Plaintiff - Appellee,
vs.

DONNA SHALALA, in her official
capacity as Secretary of the United States
Department of Health and Human
Services; MICHAEL FRIEDMAN, in his
official capacity as First Deputy
Commissioner of the Food and Drug
Administration,

Defendants - Appellants.

No. 99-4087

NATIONAL ORGANIZATION OF
RARE DISORDERS; MERCK & CO.,
INC.; NATIONAL NUTRITIONAL
FOODS ASSOCIATION,

Amicus Curiae.

**APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF UTAH
(D.C. No. 97-CV-262-K)**

Richard M. Cooper (and Helen I. Dooley, Williams & Connolly, Washington, D.C. and
Alan L. Sullivan, Snell & Wilmer, Salt Lake City, Utah, and Stuart M. Pape and Daniel
A. Kracov, Patton Boggs, Washington, D.C., with him on the brief), for Plaintiff -
Appellee.

Irene M. Solet (and Scott R. McIntosh, Attorneys, Appellate Staff, Civil Division, and David W. Ogden, Acting Assistant Attorney General, Department of Justice, Washington, D.C.; David J. Schwendiman, United States Attorney, Salt Lake City, Utah; Margaret Jane Porter, Chief Counsel and Neal Parker, Associate Chief Counsel, Food and Drug Administration, Rockville, Maryland, with her on the briefs), for Defendant - Appellant.

Kenneth C. Bass, III, David G. Adams, Nathan A. Beaver, Venable, Baetjer, Howard & Civiletti, Washington, D.C., for Amicus Curiae National Organization of Rare Disorders and Merck & Co., Inc.

Alan Charles Raul, Sidley & Austin, Washington, D.C., for Amicus Curiae National Nutritional Foods Association.

Before **KELLY, PORFILIO**, Circuit Judges, and **ALLEY***, Senior District Judge.

KELLY, Circuit Judge.

This case requires that we address the scope of 21 U.S.C. § 321(ff)(3)(B) as it relates to the FDA's power to regulate dietary supplements. Appellants (hereinafter, "FDA") appeal from the federal district court's order setting aside the FDA's Administrative Decision of May 20, 1998. Our jurisdiction arises under 28 U.S.C. § 1291, and we reverse and remand for resolution of record based arguments not reached below.

Background

Plaintiff-Appellee, Pharmanex, markets a product, Cholestin, that is intended to promote healthy cholesterol levels. Cholestin is made from red yeast rice, and contains a

*Honorable Wayne E. Alley, Senior District Judge, United States District Court of the Western District of Oklahoma, sitting by designation.

natural substance, mevinolin, which is chemically identical to the active ingredient, lovastatin, in the prescription drug, Mevacor.¹ Mevacor was approved by the FDA in 1987 for the treatment of high cholesterol and heart disease. On April 7, 1997, the FDA advised Pharmanex that it considered Cholestin to be a drug, which may not be marketed without FDA approval. While discussions between the parties were ongoing, the FDA issued a Notice of Detention and Hearing that prevented importation of a shipment of red yeast rice for encapsulation into Cholestin. On May 20, 1998, the FDA issued a final decision, holding that Cholestin does not meet the definition of "dietary supplement" provided by 21 U.S.C. § 321(ff)(3)(B)(i), and is thus subject to regulation as a drug. Subsequently, Pharmanex filed an action in district court, seeking declaratory and injunctive relief, and asking the court to hold unlawful and set aside the FDA's decision. The district court granted a preliminary injunction, and ultimately entered a final order setting aside the FDA decision, holding that Cholestin is a "dietary supplement" within the definition set forth by § 321(ff). The district court based its decision on the determination that § 321(ff)(3)(B) refers unambiguously to finished drug products, rather than their individual constituents. Thus, it was unnecessary for the district court to reach a number of issues raised by both parties. It did not reach Pharmanex's claim that the FDA was arbitrary and capricious in determining (1) that Pharmanex, in manufacturing and marketing Cholestin, was manufacturing and marketing lovastatin; and (2) that lovastatin had not been marketed as a dietary supplement or as a food before its approval as a new drug. While the district court remarked in passing that red rice yeast is a food that has been consumed for centuries in China and decades in the U.S., both parties agree that this was not equivalent to ruling on the FDA's prior determinations. Moreover, the district court did not pass on Pharmanex's claims that (1) under § 321(ff)(3), how a supplement is manufactured (i.e., to enhance the presence of one of its ingredients) is

¹ Hereinafter, "lovastatin" will refer both to mevinolin and lovastatin.

irrelevant; and (2) the FDA did not adequately explain its departure from its prior interpretation that approval of a new drug is an approval only of a product, not an active ingredient.

