

Food and Drug Administration
Rockville MD 20857

MAY 20 1998

Stuart M. Pape
Patton Boggs, L. L.P.
2550 M Street, N.W.
Washington D.C. 20037

Re : Pharmanex, Inc. , Administrative Proceeding,
Docket No. 97P-0441; Final Decision

Dear Mr. Pape,

In this letter the Food and Drug Administration (FDA) announces its decision that Cholestin, a product made from a fungus fermented on rice (red yeast rice), marketed by your client Pharmanex, Inc. (Pharmanex), is not a "dietary supplement," and that it is a "drug" and a "new drug" under the terms of the Federal Food, Drug, and Cosmetic Act (FDCA). This letter constitutes FDA's final decision in the administrative proceeding initiated by the agency to determine the regulatory status of Cholestin.

I. Procedural History of The Cholestin Matter

FDA first met with Pharmanex to discuss the regulatory status of Cholestin on April 7, 1997, following a complaint submitted to the agency by a pharmacist regarding the product. See Minutes, Meeting with Pharmanex (April 7, 1997), MM1at2 [hereinafter First Pharmanex Meeting].^{1/} At that meeting, Pharmanex presented arguments to FDA that Cholestin is a dietary

^{1/} Materials cited in this decision appear in public docket, No. 97P-0441. For ease of citation, each submission to the docket has been assigned a particular code: "PSA" (petition for Stay of Action), "Sup" (Supplement to PSA), "Let" (Letter), "C" (Comment), "RC" (Reply Comment), "M" (Memorandum), "Ans" (Answer), "Ref" (Reference), "MM" (Memorandum of Meeting), "Ext" (Extension Request), "Rpt" (Report), "CR" (Correction), or "GDL" (Guideline). To facilitate reference to these submissions, a CD-Rom disk provided to Pharmanex has stored on it each submission with all respective attachments. All materials in each submission are assigned consecutive page numbers. For example, comment 81 contains 47 total pages. Page 30 of this comment (part of an attachment) is cited as "C81 at 30." Parallel citations to actual page numbers appearing on submissions have been provided when it was practicable to do so. The CD-Rom disk may be read using Adobe Acrobat Reader 3.0, Windows 95, and a CD-Rom driver capable of reading long file names.

97P-0441

ANS 2

supplement, rather than a drug. FDA employees present at the meeting expressed the view, based on the information then available to the agency, that Cholestin is a drug based on its labeling and formulation. Following the meeting, Pharmanex filed a lawsuit in the United States District Court for the District of Utah seeking to challenge that opinion. On May 16, 1997, the Court granted the government's motion to dismiss, while retaining jurisdiction to consider any amended complaint that Pharmanex may file in this matter.

On or about May 20, 1997, Pharmanex attempted to import approximately 5,450 pounds of Monascus purpureus Went yeast fermented on premium rice powder, the bulk red yeast rice that Pharmanex processes into Cholestin capsules. Based on the record then before the agency, this product appeared to FDA to constitute an unapproved new drug in violation of FDCA § 505, that was therefore subject to detention pursuant to § 801. FDA, accordingly, issued a Notice of Sampling for the bulk Cholestin on May 30, 1997, and a Notice of Detention and Hearing on June 11, 1997. Pharmanex chose not to have a hearing on the regulatory status of the product, but instead reexported the bulk Cholestin, as provided for by the statute. See FDCA § 801(a).

Thereafter, at Pharmanex's request, FDA met with representatives of the company on July 22, 1997, to further discuss the regulatory status of Cholestin. Following that meeting, Pharmanex provided the agency with more information concerning Cholestin and red yeast rice. In a subsequent letter, the company requested that FDA "conclude its review" of Cholestin "and confirm that Pharmanex may import its red yeast rice for production and sale of Cholestin." Letter from Stuart M. Pape, Counsel to Pharmanex, to Neal Parker, Associate Chief Counsel, FDA, at 4 (Sept. 8, 1997), PSA1, vol. 2 at 106. In response to this request, FDA advised Pharmanex that, based on the information then available to the agency, FDA continued to believe that Cholestin is a new drug and did not agree with Pharmanex that Cholestin is a dietary supplement. Letter from Ilisa B.G. Bernstein, Pharm. D., J.D., Senior Science Policy Advisor, FDA, to Stuart M. Pape, Counsel to Pharmanex (Sept. 30, 1997), PSA 1, vol. 2 at 111 [hereinafter Sept. 30 Letter]. Accordingly, FDA did not confirm at that time that Pharmanex could lawfully import or sell Cholestin. The agency also asked in the Sept. 30 letter that Pharmanex submit, in the form of a citizen petition pursuant to 21 C.F.R. § 10.30, a request for FDA to declare the regulatory status of Cholestin.

On October 29, 1997, Pharmanex filed a document styled "Petition to the Food and Drug Administration for a Stay of Action With Respect to Cholestin Dietary Supplement." PSA1, vol. 1-3 [hereinafter Pharmanex petition]. In this filing, the

company asked FDA to stay the Sept. 30 letter and to stay any form of enforcement action adverse to Pharmanex or Cholestin. Pharmanex Petition at 5, PSA1, vol. 1 at 10. In a letter from FDA to Pharmanex dated November 14, 1997, Let1 [hereinafter Nov. 14 Letter], FDA informed the company that it was not acting on the Petition because the Sept. 30 letter did not describe any administrative action taken by the Commissioner capable of being stayed, and because FDA decisions to take enforcement actions are not subject to petitions or other action by interested persons outside the agency.

In the Nov. 14 letter, FDA also noted that the Pharmanex Petition included new data and raised new issues, not previously submitted to FDA, relating to the merits of the tentative positions FDA had taken in the Sept. 30 letter. The agency stated that because Pharmanex did not file a citizen petition, FDA believed that, given the circumstances of this case, the most expeditious and appropriate process for reaching a final agency decision would be for the agency to initiate an administrative proceeding pursuant to 21 C.F.R. § 10.25(b) to decide the regulatory status of Cholestin. As explained in FDA's Nov. 14 letter, to expedite the decision-making process, the agency would maintain the materials submitted with the pharmanex Petition in a public docket, and the agency, Pharmanex, and interested persons would submit additional materials to the docket. Today's letter represents the final decision of the agency in the administrative proceeding referred to in FDA's Nov. 14 letter.^{2/}

II. Cholestin Not A Dietary Supplement Under FDCA § 201(ff)(3).

A. Summary of decision

In 1994, Congress amended the FDCA by passing the Dietary Supplement Health and Education Act (DSHEA). Pub. L. No. 103-417, 108 Stat. 4325. Pursuant to FDCA § 201(ff)(3)(B), added by DSHEA, the term "dietary supplement" does "not include an article that is approved as a new drug" or an article "authorized for investigation as a new drug" which was not before such approval or authorization "marketed as a dietary supplement or as a food." Either an entire product, or any of a product's individual

^{2/} In its Nov. 14 letter, FDA committed to using its best efforts to issue its final decision by the end of 1997. Subsequent submissions by Pharmanex to the docket and several requests for extensions of time received by the agency made it apparent that additional time was required to afford all interested parties adequate opportunity to submit comments. See 63 Fed. Reg. 1973 (Jan. 13, 1998), N1.

components may be "an article that is approved as a new drug" or an article "authorized for investigation as a new drug" within the meaning of § 201(ff) (3) (B). See infra at 5-7. Cholestin contains lovastatin. Lovastatin is also the active ingredient in the prescription drug product approved by FDA and marketed as Mevacor. See infra at 7-10. In marketing Cholestin, Pharmanex is marketing, for purposes of § 201(ff) (3), the "article" lovastatin, not the traditional food product red yeast rice. See infra at 10-22. Because lovastatin was not "marketed as a dietary supplement or as a food" before FDA approved the Mevacor new drug application (NDA) , or before lovastatin was authorized for investigation as a new drug, see infra at 22-27, Cholestin is not a dietary supplement within the meaning of § 201(ff) (3) .

- B. FDCA § 201(ff) (3) excludes from the definition of "dietary supplement" articles that were first approved as new drugs.

FDA's decision that Cholestin is not a dietary supplement is based on FDCA § 201(ff) (3), which includes and excludes from the definition of dietary supplement certain "articles" based on their regulatory and marketing history. While the term dietary supplement "does include an article that is approved as a new drug under section 505 . . . and was, prior to such approval . . . marketed as a dietary supplement or as a food," § 201(ff) (3)(A), the term dietary supplement does

not include an article that is approved as a new drug under section 505 . . . or an article authorized for investigation as a new drug . . . for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval . . . or authorization marketed as a dietary supplement or as a food.

