DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FILE COPY

October 30, 1997

Mr. Stuart M. Pape
Patton Boggs, L.L.P.
2550 M. Street, N.W.
Washington, D.C. 20037-1350

Dear Mr. Pape:

Your petition on behalf of Pharmanex, Inc requesting the Food and Drug Administration to approve a Petition for Stay of Action on determination of Pharmanex's Cholestin red yeast rice dietary supplement, was received by this office on 10/29/97. It was assigned docket number 97P-0441/PSA1 and it was filed on 10/29/97. Please refer to this docket number in future correspondence on this subject with the Agency.

Please note that the acceptance of the petition for filing is a procedural matter in that it in no way reflects an agency decision on the substantive merits of the petition.

Sincerely,

Helen K. Harris

Helen K. Harris
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October 29, 1997

2261 '97 OCT 29 P3:49

By Hand

Michael A. Friedman, M.D.
Lead Deputy Commissioner
Food and Drug Administration
HF-28, Room 14-71
5600 Fishers Lane
Rockville, MD 20857

Re: Cholestin™ Dietary Supplement

Dear Dr. Friedman:

Enclosed please find a copy of a Petition for Stay of Action, filed earlier today on behalf of Pharmanex, Inc. in response to FDA's September 30, 1997 determination that the agency considers Pharmanex's Cholestin red yeast rice dietary supplement to be an unapproved new drug. Absent a prompt reversal of this ruling, the Petition seeks a stay of agency enforcement action during the pendency of a voluntary Citizen Petition process requested by the agency.

As you will see from the Petition, the agency's position in the Cholestin matter raises fundamental questions under the Dietary Supplement Health and Education Act (DSHEA). In addition to the harm suffered by Pharmanex, the agency's decision in this matter could have enormous implications for consumers and the dietary supplement industry as a whole.

The legal and scientific basis for the dietary supplement status of Cholestin is quite strong. Pharmanex remains of the view that this matter is best resolved through a dialogue with FDA. We will contact your office shortly to seek a convenient time to discuss the matter.

Sincerely,

Stuart M. Pape

Enclosures

cc: William F. Schultz, Esq.
Janet Woodcock, M.D.
Robert Temple, M.D.
Fred Shank, Ph.D.
Elizabeth Yetley, Ph.D.
Ilisa Bernstein, Pharm.D., J.D.
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PSA1

97P-0441

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2260 '97 OCT 29 P3:49

Petition to the Food and Drug Administration for a Stay of Action With Respect to Cholestin™ Dietary Supplement

October 29, 1997

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Pharmanex, Inc.

Petition for Stay of Action

The undersigned, on behalf of Pharmanex, Inc., submits this Petition under 21 C.F.R. §10.35 requesting that the Commissioner of Food and Drugs immediately issue a stay of enforcement based on the agency's September 30, 1997 letter concerning the regulatory status of Pharmanex, Inc.'s Cholestin™ red yeast rice dietary supplement product.

Pharmanex, based in Simi Valley, California, is a science-based company providing standardized dietary supplement products bearing substantiated statements of nutritional support. In addition to assembling a first class scientific team that includes renowned experts in medicine, nutrition and natural product chemistry, Pharmanex has invested enormous sums in research and development, and has put in place manufacturing facilities that employ sophisticated quality control and quality assurance methods. Pharmanex represents precisely what the Dietary Supplement Health and Education Act (DSHEA) was intended to foster -- responsible companies producing quality products that benefit the health and well-being of consumers.

I. Decision Involved and Summary of Pharmanex's Position

On September 30, 1997, in a letter from Ilisa B.G. Bernstein, Pharm.D., J.D., Senior Science Policy Advisor, Food and Drug Administration, to Pharmanex's Counsel, Stuart M. Pape (hereinafter "September 30 Letter"), the Food and Drug Administration stated that it considers Pharmanex's red yeast rice dietary supplement product, tradenamed Cholestin, to be an unapproved new drug rather than a dietary supplement. Moreover, the agency explicitly declined to confirm that Pharmanex may lawfully import red yeast rice or sell Cholestin.

FDA's September 30 Letter is the culmination of months of discussions between Pharmanex and FDA and extensive factual and legal submissions to the agency.[1] These consultations were initially undertaken after Pharmanex agreed to suspend a lawsuit against the agency seeking a judicial ruling on the dietary supplement status of Cholestin. FDA thereafter detained imports of Pharmanex's red yeast rice. Pharmanex then reinitiated the discussion after it agreed to reexport red yeast rice that the agency had detained -- all with the understanding that such consultations would result in a final determination from FDA, without further administrative procedures -- on the regulatory status of Cholestin. Given the practical effect of

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[1] A chronology and a compilation of correspondence between Pharmanex and FDA on the Cholestin matter is provided at Attachment 1.

the agency's actions, detailed below, the September 30 Letter is legally final agency action, and is considered as such by Pharmanex.