Discussion

As noted at the outset, this case involves an interpretation of 21 U.S.C. § 321(ff)(3)(B) of the Food, Drug, and Cosmetic Act (hereinafter, "FDCA"), as amended by the Dietary Supplement Health and Education Act, Pub. L. No. 103-417 (1994) (hereinafter, "DSHEA"). Because we are confronted with conflicting interpretations of the statute that the Food and Drug Administration is charged with administering, the analytic framework set forth in Chevron, U.S.A. v. Natural Resources Defense Council, Inc., 467 U.S. 837 (1984), governs our analysis. See FDA v. Brown & Williamson Tobacco Corp., 120 S.Ct. 1291, 1300 (2000). That is, we must decide, using the traditional tools of statutory construction, "whether Congress has directly spoken to the precise question at issue." Id. (quoting Chevron, 467 U.S. at 842). If so, that is the end of the matter, and Congress' clear intent controls. If the statute is silent or ambiguous as to the specific issue before us, then we must defer to the agency's interpretation, if it is based on a permissible construction. Id. We need not conclude that the agency construction is the only one possible, or even that we would have so construed the statute had the issue arisen in a judicial proceeding. Rather, we will give effect to the agency's interpretation unless it is arbitrary, capricious, or manifestly contrary to the statute. See Chevron at 844. We accord the agency such deference, given its special institutional competence regarding the "facts and circumstances surrounding the subjects regulated," particularly those which touch and concern competing views of the public interest. See Brown & Williamson, 120 S.Ct. at 1300.

In evaluating whether Congress has squarely and unambiguously addressed the question before us, we need not limit ourselves to scrutiny of the discrete statutory

section in isolation. Rather, we examine the statutory provision in context. See Brown & Williamson, 120 S.Ct. at 1300-01. We must “interpret the statute ‘as a symmetrical and coherent regulatory scheme,’ and ‘fit, if possible, all parts into an harmonious whole.’” Id. (citations omitted). In this case, we must determine whether Congress unambiguously manifested its intent to exclude only finished drug products (rather than ingredients) from the definition of dietary supplement in § 321(ff)(3)(B), which states in relevant part:

The term 'dietary supplement' . . . does . . . not include . . . an article that is approved as a new drug under section 355 of this title¹, . . . which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food. . . .

¹ "Section 355 of this Title" refers to 21 U.S.C. § 355, "New Drugs," which sets forth the requirements for applications for approval of drug products, and discusses market exclusivity provisions.

The Parties' Contentions

The FDA argues that the phrase "an article that is approved as a new drug" is properly understood to contemplate active ingredients¹ as well as finished drug products.² To support this claim, FDA makes what is effectively a textual argument, pointing out that the word "article" is used throughout the FDCA to connote both component and finished drug product. The FDA notes that § 321(ff)(1) and (2) refer to a dietary supplement as a "product" with certain qualities, whereas § 321(ff)(3)(B) uses the word "article," a much broader term. Moreover, the FDA contends that the district court erred in finding that the phrase "approved as a new drug" is dispositive evidence of Congress' unambiguous intent to restrict the application of § 321(ff)(3)(B) to finished drug products. Additionally, the FDA argues that the district court misconstrued judicial and regulatory authorities to support its finding of clear Congressional intent, and its conclusion that in the past, the FDA has endorsed statutory interpretations squarely contrary to those of the instant case. The FDA also asserts that the district court's reliance on legislative history was misplaced. Finally, the FDA argues that the interpretation advanced by the district court and Pharmanex would undercut the broad purposes of the FDCA, with respect to orphan drugs, pioneer drugs, and leave a gap in protection for the public.

The essence of Pharmanex's argument is that the plain meaning of 21 U.S.C. § 321(ff)(3)(B)(i) cannot exclude Cholestin or lovastatin from the definition of "dietary supplement." Pharmanex contends that Cholestin cannot be "an article that is approved as a new drug" because it was never approved as a new drug. Additionally, Pharmanex

¹ "Active ingredient" means "any component that is intended to furnish pharmacological activity or other direct effect. . . ." 21 C.F.R. 210.3(b)(7).