FDCA § 201(ff) (3) (B).

Section 201(ff) (3) seeks to establish a system for determining whether articles will be deemed dietary supplements or drugs, and regulated accordingly, depending on how such articles were marketed and categorized when they first entered the marketplace. Stated simply, the statute prohibits the marketing as dietary supplements of articles that have gained recognition in the marketplace as new drugs by either being approved or studied as new drugs. DSHEA reflects Congress's determination that to allow such an article to be marketed as a dietary supplement would not be fair to the pharmaceutical company that brought, or intends to bring, the drug to market, and would serve as a disincentive to the often significant

investment needed to gain FDA approval of new drugs.^{3/} The statute does, however, permit continued marketing of an article that was marketed as a food or a dietary supplement even if that article is subsequently shown to have therapeutic benefit and is studied or approved as a new drug. In such a case, the dietary supplement was on the market first and should not be penalized simply because some drug manufacturer chooses to seek approval for the product as a new drug.

- C. Either an entire product or any of a product's individual components may an "article" approved as a new drug within the meaning of FDCA § 201(ff) (3) (B).

Pharmanex argues that Cholestin is not approved, and was never authorized for investigation as, a new drug, and that therefore § 201(ff) (3) does not apply to the product. Pharmanex Petition at 17, PSA1, vol. 1 at 22. The relevant inquiry, however, is not limited to whether the entire product Cholestin was ever approved or studied as a new drug. Either an entire product, or any of a product's individual components, may be an "article that is approved as a new drug" or an article "authorized for investigation as a new drug" within the meaning of § 201(ff) (3) (B) .

The dietary supplement definition refers to an "article" as something "used as or in a dietary supplement." FDCA § 201(ff) (3) (A) (emphasis added). By using the word "in" Congress indicated that the term "article" can refer to any of a product's individual components. If Congress had intended to exclude components from the scope of § 201(ff) (3), Congress could have used the word "product" in the section, as it did elsewhere in § 201(ff), instead of the word "article," but Congress chose not to do so. compare FDCA §§ 201(ff) (1) and (2) (dietary supplement means certain "product[s]") with FDCA § 201(ff) (3) (dietary supplement does and does not include certain "article[s]") .

Pharmanex argues that other definitions in the FDCA use "article" to refer to entire products. The company cites § 201(h), which defines devices as instruments, apparatuses, implements, machines, contrivances, implants, in vitro reagents,

^{3/} Senator Hatch, while not taking a position on the merits, stated in a comment submitted to this administrative proceeding that DSHEA should not be interpreted to "undermine the incentive of pharmaceutical manufacturers to develop and bring new drugs to market. That is clearly the genesis of sec. 201(ff) (3) ." Letter from Orrin G. Hatch, United States Senator, to Dr. Michael A. Friedman, M.D., Lead Deputy Commissioner, FDA (Dec. 22, 1997), Let14 at 8.

or "related article [s] , " and § 201(i), which defines cosmetics as "articles intended to be rubbed, poured, sprinkled, or sprayed on . . . the human body." See Pharmanex Petition at 17, PSA1, vol. 1 at 22. FDA agrees that the term "article" as used in the FDCA may refer to an entire product, but nothing about the language cited by Pharmanex suggests that the term "article" can only refer to entire products. Indeed, language in the statutory sections cited by Pharmanex expressly states that "article" can mean component, as well as finished product. See FDCA § 201(h) (device means instrument, implement, machine or "similar or related article[s] , including any component, part, or accessory") (emphasis added); FDCA § 201(i) ("cosmetic" means articles intended to be rubbed, poured, sprinkled, or sprayed on the human body and "articles intended for use as a component of any such articles.") (emphasis added); see also FDCA § 201(g) (1) (D) (drug means articles "intended for use as a component" of any article recognized in the United States Pharmacopoeia, intended for use in the diagnosis, cure, mitigation, treatment of disease, or intended to affect the structure or any function of the body) (emphasis added).

The fact that a product component may be an "article approved as a new drug" or an article "authorized for investigation as a new drug" ensures that substances that have gained recognition in the marketplace as new drugs may not be incorporated into, and marketed as, dietary supplements. This is consistent with the purpose of § 201(ff) (3) that DSHEA not undermine incentives to develop new drugs, and is also consistent with other provisions of the FDCA governing approval of generic drugs.

For example, a generic drug may presently be marketed only after a manufacturer has filed and had approved pursuant to § 505(j) an abbreviated new drug application (ANDA) . Were the term "article" to refer solely to "products," a company could formulate a product by adding to, or causing additional components to be present in, an approved drug product (or by causing an approved drug product to be present in a purported dietary supplement), thereby creating a new product complying with § 201(ff) (3) that could be marketed as a dietary supplement (provided, of course, that all other applicable sections of DSHEA were met) . To allow such marketing would serve as a disincentive to new drug development because drug manufacturers would not be as willing to bring new drugs to market knowing that products containing the new drugs as components could be marketed as dietary supplements without having to go through the ANDA process. Nor would generic drug companies be as willing to seek approval as new drugs under 505(j) for products they could more easily market as dietary supplements. Nothing in the language of

DSHEA indicates that Congress intended that DSHEA vitiate the new drug and ANDA provisions of the FDCA in this manner.

Finally, several comments to this proceeding appear to confuse the term "article" with the term "dietary ingredient." See e.g., C153. FDA emphasizes that, in interpreting DSHEA, care must be taken to distinguish these two terms. Under § 201(ff) (1), a dietary supplement is a product "intended to supplement the diet" that bears or contains one or more enumerated "dietary ingredients."^{4/} Even if the § 201(ff) (1) requirements are met, however, a product, to be a dietary supplement, may not include an article approved or studied as a new drug, as specified by § 201(ff) (3). The § 201(ff) (1) dietary ingredient present in any purported dietary supplement product is not the same as the "article" referred to § 201(ff) (3). Had Congress intended to equate the "article" in § 201(ff) (3) with the "dietary ingredient" in § 201(ff) (1), Congress would not have used different terms in each of these statutory sections. The different language in each statutory provision means that a different analysis is required to determine whether the conditions precedent for dietary supplement status set forth at each section have been met. In order to determine whether a product satisfies the conditions in § 201(ff) (1), one must ask whether the product is intended to supplement the diet, and then also ask whether the product contains one or more of the enumerated dietary ingredients. Whether a product is precluded from being a dietary supplement pursuant to § 201(ff) (3) (B), however, requires the separate analysis of whether a manufacturer is marketing an article that has been approved or studied as a new drug. See infra at 10-22.

D. Cholestin contains lovastatin.

FDA has determined that Cholestin contains lovastatin as a component, which is the active ingredient contained in the prescription drug product approved by FDA and marketed as Mevacor. See FDA, Approved Drug Products With Therapeutic Equivalence Evaluations 3-196 (17th ed. 1997) [hereinafter the Orange Book].^{5/} Pharmanex disputes this, arguing that, even if

^{4/} The enumerated ingredients include vitamins; minerals; herbs or other botanical; amino acids; dietary substances for use in supplementing the diet; or concentrates, metabolites, constituents, extracts of any combination of the foregoing.

^{5/} Lovastatin belongs to a group of compounds referred to as HMG-CoA reductase inhibitors. These compounds act to reduce serum cholesterol levels in humans by inhibiting HMG-CoA

the term "article" does encompass components, Cholestin does not contain lovastatin and therefore Pharmanex does not market an article approved as a new drug. In statements to the agency, Pharmanex has asserted that Cholestin contains a substance "similar" to lovastatin, which Pharmanex has alternatively called "Mevinolin" or "Monacolin K." See e.g., Letter from Stuart M. Pape, Counsel to Pharmanex, to Ann M. Witt, Senior Policy Advisor, FDA, at 4 (July 18, 1997), PSA1, vol. 2 at 14. The record in this matter does not support Pharmanex's assertions.

Analytical test results demonstrate that Cholestin contains lovastatin at significant levels. FDA analyses of Cholestin show that the recommended daily dose of Cholestin will result in the intake of approximately 5mg. of lovastatin. Ref5, 15, 17, 18.^{6/} Pharmanex has submitted no test data to FDA indicating otherwise.