FDA's September 30 decision is premised upon three erroneous findings--

First, FDA believes that in marketing Cholestin, Pharmanex is marketing the drug lovastatin rather than a food product, red yeast rice, containing a range of naturally beneficial constituents. The agency states that "Pharmanex purposely designed a manufacturing process intended to consistently maximize and standardize levels of lovastatin in Cholestin." September 30 Letter at 4.

Second, FDA interprets Section 201(ff)(3) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. §§ 321(ff)(3), as prohibiting any dietary supplement that contains lovastatin as a constituent. Section 201(ff)(3) prohibits dietary supplements that are an "article that is approved as a new drug" if the article was not marketed as a food or dietary supplement prior to the drug's approval. The agency contends that Pharmanex failed to demonstrate that lovastatin was marketed as a food or dietary supplement prior to the approval of Merck's Mevacor™ lovastatin drug product. September 30 Letter at 4-9.

Third, FDA takes the position that DSHEA does not permit statements of nutritional support relating to cholesterol, and that all such statements are drug claims rather than structure/function statements of nutritional support authorized by DSHEA. September 30 Letter at 9-10.

FDA's decision ignores the facts placed before the agency and is in conflict with Congress's framework for the regulation of dietary supplements. As this Petition for Stay of Action reiterates, Cholestin is properly considered a dietary supplement under DSHEA --

Red Yeast Rice, Which Naturally Contains a Complex Range of Beneficial Constituents -- Including Mevinolin -- Has Long Been Marketed in the United States

- Pharmanex does not manufacture or market the drug lovastatin. Rather, Cholestin is a natural dietary supplement composed entirely of red yeast rice made by the traditional Chinese method. Red yeast rice, which is a solid fermentation of the yeast on rice, has a documented history of food use that goes back almost a millennium. The species of yeast in Cholestin, *Monascus purpureus* Went, was originally identified in red yeast rice in 1895. Among other yeast strains, *Monascus purpureus* Went strains are widely used in traditional methods of fermentation in China, Hong Kong and Taiwan for the manufacture of red yeast rice and red sake -- products long available in the United States. Many of these traditional red yeast rice products *naturally* contain a range of HMG-CoA reductase inhibitors -- including mevinolin (which the agency equates chemically with lovastatin) -- as well as unsaturated fatty acids.

- FDA's attempted rebuttal of the history of marketing of red yeast rice containing mevinolin is superficial and result-oriented. At the agency's specific request, Pharmanex provided samples to the agency to demonstrate that red yeast rice products found in this country today contain mevinolin. The samples document that fact. More generally, however, the agency ignored the extensive evidence documenting the long history of sales of red yeast rice in this country and in Asia.

- In fact, it appears that the earliest reported attempt to manufacture *Monascus purpureus* Went red yeast rice in the United States -- in 1920 -- was undertaken by Margaret B. Church, an employee of the Bureau of Chemistry, U.S. Department of Agriculture -- *the direct predecessor to the Food and Drug Administration.*

- The presence of mevinolin in a food product like red yeast rice is not unusual. The ability to produce HMG-CoA reductase inhibitors has been found to be widespread among fungi originating from different taxonomic groups and habitats. Mevinolin is found at high levels in a species of mushroom that is widely consumed in the United States. FDA's September 30 Letter totally ignores these facts and supporting scientific literature.

Pharmanex Does Not Add, Enhance or Maximize Mevinolin in Cholestin

- Pharmanex does not enhance or maximize mevinolin or any other constituent in red yeast rice. Rather, Pharmanex has employed quality control measures common to the food industry to standardize the *overall* level of beneficial constituents. Such standardization is precisely what Congress sought to encourage in DSHEA, and it is a common and legal practice in the industry. The agency's position is particularly puzzling in that, although Cholestin is simply ground red yeast rice, DSHEA specifically authorizes the use of metabolites, extracts and concentrates as dietary supplements.

Cholesterol-Related Statements of Nutritional Support are Permitted Under the Dietary Supplement Health and Education Act

- The agency's position that dietary supplements may not bear statements relating to cholesterol is contrary to the plain language of the DSHEA. The statute states, in relevant part, that a statement for a dietary supplement may be made if it "describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans" or "characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function." 21 U.S.C. § 343(r). The nutritional support statements made for Cholestin fall well within these statutory parameters, and extensive foreign clinical trials and one recently completed U.S. clinical trial provide substantiation for these statements.