² "Drug product" is defined as "finished dosage form. . . that contains a drug substance, generally, but not necessarily, in association with one or more drug ingredients." 21 C.F.R. 314.3(b).

asserts that “an article that is approved as a new drug” cannot apply to lovastatin because an ingredient is never “approved as a new drug.” Moreover, Pharmanex claims that the definition of “new drug,” § 321(p), itself precludes § 321(ff)(3)(B) from applying to drug components, as they are not approved, are not the subject of investigation, and do not have labeling. Additionally, Pharmanex contends that in the past, the FDA has advanced the very definition of “new drug” that it now resists. Pharmanex also argues that the FDA’s interpretation defeats the unambiguously articulated policies enshrined in DSHEA and would produce absurd results. Pharmanex disputes the FDA’s claim that limiting § 321(ff)(3)(B) would leave a gap in public protection, arguing that dietary supplements are adequately regulated by other provisions of FDCA. Finally, Pharmanex asserts that the FDA’s arguments about statutory ambiguity are in error.

Plain Language

a. Statutory Text

The district court resolved this matter by concluding that Congress had clearly and unambiguously expressed its intent to limit the application of § 321(ff)(3)(B) to finished drug products. Having carefully reviewed the text of the provision in question, other relevant statutory materials, legislative history, and the parties’ above arguments, we reach the opposite conclusion. We begin, as always, with the language of the provision in question. First, the use of the word “article” creates ambiguity. As the FDA points out, the term has a broad meaning throughout the FDCA, alternatively referring both to products and their individual constituents. See 21 U.S.C. § 321(g)(1)(A)-(D) (using “article” to refer to both drugs and their components). The use of the broad term “article” in § 321(ff)(3)(B) is especially striking in contrast with the immediately preceding sections, §§ 321(ff)(1) and (2), which use the word “product” to expand on the definition of dietary supplement. The drafters could have clarified their intent by using the words “active ingredient” rather than “article,” as is used in other provisions of the FDCA. See generally, 21 U.S.C. §§ 355(c)(3)(D)(i), 355(j)(2)(A)(ii)(I)-(II). Instead of using the

more precise terms such as “product” and “active ingredient” or some combination of the terms, the drafters opted for the more general expression “article.” This suggests ambiguity.

Further suggesting ambiguity, the previous section, § 321(ff)(3)(A), refers to “the article, when used *as or in* a dietary supplement . . .(emphasis added).” The clause at issue here, § 321(ff)(3)(B), omits these descriptive phrases. It could be that the omission reflects the drafters’ intent to use “article” to comprehend both product and components in § 321(ff)(3)(A), but not for purposes of § 321(ff)(3)(B). Alternatively, the drafters could have omitted the prepositions because they were superfluous, as 321(ff)(3)(A) has already established that “article” contemplates both product and ingredient. The drafters’ intent in this respect is altogether unclear.

We reject Pharmanex’s contention that the phrase modifying “article,” namely, “approved as a new drug,” sufficiently clarifies the section for purposes of our analysis. Pharmanex argues that this phrase resolves any doubt as to the scope of § 321(ff)(3)(B). That is, the clause could not possibly apply to drug components because components are never “approved as a new drug.” Pharmanex argues that approval only attaches to drug products. Additionally, the very definition of “new drug,” 21 U.S.C. § 321(p), refers by its terms only to drug products. We do not find these arguments persuasive.

While it is true that the FDCA provisions relating to approval of new drugs, 21 U.S.C. § 355, discuss approval in the overarching context of finished product approval, it is too simple to suggest that ingredients are in no sense “approved” in the new drug approval process. See e.g., 21 U.S.C. § 355(c)(3)(D)(i)-(ii) (referring to a drug, “no active ingredient . . .of which has been approved” as part of the new drug approval process). It is evident from § 355 that approval of active ingredients is integral to the overall new drug approval process. See e.g. 21 CFR § 314.50(d)(1)(i)-(ii) (requiring a listing and description of drug substance and drug product components as part of the application for new drug approval). The use of the phrase “approved as a new drug”

cannot bear the interpretive weight Pharmanex applies to it. It does not clarify the scope of § 321(ff)(3)(B) to the extent Pharmanex suggests.

We likewise reject Pharmanex's contention that because the definition of "new drug" in § 321(p) refers to composition, investigation, and labeling, it clarifies the intent of § 321(ff)(3)(B), and precludes its application to active ingredients. The definition of "new drug" found in § 321(p) provides in relevant part:

(1) Any drug . . . the composition of which is such that such drug is not generally recognized, . . . as safe and effective for use under the conditions prescribed . . . in the labeling thereof. . . .