In addition, numerous articles, including several authored by Pharmanex officers, establish that Cholestin contains lovastatin. According to one paper written by, among others, Pharmanex's vice-president Michael Chang, Cholestin contains a number of related compounds, including one compound called "Monacolin K." As stated in this document

[plowdered Cholestin . . . was extracted with methanol.
. . . Repeated chromatography led to the isolation of
the following compounds 1 (100mg), 2 (20mg), 3 (15mg),
4 (10mg), 5 (10mg), 6 (8mg) , and 7 (2mg) . compound[] 1
.. [was] identified as monacolin K .

. . . .
. . . monacolin K [is] also known as mevinolin, and
lovastatin.

(...continued)

reductase, a naturally-occurring enzyme necessary for the formation of cholesterol in the human body. The approved drug Mevacor, consisting of the article lovastatin, is indicated for treatment of hypercholesterolemia (elevated blood serum cholesterol and triglyceride levels) , atherosclerotic disease, and coronary heart disease. See Physicians Desk Reference 1694-98 (52nd ed. 1998) [hereinafter PDR] .

^{6/} This dosage is approximately half the 10 mg. dosage of lovastatin delivered by the prescription drug Mevacor. See PDR at 1694. FDA previously reported these test results in grams. See Sept. 30 letter at 3 n.3, PSA1, vol. 2 at 113 n.3. The correct measurement should be in milligrams (mg.) .

Ma et al., New Monacolins From Red Yeast Rice at 3-5, C156 at 616-18 (emphasis added). Thus, according to this Pharmanex document, the compound present in Cholestin in the highest concentration by weight (5 times higher than the next highest compound) is lovastatin. See also Gurr and Chang, All Natural Cholestin, A New Cholesterol-lowering Dietary Supplement: A Scientific Product Review at 2, Let5 at 12 ("Pharmanex scientists have identified all eight HMG-COA reductase inhibitors that are present in Cholestin in significant amounts, among which lovastatin . . . [is] the most abundant.") (emphasis added) [hereinafter Pharmanex Scientific Product Review].

Another article submitted by Pharmanex to the agency states that Monacolin K has the molecular formula $C_{24}H_{36}O_5$. Endo, Monacolin K, A New Hypocholesterolemic Agent Produced by A Monascus Species, XXXII:8 J. Antibiotics 852 (Aug. 1979), PSA1, vol. 2 at 331. This formula is the same formula listed for lovastatin in the approved Mevacor labeling. PDR at 1694; see also Juzlova et al., Secondary Metabolites of the Fungus Monascus: A Review, 16 J. Ind. Microbiol. 163, 167 (1996), PSA1, vol. 3 at 49 ("mevinolin [is] also referred to as Lovastatin, monacolin K, [and] Mevacor.") . Another Pharmanex promotional document states that the active ingredient in Cholestin is "essentially the same as the active ingredient for a currently available prescription drug [Mevacor] ." Natural Products Update: What Pharmacists Need to Know to Advise Consumers 9 (June 1997), Ref1 at 9 [hereinafter Pharmanex Pharmacist Update]. Not only has the Cholestin labeling itself, including information on the Pharmanex internet website (www.pharmanex.com), expressly stated that the product contains lovastatin, See e.g., Ref2 at 4, but the listing for Mevinolin in the USP Dictionary of USAN and International Drug Names at 450 (1996), states "Mevinolin (previously used name) - See Lovastatin."^{1/}

Finally, one letter written by a Pharmanex consultant, Dr. Alfred Alberts, notes that "[t]here is apparently some confusion as to the relationship between mevinolin and lovastatin. In fact these names are used synonymously. Monacolin K is also synonymous with lovastatin." Letter from Dr. Alfred W. Alberts, Pharmaceutical and Scientific Consulting, to Michael Chang, Pharmanex, Inc. (Dec. 19, 1997), C6 at 3 (emphasis added) [hereinafter First Alberts Letter]. Indeed, in response to Pharmanex's repeated attempts to distinguish these substances, Dr. Alberts felt compelled to write a second letter to Pharmanex making clear his opinion that "mevinolin is identical to

^{1/} FDA recognizes the USP Dictionary as an authoritative source for information regarding drug nomenclature. See 21 C.F.R. § 299.4.

lovastatin. There are no other 'atural forms of mevinolin.'" Letter from Dr. Alfred W. Alberts, Pharmaceutical and Scientific Consulting, to Stuart M. Pape, Counsel to Pharmanex (Jan. 12, 1998), C136 at 1 (emphasis added) [hereinafter Second Alberts Letter]. Ultimately, it seems that even Dr. Chang, vice-president of Pharmanex, agreed that monacolin K, mevinolin, and lovastatin are identical, and stated so at a meeting with FDA. Memorandum of Meeting at 1 (Jan. 20, 1998), MM2 at 1 [hereinafter Second Pharmanex Meeting].^{8/}

- E. The lovastatin component of Cholestin, rather than the entire Cholestin product, is the "article" for purposes of FDCA § 201 (ff) (3).

As explained above, FDA has determined that (1) Cholestin contains lovastatin, and (2) under the statute, either an entire product or any of a product's individual components may constitute the "article" for purposes of § 201(ff) (3). In this case, lovastatin, a component of Cholestin, is the relevant "article." This determination is not based simply on the mere presence of lovastatin in the product. Rather, FDA makes this decision based on the particular circumstances surrounding the Cholestin product, which indicate that Pharmanex, in marketing and manufacturing Cholestin, is marketing and manufacturing lovastatin, not the traditional food product red yeast rice.

1. Pharmanex is marketing lovastatin.

That Pharmanex is marketing lovastatin is demonstrated in part by the company's promotion of lovastatin in Cholestin. One

^{8/} One Pharmanex scientific advisory board member states in an affidavit that lovastatin is the name given to a crystalline form of diterpene, whereas mevinolin is the name for a diterpene with an identical organic structure including the relative and absolute configurations. According to this affidavit, "the solid state structures are different because of the different protocols for the preparations." Affidavit of Koji Nakanishi, PSA1, vol. 3 at 30. Mr. Nakanishi provides no documentation to support what he admits are only his "beliefs." In any case, the most the affidavit suggests is that mevinolin and lovastatin may have different crystalline forms, not that they are different molecules. Neither the Nakanishi affidavit nor the letters from Dennis J. McKenna, Lester A. Mitscher, or Chi-Huey Wong, all submitted by Pharmanex, see PSA1, vol. 3 at 8, 27, 34, support Pharmanex's position. These writers merely assert that the entire product Cholestin is not the same as Mevacor. None of the documents contain evidence that the lovastatin in Cholestin is different from the active ingredient in Mevacor.

promotional document directed at pharmacists disseminated by Pharmanex explains that Cholestin contains the same "active ingredient [found in] a currently available prescription drug for treating hypercholesterolemia" and warns that "[s]ince the natural ingredients of Cholestin include lovastatin . . . the adverse-effect profile, precautions, and contraindications for this product are somewhat similar to those of lovastatin." Pharmanex Pharmacist Update at 9, Refl at 9 (emphasis added). Pharmanex has also provided trade publications and the mass media with background information emphasizing the presence of lovastatin in the product. See Jeff M. Jellin, Cholesterol, Pharmacist's Letter, vol. 13, no. 4, April 1997, Let2 at 113 ("This is NOT your ordinary dietary supplement. It actually contains LOVASTATIN.") (emphasis in original). One Pharmacist associated with Pharmanex has contributed directly to consumer magazines by writing articles that link Cholestin with lovastatin. Varro E. Tyler, Shi He Herbalist: A New Way to Lower Cholesterol?, Prevention, Sept. 1997, at 58, Let5 at s5 ("Of all the reductase inhibitors in Cholestin, the most abundant is lovastatin. (If that name sounds familiar, its because lovastatin is also the generic name of a common prescription drug proven to reduce high LDL levels.)") (emphasis in original).^{9/} Little wonder, therefore, that individual consumers of Cholestin believe they are consuming a drug product. See Letters from Robert Conrad, Roy Duff, Betty Hertzmark, and James McGuire to Dr. Michael Friedman, Lead Deputy Commissioner, FDA (Dec. 11, 15, 1997, Jan. 2, 14, 1998), C37, C148, C118, C137.

Pharmanex's promotional documents also link Cholestin to Xuezhikang, a Chinese pharmaceutical product made from red yeast rice that is expressly designed and intended to deliver lovastatin to humans as a substitute for the Merck drug Mevacor.^{10/} These Pharmanex documents describe Xuezhikang as a

^{9/} Dr. Tyler has also written on behalf of Pharmanex a March 7, 1997 "Dear Colleague in Pharmacy" letter stating that Cholestin "contains numerous naturally occurring HMG-COA reductase inhibitors (e.g., lovastatin)." Let5 at 4.

^{10/} A Chinese patent document for this product notes that it is

a type of biologically produced drug, in particular . . . a drug produced by microbial fermentation for reducing blood lipids The blood lipid-lowering effects of traditional red yeast rice (from hereon referred to as Hongqu) are minimal, while the hypocholesterolemic western drug Mevacor is a purified

(continued. . .)

"more concentrated form of Cholestin sold in China. " These same documents also promote Cholestin by describing clinical studies comparing the cholesterol-lowering properties of Xuezhikang and lovastatin to simvastatin, another cholesterol-lowering drug approved by FDA. Pharmanex Pharmacist Update at 9, Refl at 9. Another Pharmanex document refers to Xuezhikang as "an extract of Cholestin," and promotes Cholestin by discussing extensive research on Xuezhikang in China. Pharmanex Scientific Product Review at 4, Let5 at 14. Moreover, as part of the company's promotional efforts, Pharmanex distributes studies on Xuezhikang and Zhi Tai, another Chinese drug described as containing Cholestin, to media outlets and consultants, who then repeat Pharmanex's description of Xuezhikang as an "extract" of Cholestin in trade press distributed to pharmacists and the public. See Jill Allen, Over-the-Counter Cholesterol-Lowering Dietary Supplement Cholestin, Pharmacist's Letter Dec. # 130419 (1997), Let2 at 115-16.

In addition, Pharmanex is linked to Xuezhikang by a separate patent submitted to the World Intellectual Property Organization (WIPO), published on April 9, 1998, for red yeast products that lists Pharmanex as the applicant and Pharmanex's vice-president Michael Chang as co-inventor with the same persons who submitted the Chinese patent on Xuezhikang. WIPO Patent No. WO 98/14177, C171 at 8 [hereinafter WIPO Patent] . Indeed, Pharmanex's WIPO patent is supported by clinical studies on Xuezhikang, WIPO Patent at 16-38, C171 at 25-46, as is Cholestin, as documented by the Pharmanex promotional materials described above. Pharmanex's promotional and patent documents identifying Cholestin with Xuezhikang belie the company's attempts in this proceeding to distance Cholestin from the Chinese pharmaceutical product.

(...continued)

form of mevinolin, having a significantly higher price and side effects. The present invention as described here, combines the advantages of traditional Chinese medicine and western medicine and minimizes their deficiencies. It is the first to produce a Hongqu, by using traditional Hongqu preparation methods, containing a high quantity of lipid lowering mevinolin components.

Chinese Patent Document Application No. 93100737.2 at 1-2, PSA1, vol. 2 at 94-95 (emphasis added) [hereinafter Chinese Patent Application] . Several translations of this Chinese document have been submitted to the agency. The quoted language comes from the version submitted by Pharmanex.

2. pharmanex is manufacturing lovastatin.

Evidence that Pharmanex is manufacturing lovastatin consists of materials indicating that Pharmanex purposely designed a manufacturing process intended consistently to maximize and standardize levels of lovastatin in Cholestin. According to a company promotional document distributed to pharmacists and consumers, Pharmanex developed its own "proprietary process" in 1993 to make a red yeast rice product containing levels of lovastatin that could "maximize red yeast's health-enhancing properties" and "duplicate [its] medicinal properties." Pharmanex Scientific Product Review at 2, Let5 at 12. The Cholestin manufacturing process is designed to maximize lovastatin in at least three ways.

First, Pharmanex is deliberately controlling temperature conditions during the manufacturing process to promote consistently high levels of lovastatin in Cholestin. Scientific papers submitted by Pharmanex explain that temperature controls are required in order to produce a final product containing significant amounts of lovastatin because "if culturing [of red yeast rice] is carried out at conventional temperatures (30 to 37°C), even strains that [can] produce monacolin K . . . will stop producing monacolin K." Negishi, et al., Productivity of Monacolin K (mevinolin) in the Genus Monascus, 64 Ferment. Engin. 509 (1986), PSA1, vol. 2 at 58.^{11/} According to the Pharmanex consultant, Dr. Alberts, amounts of "lovastatin" produced "are highly dependent upon culture conditions. Key factors for production [are] both temperature and oxygen tension." First Alberts letter, C6 at 3. At a meeting with FDA, Pharmanex stated that the company holds the temperature at certain levels during the Cholestin manufacturing process. Second Pharmanex meeting at 3, MM2 at 3. In order to make Xuezhikang, the concentrated form of Cholestin described above, fermentation is conducted at 30°C for three days, followed by a reduction in the fermentation temperature to 25°C for 7-9 days. See Chinese Patent Application at 3, PSA 1, vol. 2 at 96.^{12/}

^{11/} To like effect see U.S. Patent No. 4,323,648 at 3, PSA1, vol. 2 at 349 (preferred temperature for monacolin K production is 20 to 30°C); First Alberts Letter, C6 at 3 (optimum temperature is about 25°C; little or no lovastatin production was seen at 30°C whereas growth was unaffected) .

^{12/} According to the Chinese patent materials, these temperature controls "greatly optimize[] the content of Lovastatin" resulting in a product "containing a high quantity of lipid-lowering mevinolin components." Zhang, et. al., Red yeast
(continued. ..)

Second, Pharmanex tracks the level of HMG-CoA reductase inhibitors in Cholestin, of which lovastatin is the most abundant, during the production process. This tracking ensures significant levels of the drug in the final Cholestin product. Pharmanex argues that it uses the level of HMG-CoA reductase inhibitors merely as "a biochemical marker with which to monitor the level of yeast . . . in the manufacturing process." Pharmanex Petition at 14, PSA1, vol. 1 at 19. HMG-CoA reductase inhibitors, however, are secondary metabolites, which do not follow fungal mycelial growth but rather accumulate extracellularly and in association with the fungal mycelium during fermentation even after growth has ceased. These substances are simply not useful as a marker for mycelial growth. See U.K. Patent GB 2046737A and U.S. Patent No. 4,323,648, PSA1, vol. 2 at 342 and 347. If Pharmanex were in fact interested in monitoring only the amount of yeast growth on the rice kernels, there are more reliable and direct ways to do so, e.g., a reliable measurement would be to determine by high performance liquid chromatography (HPLC) the ergosterol content in the red yeast rice. See Schumacher et al., A Study of Natural Pigment Production with Monascus Purpureus by Solid State Fermentation Model Systems, 18:314 Adv. Food Sci. 113-20 (1996), PSA 1, vol. 2 at 367-74.

Third, Pharmanex's careful selection of a particular fungal strain to manufacture Cholestin indicates that the company seeks to manufacture lovastatin. Only select strains of Monascus fungus are capable of producing lovastatin, see ea., Negishi, et al., PSA1, vol. 2 at 58-59, and Pharmanex selects one of these strains to make Cholestin. According to a Pharmanex research and development memorandum, a "single pure strain of Monascus purpureus Went yeast is combined with non-glutinous rice to produce the red yeast fermented rice that is Cholestin." Memorandum from Michael N. Chang, R&D Division, Pharmanex, Inc. at 4 (May 24, 1997), Let3 at 6 [hereinafter Pharmanex R&D Memo]. Dr. Alberts, the Pharmanex consultant, confirms that to make Cholestin, "a single strain of yeast is used." Second Alberts Letter, C136 at 2. Doctor Chang himself stated to FDA that Pharmanex selects one particular strain to make Cholestin in order to produce the best HMG-CoA reductase inhibitor concentration, e.g., lovastatin, in the finished product. See First Pharmanex Meeting at 2, MM1 at 2.

^{12/} (...continued)

Rice (Hongqu) For Prevention and Treatment of Hyperlipidemia and Related Cardiovascular and Cerebrovascular Diseases at 7, PSA1, vol. 2 at 92; Chinese Patent Application at 1-2, PSA1, vol. 2 at 94-95.

Pharmanex maintains that "[n]othing in DSHEA prohibits dietary supplement manufacturers from optimizing the manufacturing process for a product to maximize quality and functionality." Pharmanex Petition at 14, PSA1, vol. 1 at 19. FDA supports attempts by manufacturers to improve the quality of dietary supplements. All dietary supplements, however, must comply with the statute. Section 201(ff) (3) may prevent a product from being a dietary supplement when that product is manufactured in a manner designed to produce an article already approved as a new drug.

3. Cholestin is not traditional red yeast rice.

Pharmanex repeatedly asserts that in marketing Cholestin, it is simply marketing traditional red yeast rice, not lovastatin. Thus, argues Pharmanex, the relevant "article" is traditional red yeast rice, not lovastatin. For several reasons, FDA rejects this contention.