(2) Any drug . . . the composition of which is such that such drug, as a result of investigations . . . has become so recognized, but which has not . . . been used to a material extent or for a material time under such conditions.

As the FDA points out, this definition (including references to composition, labeling and investigation) modifies the initial phrase “any drug.” As stated previously, the term “drug” is defined in § 321(g) to include both finished drug products as well as individual constituents. Thus, the definition of “new drug” is largely colored by the ambiguity that attends the broad term “drug.” Moreover, the claim that an ingredient cannot have composition finds no support in the FDCA or common sense. Similarly, it is not accurate to suggest that drug components are not the subject of investigation in any sense. See generally, 21 CFR § 312.23(a)(7)(i) (“Therefore, the emphasis in an initial Phase I submission should generally be placed on the identification and control of the raw materials and the new drug substance [defined in 21 CFR 314.3(b) as active ingredient]”). In view of the preceding, we find that the definition of “new drug” does not itself sufficiently clarify the drafters’ intent with respect to § 321(ff)(3)(B).

a. Prior Judicial and Regulatory Authorities

The district court emphasized that a court must assume that Congress drafts legislation with knowledge of relevant pre-existing authorities that bear on judicial interpretations of statutory terms. See Molzof v. U.S., 502 U.S. 301, 307 (1992). Even so, the judicial and regulatory authorities upon which the district court relied (and upon which Pharmanex now relies) for the proposition that only finished drug products are approved under § 355, do not sufficiently illuminate the meaning of § 321(ff)(3)(B) for our purposes.

United States v. Generix Drug Corp., 460 U.S. 453 (1983), lends no support to Pharmanex’s position, as this case only held that § 321(g)(1) is “plainly broad enough to describe a completed drug product.” Id. at 458. The inclusion of drug product within the ambit of § 321(g)(1) does not resolve the question of the exclusion of drug ingredient, and is thus irrelevant to the questions before us. Similarly, USV Pharm. Corp. v. Weinberger, 412 U.S. 655 (1973), does not support Pharmanex’s contentions. In USV, the Court held that in the specialized context of the “grandfather clause” of the 1962

amendments to the FDCA, the phrase “any drug. . .covered by an effective [New Drug Application]” includes both the specific product in the new drug application and all similar drugs containing the same active ingredient. *Id.* at 664. It is true that the Court noted in passing that generally speaking, the new drug approval process is manufacturer specific. This dicta, however, does not elucidate the meaning of “approved as a new drug” in § 321(ff)(3)(B) in such a way that precludes the FDA’s interpretation.

In *Pfizer, Inc. v. FDA*, 753 F. Supp. 171 (D. Md. 1990), the FDA successfully argued that “drug” in § 355(b)(1) and (c)(2) means “drug product,” thus requiring Pfizer to get a new NDA for its tablet version of its previously approved soft gelatin capsule version of nifedipine, on the grounds that although it contained the same active ingredient, it was nevertheless a different drug. In *Apotex, Inc. v. Shalala*, 53 F. Supp. 2d 454 (D.D.C.) aff’d without comment, No. 99-5231, 1999 WL 956686 (D.C. Cir. Oct. 8, 1999), the FDA successfully argued that the market exclusivity accorded to one drug product did not extend so as to preclude a generic product with the same active ingredient, (although of a differing strength), from receiving a 180-day period of market exclusivity pursuant to § 355(j)(5)(B)(iv). In an FDA decision that was part of the *Apotex* litigation, the agency noted that “FDA could not approve an application that requested approval of only the active ingredient . . . The Agency, therefore, can only award such exclusivity to an [Abbreviated New Drug Application] applicant for a drug product, and a particular strength.” FDA Decision, Docket No. 98P-0547/CP1 & SUP at 3 n.3 (Dec. 4, 1998).

From these authorities, Pharmanex invites us to infer that because it is the drug product, not the active ingredient to which approval attaches, it would not make sense for the phrase “article that is approved as a new drug” to connote an ingredient - but rather it can only refer to a finished drug product. We disagree. Because these arguments arose in the specialized context of the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417 (1984), these cases are of limited relevance to the instant matter. The

Hatch-Waxman amendments alter § 355 in certain provisions to establish periods of market exclusivity for pioneer drugs, while streamlining the approval process for less expensive generic drugs. Thus, in these cases, the FDA interpreted the word “drug” to refer only to drug products to advance these very specific policy objectives, and as such, these precedents do not illuminate Congressional intent for § 321(ff)(3)(B) in the instant case. Moreover, it bears noting that “it is not impermissible under Chevron for an agency to interpret an imprecise term differently in two separate sections of a statute which have different purposes.” Abbott Laboratories v. Young, 920 F.2d 984, 987 (D.C. Cir. 1990).