First, Pharmanex itself has admitted that Cholestin is not traditional red yeast rice. According to a promotional document distributed by the company, Cholestin was first "produced by a proprietary process" in 1993, but red yeast rice has been around for centuries. Pharmanex Scientific Product Review at 2, Let 5 at 12.

Second, traditional red yeast rice is made from a mixture of fungal strains. See Pharmanex R&D Memo at 4, Let3 at 6; Second Pharmanex Meeting at 2, MM2 at 2. As discussed above, however, Cholestin contains one particular fungal strain chosen for its ability to produce lovastatin. After reading all the literature Pharmanex provided him, Dr. Alberts, the Pharmanex consultant, concluded that "a single strain of yeast is used [to make Cholestin] as opposed to the mixture of organisms used in traditional production of red yeast rice." Second Alberts Letter, C136 at 2.

Third, evidence in the record indicates that, whereas Cholestin contains significant amounts of lovastatin, traditional red yeast rice does not. Documents from China submitted by Pharmanex to this proceeding discussing the history of red yeast rice state that traditional red yeast rice does "not contain the active component mevinolin." Chinese Patent Application at 3, PSA1, vol. 2 at 96. When Pharmanex asserted that its consultant, Dr. Alberts, supported the proposition that traditional red yeast rice contains lovastatin, Dr. Alberts felt it necessary to send a separate clarifying letter stating that "[n]owhere in my [first] letter did I acknowledge that red yeast rice 'always has contained significant levels of mevinolin.'" Second Alberts Letter, C136 at 2.

Scientific articles submitted by Pharmanex to this proceeding explain that the lack of lovastatin in traditional red yeast rice is due to the presence of pigments in the traditional product and by the high temperature at which traditional red yeast rice is cultured, which are both inconsistent with significant lovastatin levels. According to one article submitted by Pharmanex, "strains [of yeast] with Monacolin K productivity have little capacity for producing pigments." Negishi et al., PSA1, vol. 2 at 58; see also Juzlova et al. at 167, PSA1, vol. 3 at 49 ("[a]ll mevinoлин-producing strains [are] inferior in red pigment formation."). Traditional red yeast rice, however, is used as a food pigment. See ea., Hesseltine, Microbiology of Oriental Fermented Foods, 37 Ann. Rev. Microbiol. 575, 577, 595 (1983), PSA1, vol. 2 at 171, 173, 191.^{13/} Thus, traditional red yeast rice, unlike Cholestin, would not be expected to contain significant amounts of lovastatin. Similarly, traditional red yeast rice is manufactured at culturing temperatures ranging from 33°C-42°C. See Endo, History and Recent Developments of Monascus and Monascus Fungi 43:6 Ferment. Indust. 544-52, Let14 at 15-16. As discussed above, however, temperatures need to be below 30°C to produce significant amounts of lovastatin.

Test results also indicate that, unlike Cholestin, red yeast rice on the market today does not contain significant amounts of lovastatin. Five separate bodies of test data, discussed below, have been submitted to the record of this administrative proceeding: (1) data generated by tests conducted by FDA on red yeast products in April-June 1997, Ref6-13; (2) data generated by tests on what Pharmanex asserts are red yeast rice food products conducted by Pharmanex's Shanghai Research and Development Center (Pharmanex Shanghai) and an outside laboratory, Alpha Chemical & Biomedical Laboratories, Inc. (Alpha), PSA1, vol. 3 at 86-242 and Sup1 at 47; (3) data generated by tests conducted by FDA on 25 red yeast rice products in February-April 1998, Ref19-43; (4) data generated by test results on red yeast rice and red yeast food products submitted to FDA by Merck, the manufacturer of Mevacor, C156 at 91-478 and; (5) data from tests conducted by FDA on the bulk and finished Cholestin product. Ref5, 14-15, 17-18.

FDA analyses of the finished Cholestin product indicate that Cholestin contains, on the average, approximately 0.17% of lovastatin. Ref5, 14-15, 17-18. Of the 33 samples of red yeast

^{13/} According to Pharmanex's vice-president, Dr. Chang, people making traditional red yeast rice know they are successful if the final product is red in color. See Second Pharmanex Meeting at 2, MM2 at 2.

rice and red yeast food products tested by the agency, however, 30 contained no lovastatin whatsoever. Ref6-13, 20-40, 42. Of the three samples that tested positive for lovastatin, two contained approximately 0.012% lovastatin and one contained approximately 0.066% lovastatin, all three samples well below the approximately 0.17% lovastatin found in Cholestin. Ref19, 41, 43.^{14/}

FDA finds the test data supplied by Pharmanex purporting to show lovastatin in traditional red yeast rice to be confusing, incomplete, contradictory, and not scientifically reliable. Pharmanex first alleges that samples the company obtained from two of the largest Chinese manufacturers of red yeast rice contain lovastatin. Pharmanex Petition at 22, PSA1, vol. 1 at 27. Pharmanex alleges that the first sample, from Yiwu Natural Pigment Industrial Corp. contains .5% lovastatin, according to data supplied by Alpha, PSA1, vol. 3 at 88-89, and .544% lovastatin, according to data supplied by Pharmanex Shanghai. Id. at 91. Alpha, however, appears to have tested sample no. 97081-A, id. at 90, which was not the same sample that Pharmanex Shanghai tested. Id. at 91. The sample that Alpha tested also does not agree with the photostat of the sample bag that was submitted by Pharmanex for purposes of sample identification along with these data. Id. at 88. Analytically, no information concerning sample weight, extraction volume, reference standard chromatogram, or reference standard concentration were provided for the Alpha or the Pharmanex Shanghai data. Thus, it is not possible to verify the calculations for lovastatin content. For both sets of test results, the chromatographic peaks are very broad, see id. at 90-95, indicating a poor high performance liquid chromatography (HPLC) method, and specificity and resolution can not be confirmed, and for the Pharmanex Shanghai results, neither of the peaks were identified as lovastatin or mevinolin, nor was a reference chromatogram provided to indicate the identity of the components. Id. at 92-95. Finally, for the Alpha data, the test method used was identified as "USP 23, page 907, modified," id. at 89, but the details of, and reasons for, the modification were not provided, and for the Pharmanex Shanghai results, the chromatographic method used was not mentioned at all, thus making it impossible for FDA to verify the validity of the lovastatin content analyses.

^{14/} Merck submitted test results on red yeast rice and red yeast food products to FDA that corroborate FDA's results, see C156 at 91-478, but the test methods Merck used are not adequately documented for FDA to assess their validity. Thus, FDA is not relying on the Merck data in this decision.

The second Chinese sample, from Fujian Province Gutian County Red Yeast Factory HongQu Chang, contains, according to Pharmanex, .5% lovastatin. Id. at 108. Results on this sample from Pharmanex Shanghai were not supplied to the agency. The Alpha report states that Alpha tested product number 97081-B, but this number appears on a photostat of the Yiwu sample discussed above, id. at 88, so it seems that the Alpha data do not report results on the Fujian product, as stated by Pharmanex. These data also suffer from deficient sample weight, extraction volume, reference standards, and chromatographic peak information as discussed above. Finally, Pharmanex submitted five pages of labeling and literature regarding the test sample in untranslated Chinese, making the evidence submitted for this sample impossible to assess. Id. at 101-05.^{15/}

Pharmanex also argues that test results of red yeast rice from four additional companies in Asia show significant levels of lovastatin. Pharmanex Petition at 22, PSA1, vol. 1 at 27. The data presented in this section of the Pharmanex Petition are also confusing. Data for two samples of red yeast rice collected from Shanghai E & W Industry Co. were submitted, PSA1, vol. 3 at 112-24, but a label and sample identification information was provided for only one. Id. at 110-11. Another sample was identified by the words "Sample No.4 from New York City" that appear on a photocopy of a plastic bag, id. at 138, but it is not possible to confirm Pharmanex's assertion that this sample is from Asia, or where in New York Pharmanex had obtained the sample. This omission was especially significant because the results for the "New York No. 4" sample purportedly showed lovastatin at a concentration of .213%, id. at 136, but from the documentation submitted, FDA had no way to confirm these results through its own testing.^{16/}

Analytically, no information concerning sample weight, extraction volume, or reference standard concentration were provided for any of the test results located at this section of the pharmanex petition, see id. at 110-87, and for each result

^{15/} Several documents Pharmanex submitted to the docket were submitted in a foreign language in untranslated form, or were translated, but not verified. Pursuant to 21 C.F.R. § 10.20 (C), these materials, as well as certain references cited by pharmanex that were not readily available to the agency, have not been considered in rendering this decision.

^{16/} Where possible, FDA visited each establishment referred to in the data submitted by Pharmanex to obtain samples of red yeast rice to test for lovastatin. The results of data obtained as a result of these samplings are discussed infra at 21-22.

presented, the chromatographic peaks are very broad, indicating a poor HPLC method. For test results on at least six of the samples, the method used was identified as a modified USP, or otherwise modified, method but the details and reasons for the modifications were not provided, and therefore cannot be scientifically credited.^{17/} Finally, Alpha test data were submitted for all the samples in this section of the Pharmanex Petition, but test results from Pharmanex Shanghai were submitted for only one sample. *Id.* at 141-45. FDA finds this relevant because, for the one sample where Pharmanex did appear to submit test data gathered by both Alpha and Pharmanex Shanghai, those test results disagreed with each other.^{18/}

Finally, Pharmanex alleges that test results on red yeast rice currently on the market in the U.S. show that seven such products tested by Pharmanex contain substantial amounts (> .05%) of lovastatin. Pharmanex Petition at 22, PSA1, vol. 1. at 27; PSA1, vol. 3 at 189-242; Supl at 47. FDA finds these data unconvincing. As a preliminary matter, FDA notes that a Pharmanex Research and Development memorandum submitted with these test results, PSA1, vol. 3 at 189, states that Pharmanex tested a total of 37 samples, suggesting to FDA that Pharmanex's tests showed that 30 samples of traditional red yeast rice tested did not contain lovastatin. In addition, the test results reported by Pharmanex on the seven samples are unreliable for many of the same reasons discussed above. Specifically, FDA has identified the following deficiencies:

- The Alpha data purportedly showing test results on a sample taken from Kamwo Trading Co. are a copy of the data submitted for the Maypro sample (Alpha number 2173-97) , discussed

^{17/} These six samples were Shanghai Flower and New Continent, PSA1, vol. 3 at 112-24; New York Sample No. 4, *id.* at 136-37; WPU 1013, *id.* at 142, 146-47; Gallard-Schlesinger Inc. "Monascus MK F Powder, " batch #BM08-018, *id.* at 152-53; and Maypro Red Yeast Rice sample No. 2173-97, *id.* at 157-65. In the report on the Maypro sample, Alpha noted that the modification from U.S.P. standards was required to allow for the analysis of the formulation matrix tested, and that the chromatographic conditions, extraction solvent, and eluent were prepared as per the method. *Id.* at 157. This notation suggests to FDA that the sample preparation was different than prescribed U.S.P. methods and that the concentration of lovastatin in the sample was so low it could not be determined by Alpha's usual method.

^{18/} Alpha reported that the WPU sample contained .015% lovastatin, PSA1, vol. 3 at 146, while Pharmanex Shanghai said it contained .042% lovastatin. *Id.* at 141.

above. Compare PSA1, vol. 3 at 193-99 with id. at 159-65. Not only were data submitted for the wrong sample, but the data that were submitted reported a result of .026% lovastatin, which is below the .05% that Pharmanex claimed for all seven of the samples discussed in this section of the Pharmanex Petition. See id. at 191.

- Data on samples obtained from Ou's Acupuncture and Herb store are ambiguous in that Pharmanex submitted two receipts from the Ou Li Chin store containing consecutive serial numbers (217253 and 217254), one for the purchase of "Red Rice" for \$5.00, and one for the purchase of "Herb Supply Red Rice" for \$100.00. Id. at 209-210. Both receipts are identified as representing "Sample #2 bought in California, " but they are obviously not the same, and there is no indication which sample was tested and how it differed from the other sample, which presumably was not tested. In addition, the data that were presented contain no information concerning sample weight, extraction volume, reference standard chromatogram, and reference standard concentration, making it impossible to verify the lovastatin content calculation. The chromatographic method used was not mentioned at all, making it impossible to verify its validity, and none of the peaks reported was identified as mevinolin or lovastatin, nor was a reference chromatogram provided to indicate the identity of the components. See id. at 212-14.

- Data on the sample from Hui Kang Co. contain labeling in untranslated Chinese. Id. at 218. The standard used in the testing is unidentified and, upon examination, appears to be very impure when compared to the Monacolin K reference standard chromatogram provided elsewhere by Alpha. See id. at 219-20. There is no information that this standard had been qualified by comparison against the USP standard for lovastatin and, therefore, this reference standard is not useful for quantitative purposes. Again, in both the reference standard trace and the sample trace, the peaks are much too broad, indicating use of a poor HPLC method and making specificity and resolution impossible to confirm. No information concerning sample weight, extraction volume or reference standard concentration are provided, making it impossible to verify the calculation for lovastatin content, and the chromatographic method used is not mentioned at all, making it likewise impossible to verify its validity.

- The "New York City Sample" is a one page duplicate of an Alpha test result submitted previously by Pharmanex. compare Supl at 47 with PSA1, vol. 3 at 137. The deficiencies of this test result are discussed above.

● For the purported "San Francisco Sample # 5, " Pharmanex submitted no data, just a photocopy of a plastic bag. PSA1, vol. 3 at 224. Similarly, for purported samples from Wing Hop Fung Ginseng & China Product, Inc., and Far-East Center, pharmanex submitted only photocopies of plastic bags and some cash register receipts. Id. at 227-31.

In an attempt to make sense of the data submitted by Pharmanex and summarized above, FDA in January-April 1998, attempted to collect and test the same products that Pharmanex had purported to test. Although this was impossible in certain instances, e.g., those samples identified by Pharmanex as "New York Sample No. 4," and "San Francisco Sample No. 5," FDA was able to visit seventeen establishments identified in the Pharmanex submission as sources of traditional red yeast rice.^{19/} From these seventeen establishments, FDA investigators were able to purchase samples of red yeast rice from ten.^{20/} Of eleven samples collected at these ten establishments, eight contained no lovastatin. Notably, these eight included product from Far-East Center and Wing Hop Fung Ginseng & China Product, Inc., two establishments that Pharmanex alleged sold red yeast rice containing significant amounts of lovastatin. compare Ref22, 42 with PSA1, vol. 3 at 189. Of the three samples that FDA found to contain lovastatin, two contained approximately 0.012% lovastatin, Ref19, 41 and one contained 0.066% lovastatin. Ref 43. These amounts were all well below the levels of lovastatin found in Cholestin. One sample result was also well below the

^{19/} The 17 establishments were Lanka Spice Importers & Dist., TAK Shing Hong, Inc., Far-East Center, Hong Ning CO., Man Cheong Ginseng & Herbs, Inc., Tin Bo Co., Wing Hop Fung Ginseng & China Product, Inc., Henry's Herb (now called Draline Tong Herbs), Hui Kang Co., Ou's Acupuncture & Herb Center, Bay Area Food Import Ass., Tran Trading Co., Red China Herb CO., Mings Import Inc., (d.b.a. Ming's Supermarket), Maypro Industries Inc., Mong Chong Loong Trading Corp., and Kamwo Herb & Tea Co. Two related companies, MSKL International Trading Co. and Lotus Foods, referenced in the Pharmanex Petition, were not visited but the owner directed the FDA investigator by telephone to another market where the MSKL and Lotus products could be purchased. Ref20 at 35.

^{20/} Six of these establishments did not sell red yeast rice, and one was listed at an address where the building was being demolished and the phone disconnected. M3-4, 6-7, 9.

result reported by Pharmanex for the red yeast rice obtained from that establishment.^{21/}

* * *

In summary, FDA has determined that the lovastatin component of Cholestin is the relevant article for purposes of § 201(ff) (3) because Pharmanex is promoting the presence of lovastatin in the product and manufacturing the product in a manner designed to maximize levels of lovastatin in Cholestin. FDA does not believe the relevant article in this case is traditional red yeast rice because Cholestin is not traditional red yeast rice. This conclusion is supported by evidence in the record indicating that (1) Cholestin was developed in 1993 pursuant to a proprietary process, while traditional red yeast rice has existed for centuries; (2) traditional red yeast rice comes from a mixture of fungal strains while Cholestin is manufactured from only one fungal strain; (3) traditional red yeast rice contains pigments, which indicates that the traditional product does not contain significant levels of lovastatin, as does Cholestin; (4) traditional red yeast rice is fermented at temperatures that preclude the production of significant levels of lovastatin, such as those found in Cholestin; and (5) test results indicate that traditional red yeast rice on the market today does not contain lovastatin at the levels found in Cholestin, if at all.