In sum, we reject Pharmanex’s argument that the plain language of § 321(ff)(3)(B) evinces a clear intent to exclude only finished drug products from the definition of dietary supplement. In Brown v. Gardner, 513 U.S. 115, 118 (1994), the Supreme Court observed that “[a]mbiguity is a creature not of definitional possibilities but of statutory context.” A corollary of this principle is that for purposes of Chevron analysis, statutory clarity is a creature not of definitional isolation, but of statutory context. Pharmanex isolates the discrete phrase “article that is approved as a new drug,” and tries to import clarity, ignoring the linguistic ambiguity that attends these words in the larger context of the surrounding DSHEA provisions, and the FDCA more generally. As the following section shows, Pharmanex’s argument is further undercut by the policies that undergird DSHEA and FDCA.

Legislative History and Policies of DSHEA and FDCA

a. Legislative History

Turning to the legislative history, we find that the intended application of § 321(ff)(3)(B) is not elucidated, but rather becomes less clear. First of all, the Senate Report upon which the district court relied, and which Pharmanex now invokes, was explicitly disclaimed as a source of legislative intent. See Statement of Agreement, 140 Cong. Rec. S14801 (Oct. 7, 1994), reprinted in 1994 U.S.C.C.A.N. 3523 (“It is the intent of the chief sponsors of the bill. . .that no other reports or statements be considered as

legislative history for the bill.”). Without passing on the legitimacy or effectiveness of such a disclaimer, we find that it certainly contributes to an overall sense of ambiguity as to the weight we should accord to the statements contained within the disclaimed legislative materials. The Statement of Agreement sheds no light on the question at hand, as it is silent as to the application of § 321(ff)(3)(B) to finished drug products versus active ingredients. The disclaimed Senate Report, S. Rep. No. 103-410 (1994), does not support the conclusion that Congress intended § 321(ff)(3)(B) to apply solely to finished drug products. The Senate Report does reflect a certain antipathy for what is perceived as a history of onerous regulation of dietary supplements by the FDA, but this alone does not address the question at hand. The following statements, however, bear more directly on the present issue:

During consideration of S. 784, concerns were expressed that manufacturers or importers of drugs could avoid the drug approval process by marketing drug products as dietary supplements. Although current authorities should be adequate to deal with such potential problems, the committee is sensitive to those concerns. Accordingly, Senators Harkin and Hatch agreed to formulate additional language prior to consideration of S. 784 in the Senate.

Under the substitute to S. 784 as approved by committee, a substance which has been marketed as a dietary ingredient in a dietary supplement, or otherwise as a food, does not lose its status as a food. . just because FDA approves the substance for use as an active ingredient in a new drug. . . .

S. Rep. No. 103-410, at V. § 3 (1994) (emphasis added). This passage suggests that the scope of § 321(ff)(3)(B) is not limited to finished drug products, as Pharmanex suggests, in that the subject matter of the Hatch/Harkin compromise language includes “a substance which has been marketed as a dietary ingredient” and “the substance [used] as an active ingredient in a new drug.” Thus, to the extent that this report is evidence of legislative intent, it favors the FDA’s interpretation. The above example demonstrates how the prior market clause would protect a dietary supplement with an ingredient that is subsequently approved as the active ingredient in a new drug. Provided that the dietary ingredient had been previously marketed as such, it would not lose its food status. By extension to the scenario that apparently troubled some legislators, the above language suggests that if a drug manufacturer sought to market a dietary supplement containing a natural substance that is the active ingredient in a previously approved drug product, it would be subject to the strictures of § 321(ff)(3)(B)’s exclusionary clause, unless it could show that prior to approval of the new drug, the natural substance was marketed as a dietary ingredient or food.

b. Policies of DSHEA and FDCA

The policies undergirding DSHEA and FDCA do not support a finding that Congress clearly intended § 321(ff)(3)(B) to apply only to finished drug products. It is true that DSHEA was enacted to alleviate the regulatory burdens on the dietary supplement industry, allowing consumers greater access to safe dietary supplements in order to promote greater wellness among the American population. See generally Dietary Supplement Health and Education Act, Pub. L. No. 103-417, § 2 (1994). However, the clause at issue in the instant case constitutes a limiting principle to this goal. That is, § 321(ff)(3)(B) specifically excludes certain articles from the definition of dietary supplement. To find that this clause only refers to finished drug products would be to restrict this provision so as to render it without practical application. Under the interpretation proposed by Pharmanex, a manufacturer could identify a naturally

occurring substance that was identical to or had the same pharmacological effect as the active ingredient in a prescription drug, and market it in a dietary supplement. The manufacturer could evade the strictures of § 321(ff)(3)(A) by arguing, as Pharmanex does, that the naturally occurring ingredient is not a “finished drug product,” and that § 321(ff)(3)(B) would apply only if the prescription drug itself were being held out as a dietary supplement. See Aplee. Br. at 38-39.