F. Lovastatin was not marketed as a dietary supplement or as a food before Mevacor was approved as a new drug.

As discussed above, the record in this proceeding shows that, in marketing and manufacturing Cholestin, Pharmanex is marketing and manufacturing lovastatin, which is an article approved as a new drug within the meaning of § 201(ff) (3) . This determination, however, does not end the inquiry because, pursuant to what hereinafter will be referred to as DSHEA's "prior market" clause, FDCA § 201(ff) (3) (B) (ii), Cholestin could still qualify as a dietary supplement if the article, in this case lovastatin, had been "marketed as a dietary supplement or as a food" before authorized and substantial clinical investigations on lovastatin were made public and before the Mevacor NDA was approved.

^{21/} Pharmanex reported that red yeast rice from Ou's Acupuncture & Herb Center contained .317% lovastatin. PSA1, vol. 3 at 212. FDA found the sample from Ou's to contain 0.012% lovastatin. Ref19 .

To meet the prior market clause, it is not necessary to show that an article has been previously marketed as a food or dietary supplement in a pure or isolated form. Indeed, as discussed above, a component of a product may, under certain circumstances, constitute an "article" for purposes of § 201(ff)(3). See supra at 10-22. The relevant inquiry in determining whether a component present in a marketed product qualifies as an "article marketed as a dietary supplement or as a food" within the meaning of the prior market clause is whether, in marketing the product, a person was in actuality marketing the component as a food or as a dietary supplement. See id.

This said, the evidence regarding previously marketed products submitted to this administrative proceeding does not establish that the article lovastatin was marketed as a food or a dietary supplement before clinical investigations of lovastatin were made public, and before the Mevacor NDA was approved. Pharmanex has submitted evidence that lovastatin may be present in oyster mushrooms, see e.g., Statement of John Fieschko, PSA1, vol. 3 at 309, but the company has made no showing in the record that oyster mushrooms were manufactured under conditions designed to heighten lovastatin content, or marketed with any reference to any property they might have due to their lovastatin content.^{22/} Thus, even if oyster mushrooms do contain high levels of lovastatin, that fact alone does not mean that lovastatin was marketed as a food or a dietary supplement within the meaning of DSHEA'S prior market clause.

Nor does evidence on traditional red yeast rice in the record establish that lovastatin was marketed as a food or a dietary supplement before clinical investigations of lovastatin were made public, and before the Mevacor NDA was approved. Rather, the mass of evidence in this proceeding indicates that the traditional food red yeast rice does not contain lovastatin at all. One can not say, therefore, that in marketing these products, manufacturers are or were in fact marketing lovastatin.^{23/}

^{22/} In and of itself, such a showing might still not be sufficient to bring Cholestin within the scope of the prior market clause. Pharmanex would, as the statute requires, also have to show that the lovastatin in these oyster mushrooms had been marketed "as a dietary supplement or as a food."

^{23/} Pharmanex seems to admit as much when it states that, 'prior to filing of its WIPO patent, "the extraordinar[ily] broad spectrum medicinal and nutritional benefits of red yeast in

FDA tests on three samples of red yeast rice, see supra at 21, did reveal small amounts of lovastatin, but there is no evidence in the record demonstrating that the manufacturers of these products were marketing lovastatin as a food or as a dietary supplement. No documentation exists that any of these products were manufactured in a manner designed to heighten their lovastatin content, and for two of the products, Ref19, 41, there is no indication that these products have been promoted as a food or as a dietary supplement with regard to any properties they might have due to their lovastatin content. One product does contain statements on the label that the "product is from Chinese Traditional Medicine, can adjust hyperlipidemia and reduce cholesterol. It is [sic] no toxicity and no side effect." Ref43 at 71. Although these statements suggest that the product may be marketed due to its lovastatin content, the manufacturer of this product issued a statement documenting that the product had been marketed only since 1993, well after the Mevacor approval. PSA1, vol. 3, at 250.^{24/}

Similarly, data submitted to FDA on Monascus MK F Powder Batch # BM08-018 (Shen Da - Taiwan) , alleged by pharmanex to contain significant amounts of lovastatin, PSA1, vol. 3, at 149-53, does not establish that, in marketing this product, the manufacturer was in fact marketing lovastatin. Even if the test results submitted by Pharmanex showing significant amounts of lovastatin in this product were scientifically reliable (which, based on the data submitted to the agency, they are not, see supra at 19 & n.17), FDA is not aware of any documentation that this product was manufactured in a manner designed to heighten its lovastatin content, or that the product has been promoted as a food or as a dietary supplement with regard to any properties it may have due to lovastatin content. No information regarding how long this product has been marketed, or whether it has been marketed as a food or as a dietary supplement, has been made available to the agency. Indeed, no marketing information at all regarding this product was submitted to FDA.

^{23/} (...continued)
general, and certain species in particular, have not been thoroughly studied or appreciated. '" RC1 at 3-4 (quoting WIPO Patent at 3, C171 at 12) .

^{24/} The labeling of this product also suggests that even if the manufacturer had been selling this product due to its lovastatin content before Mevacor had been approved or investigated as a new drug, the product appears to have been sold as a drug, not as a food or dietary supplement, as the prior market clause requires.

Pharmanex argues that if lovastatin were present in the food supply in at least some amount before Mevacor was approved, then the requirements of the prior market clause are met, and Cholestin is a dietary supplement. See Pharmanex Petition at 22-23, PSA1, vol. 1 at 27-28. FDA disagrees. The mere existence of a substance approved as a new drug, as a component of a product present in the food supply, does not by itself bring that substance within the scope of the prior market clause. Rather, as discussed above, circumstances must establish that in marketing a product containing such a component, a person was, in actuality, marketing the component. The plain wording of § 201(ff) (3) (B) (ii) preserves dietary supplement status only for those articles approved or authorized for investigation as new drugs that were "before such approval . . . or authorization marketed as a dietary supplement or as a food." (emphasis added) . Judging by Congress's choice of language, Congress did not intend to preserve dietary supplement status for articles merely "present in the food supply, " before the relevant new drug was approved or authorized for investigation. Pointedly, Congress did use the phrase "present in the food supply" in other sections of DSHEA, but chose not to use the phrase in § 201(ff) (3) . Compare FDCA § 413(a) (1). Taken to its limit, Pharmanex's argument would mean that even a few molecules of a substance never before recognized as therapeutically beneficial would, if present in some food, defeat any incentives for pharmaceutical manufacturers to develop such a substance into a new drug.

In issuing this decision, FDA does not need to read a de minimis proviso into the prior market clause, as Pharmanex has repeatedly suggested. See Pharmanex Petition at 23, PSA1, vol. 1 at 28 ("There is no indication that an 'article' must have been marketed in a certain volume; the law does not require it to have been 'commonly marketed' or 'marketed in very large quantities.'") . Whether such a proviso exists need not be addressed in this decision because Pharmanex has not demonstrated that the article lovastatin has been marketed as a food or as a dietary supplement in any amount. The de minimis amounts of lovastatin present in a few examples of red yeast products tested by the agency are relevant to FDA's decision in this matter, but only because they contribute to the body of evidence demonstrating that, in marketing Cholestin (a product with high levels of lovastatin) Pharmanex is marketing the article lovastatin, not the traditional food product red yeast rice. See supra at 16-22.

Finally, Pharmanex has argued that evidence of marketing as a food or a dietary supplement anywhere in the world, not just in the United States, may bring an article within the scope of the prior market clause. Pharmanex Petition at 24, PSA1 vol. 1 at 29. Pharmanex has not, however, provided any evidence that

lovastatin has been marketed as a dietary supplement or as a food in the United States or elsewhere before Mevacor was approved or investigated as a new drug. Today's decision, therefore, does not reach the issue of whether the prior market clause is limited in scope to domestic marketing experience. Nevertheless, because the Pharmanex Petition specifically raises the issue, the agency notes that there are several compelling arguments for limiting the prior market clause to domestic marketing experience.

First, section 201(ff) (3) establishes a system for deciding whether any particular article approved or investigated as a new drug under § 505 can be marketed as a dietary supplement, depending on whether the article was marketed "as a dietary supplement or as a food" before being approved or studied as a new drug under § 505. "New drugs" under § 505, however, are creations of domestic law. The reference to § 505 in § 201(ff) (3) (B) (ii) indicates that Congress contemplated the prior market clause analysis to turn on domestic marketing and regulatory experience.

Second, reading the prior market clause to limit pharmaceutical companies to domestic marketing experience, but to allow products to be marketed as dietary supplements based on domestic or foreign marketing experience as foods or dietary supplements, would undermine the pharmaceutical research and development incentives that Congress sought to protect by enacting the prior market clause. If the clause were interpreted as Pharmanex argues, then before undertaking the costly research needed to bring new drugs to market, pharmaceutical companies would have to ensure that the article they plan to study was not only never marketed as a food or as a dietary supplement here in the United States, but also never marketed as food or a dietary supplement anywhere in the world, at any time. Congress could not have intended to place such a burden and such increased costs on pharmaceutical companies seeking to develop new drugs. A prior market clause not limited to domestic marketing experience for both dietary supplement and pharmaceutical companies is inconsistent with the equitable system Congress sought to establish in enacting § 201(ff) (3) .

Third, to not limit § 201(ff) (3) (B) (ii) to domestic marketing and regulatory experience would lead to irrational results and make the prior market clause impossible to apply and administer. In order to determine whether any particular article falls within the prior market clause, one must analyze whether the article was marketed as a "food" or a "dietary supplement." These terms, however, are legal terms of art, developed through sixty years of domestic case law and legislation, which have particular meanings here in the United States. Determining the

status of marketed articles in other countries, at various times throughout human history, when and where terms like "dietary supplement" are not defined legally, or defined differently than they are in separate countries or in the United States, would be impossible and/or lead to arbitrary and inconsistent results, depending on the vagaries of the foreign definition and legal system at issue. There is no evidence in DSHEA that Congress intended such a result, or intended for dietary supplement manufacturers or FDA to have to engage in such analyses of foreign law and foreign marketing experience in order to apply § 201(ff) (3).

G. FDA is not treating Cholestin differently from either Premarin or Ephedra.

Pharmanex has argued that FDA is acting towards Cholestin differently from the way it did in refusing to approve generic versions of the drug Premarin. Pharmanex Petition at 19, PSA1, vol. 1 at 24.^{25/} Pharmanex asserts that FDA found Premarin, a drug containing a mixture of active ingredients, different from the generic versions of Premarin because the generic versions could not show that they contained the same mix of active ingredients present in Premarin. By analogy, Pharmanex argues that Cholestin, composed of red yeast rice containing a mixture of active ingredients, is different from Mevacor because Mevacor contains only one active ingredient, lovastatin. As discussed above, however, FDA is not asserting that Cholestin or red yeast rice is identical to Mevacor. Rather, the agency is asserting that lovastatin, a component of Cholestin, is the relevant "article" for purposes of § 201(ff) (3), and that lovastatin, not red yeast rice or Cholestin, is an article approved as the new drug Mevacor. The fact that the red yeast rice in Cholestin is not the same as Mevacor is neither material nor relevant because the "article" in this case is the component lovastatin, not the entire Cholestin product.

^{25/} Under §§ 505(j) (2)(A) (ii) (II), a generic drug application for a drug containing more than one active ingredient must include information to show that the active ingredients in the applicant drug are the same as those present in the innovator, or "name brand" product, i.e., the reference drug listed in FDA's Orange Book. FDA's Center for Drug Evaluation and Research recently proposed to refuse to approve two generic Premarin applications because, at that time, the active ingredients in Premarin had not been sufficiently characterized or adequately defined and the generic applicants failed to show that they had the same active ingredients as Premarin. See 62 Fed. Reg. 42562 (Aug. 7, 1997) .

Pharmanex has also argued that the agency is inconsistently applying § 201(ff) (3) to Cholestin because it has not applied that section in its proposed rule on "Dietary Supplements Containing Ephedrine Alkaloids, " 62 Fed. Reg. 30678 (June 4, 1997) (the proposed rule) . In the proposed rule, the agency is attempting to address safety concerns related to a class of products marketed as dietary supplements that contain ephedrine alkaloids. The ingredient sources of the ephedrine alkaloids in this class of products include several raw botanical, including Ephedra sinica, powdered plant material, and extracts from botanical sources. There are hundreds of products containing ephedrine alkaloids from botanical sources that are marketed as dietary supplements. Pharmanex asserts that, under the agency's analysis of 201(ff) (3), the use of ephedrine alkaloids extracted and concentrated from the raw botanical necessarily means that all these products are excluded under § 201(ff) (3) from being dietary supplements, which is inconsistent with the proposed rule. See C81 at 5.

FDA disagrees. As a general matter, the agency is not aware of evidence that would show that an ephedrine alkaloid in each of the products subject to the proposed rule is, within the meaning of § 201(ff) (3), an article either approved as a new drug or authorized for clinical investigation as a new drug and, if so, whether such article was previously marketed as a food or dietary supplement . Accordingly, FDA does not believe that § 201(ff) (3) prevents the class of products subject to the proposed rule from being regulated as dietary supplements. Whether an ephedrine alkaloid in any particular product containing the raw or extracted botanical is an "article" for purposes of § 201(ff) (3) is a question beyond the scope of today's decision.

III. Cholestin Is A Drug.

The FDCA defines the term "drug" as, among other things, articles "intended to affect the structure or any function Of the body ." FDCA § 201(g) (1) (C). Under § 403(r) (6) (A), added by DSHEA, statements made for "dietary supplements" (as defined by § 201(ff)) may indicate that such products are intended to affect the structure or any function of the body without invoking drug status under § 201(g) (1) (C) . Cholestin, as described in this decision, however, is not a dietary supplement under § 201(ff) (3). Thus , if Cholestin is intended to affect the structure or any function of the body, it is a drug. Pharmanex makes claims for Cholestin related to cholesterol that it concedes constitute claims about Cholestin's affect on the structure or function of the human body. Pharmanex Petition at 29, 35; PSA1, vol. 1 at 34, 40. These claims, therefore, place

the product squarely within the § 201(g) (I) (C) definition of "drug."^{26/}

The FDCA also defines the term "drug" as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. FDCA § 201(g)(1) (B). In the Sept. 30 letter, FDA told Pharmanex that the agency believes that Cholestin is a drug because it is intended for use in the mitigation or prevention of disease, as evidenced by the name of the product and by certain statements made for the product regarding its effect on serum cholesterol levels in the human body. See Sept. 30 Letter at 9-10, PSA 1, vol. 2 at 119-20; see also 63 Fed Reg. 23624 (April 29, 1998) (proposed rule discussing criteria for determining when a statement about a dietary supplement is a claim to diagnose, cure, mitigate, treat, or prevent disease). As discussed in today's decision, however, FDA has determined that Cholestin is a drug because it (1) is not a dietary supplement, and (2) is intended to affect the structure and function of the body. This decision, therefore, does not reach the issue of whether Cholestin is intended for use in the mitigation or prevention of disease, and therefore also a drug under FDCA § 201(g) (1) (B).

IV. Legal consequences of This Decision

A. Cholestin is a new drug.

Cholestin is a "new drug." The term "new drug" means any drug

the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof.

FDCA § 201(p). In order for a drug product to be so generally recognized, there must be a consensus of expert opinion that the drug is safe and effective for its labeled indications; that expert consensus must be based upon adequate and well-controlled clinical investigations conducted on the drug product in issue;

^{26/} For this reason, the labeling changes Pharmanex offered to make for Cholestin in the company's submission to FDA dated December 18, 1997, C3, do not bring the product into compliance with the FDCA. The proposed labeling offered by Pharmanex still makes claims that the product is intended to affect the structure and function of the body.

and the studies conducted on the drug must be published in the medical literature and available to experts generally. Cholestin is a new drug because the agency is aware of no scientific consensus, based on adequate and well-controlled clinical studies that are published in the medical literature, establishing the safety and efficacy of the product.^{27/}

B. Ramifications of new-drug status

Cholestin is a new drug that does not have a new drug application approved pursuant to § 505. It is therefore illegal to introduce or deliver Cholestin for introduction into interstate commerce. FDCA § 301(d). Unapproved new drugs, such as Cholestin, are not allowed entry into the United States. Id. § 801. The FDCA provides, among other things, for seizure of illegal products, and for injunction and criminal penalties against the manufacturer and/or distributor of illegal products. Id. §§ 302, 303, 304. Continued marketing of Cholestin may subject Cholestin and persons responsible for its manufacture and distribution to regulatory action under any or all of these statutory provisions.

Sincerely yours,



William B. Schultz
Deputy Commissioner for Policy

^{27/} In assessing whether Cholestin is a new drug FDA looks at the composition of the entire product, and is not limited to assessing individual components, such as lovastatin.