To permit this result would contravene one of the primary objectives of the FDCA, namely “to ensure that any product regulated by the FDA is ‘safe’ and ‘effective’ for its intended use.” Brown & Williamson, 120 S. Ct. at 1301 (quoting 21 U.S.C. § 393(b)(2) (1994 ed., Supp. III) (defining the FDA’s mission)). We understand Pharmanex’s argument that dietary supplements are already adequately regulated by provisions such as 21 U.S.C. § 342(f)(1) (setting forth provisions governing adulterated dietary supplements), but Pharmanex has not adequately responded to the FDA’s strenuous objection that these provisions only empower the FDA to remove unsafe products rather than preclude their entry into the marketplace *ab initio*. Pharmanex represents only that premarket notification would *almost surely* be required by § 21 U.S.C. § 350b (provision governing new dietary ingredients). See Aplee. Br. at 61. This is not a sufficient response to the concerns raised by the FDA. More importantly, it is not sufficient to demonstrate the clarity necessary under Chevron to preclude deference to the FDA’s interpretation of § 321(ff)(3)(B).

To permit manufacturers to market dietary supplements with components identical to the active ingredients in prescription drugs would, as the FDA points out, contravene the incentive structures in place in the FDA for the development of orphan drugs and pediatric drugs. Pharmanex responds that DSHEA does not contemplate such incentives, and is not intended to advance these policies. This argument is unpersuasive for our purposes, as we are instructed to evaluate the statute as a harmonious whole, rather than in discrete sections. See supra, at 5-6.

Finally, we reject Pharmanex's argument that the FDA's interpretation would produce absurd results, by subjecting to regulation all the traditional food substances that are active ingredients in new drugs. The FDA's reading of the prior market clause would protect such substances if they did, in fact, have a history of marketing as a dietary supplement or food substance. As the FDA interprets § 321(ff)(3)(B), the exclusionary clause would reach naturally occurring substances identical or indistinguishable from the active ingredients in new drugs, provided that the substance in question was not previously marketed as a food or dietary substance. This comports with common sense and the overall purposes of the FDCA. It bears noting that many prescription drugs are derived from natural substances that are not benign. For example, "digitalis is extracted from purple foxglove, morphine from poppy, and quinine from cinchona bark." Laura A. W. Khatcheressian, Regulation of Dietary Supplements: Five Years of DSHEA, 54 Food & Drug L.J. 623, 634 (1999).

Thus, the policies of DSHEA and FDCA do not move this court to the conclusion that § 321(ff)(3)(B) is clearly meant only to apply to finished drug products. In fact, in light of the foregoing, it seems that to so interpret the provision would be to restrict its scope so as to render it a meaningless limitation, and also contravene the fundamental purposes of the FDCA.

Conclusion

As stated previously, § 321(ff)(3)(B) represents the limiting principle of DSHEA's general purpose, namely, to assuage the regulatory burdens on the dietary supplement industry. The provision balances this goal with the other policies of the FDCA, in effect carving out breathing room for dietary supplements while ensuring that drug manufacturers will not exploit this flexibility to make an end-run around the strictures of the new drug approval process. Congress has not specified the exact contours of this balance, choosing to use broad terminology in crafting the provision. Considering the

lack of linguistic clarity and the overall statutory context, we hold that § 321(ff)(3)(B) is sufficiently ambiguous to merit Chevron deference. While Pharmanex's argument is linguistically possible, we are not compelled to adopt the conclusion that Congress clearly intended to limit § 321(ff)(3)(b)'s application to finished drug products, in light of the statutory context and the surrounding provisions. Deference is particularly appropriate in the instant case, which involves important questions of public health and safety. Additionally, we hold that the FDA's interpretation of § 321(ff)(3)(B) is not arbitrary, capricious, or manifestly contrary to the statute. Accordingly, we **REVERSE and REMAND** for consideration of the record based issues not reached below.

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