- The statements for Cholestin have been framed to ensure that they focus on the role the dietary supplement can play in maintaining healthy blood lipid levels in the context of an overall healthy diet -- they do not make claims with respect to persons with a disease state, and do not state a disease benefit. This approach is consistent with the prevailing

public health approach to the maintenance of healthy blood lipid levels. The medical community has recognized that direct medical intervention and drug therapy are not the first steps in the maintenance of healthy blood lipid levels in the general population. The initial step must be the adoption of healthy life habits, including a good diet and appropriate exercise. Cholestin can be an important part of the dietary component of this overall approach.

- Although the exact parameters of cholesterol-related statements of nutritional support are debatable, a position that all such statements are heart disease claims cannot be maintained in a post-DSHEA environment. Indeed, members of the DSHEA-created Commission on Dietary Supplement Labels have stated that it "would be possible to craft a statement of nutritional support regarding the maintenance of healthy blood cholesterol levels that is a statement of nutritional support and not a health claim or drug claim."[2]

- Nevertheless, in a sign of Pharmanex's interest in addressing FDA's concerns in this matter, this Petition for Stay of Action includes a revised label for the Cholestin product (Attachment 2) that goes beyond Pharmanex's legal obligations and reflects the recently issued dietary supplement labeling regulations. However, these changes are not a concession that the agency's ruling on cholesterol-related claims for dietary supplements is lawful.

Cholestin Does Not Pose Safety Concerns

- No health or safety concerns have been associated with Cholestin. The product bears proper labeling, including appropriate warnings, as permitted under DSHEA.

A Federal Court Has Already Confirmed the Dietary Supplement Status of Cholestin

- In trademark litigation filed against Pharmanex by a pharmaceutical company, Federal District Judge Wendell Miles considered extensive scientific evidence on Cholestin.[3] In rejecting a preliminary injunction against Pharmanex on July 11, 1997, Judge Miles stated that the "evidence shows that Cholestin is a beneficial product." The Judge also found that the HMG-CoA reductase inhibitors in Cholestin are natural and not synthesized chemicals. FDA has taken the position that it is not bound by these legal findings. Judge Miles' decision, however, is consistent with the facts and law and should be heeded. As Congress stated in DSHEA, "the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers."

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[2] *Commission on Dietary Supplement Labels Report to the President, the Congress, and the Secretary of the Department of Health and Human Services* at 35 (Draft, June 1997).

[3] *Pharmacia & Upjohn Company v. Generation Health d/b/a Pharmanex, Inc.*, 44 USPQ 2d 1091 (W.D.Mich. July 11, 1997) (Attachment 3)

In sum, Cholestin red yeast rice is a lawful dietary supplement, and cholesterol-related statements of nutritional support are permitted under the DSHEA. Although FDA has adopted an unreasonable position with regard to the regulatory status of the product, Pharmanex -- confident that the facts and law will prevail -- is willing to engage in a Citizen Petition process to confirm the product's lawfulness -- if it is not at risk of enforcement action.

II. Action Requested

Throughout the agency's deliberations, Pharmanex has acted in good faith and has deferred pressing its legal rights, both in court and in the import detention context. This was done in the belief that, after review of the facts, the agency would come to the only conclusion possible under the DSHEA -- that the Cholestin product is lawfully sold as a dietary supplement. Despite FDA's final ruling on September 30, Pharmanex is willing to engage in a Citizen Petition process. However, Pharmanex will not engage in such a process in a context in which the agency continues to detain imported red yeast rice intended for use in Cholestin, or otherwise may enforce its ruling against the product, the Company, or Pharmanex officers and employees. Thus, we ask the agency to issue a stay of any form of enforcement, including public statements adverse to Pharmanex or Cholestin.[4] Upon issuance of such a stay, Pharmanex will engage in a Citizen Petition process, and we are confident that such a process will result in a confirmation of the lawful dietary supplement status of Cholestin.

III. Statement of Grounds

A. FDA's Position on Cholestin Is Final Agency Action

1. FDA Has Stated that Cholestin Is a Drug, Not a Dietary Supplement.

FDA's September 30 Letter states at least eight times that Cholestin is a drug, not a dietary supplement. There is nothing tentative about the statement "FDA believes Cholestin is a 'drug', and not a dietary supplement."[5] This position is definitive and in excess of the agency's statutory authority under DSHEA. The agency has also taken enforcement action against Pharmanex on the basis of its unlawful position. On June 11, 1997, FDA issued a notice of import detention blocking the importation of Pharmanex's raw material -- red yeast rice -- for Cholestin. Furthermore, on September 2, 1997, the agency rejected Pharmanex's request to import only one shipment of red yeast rice for the production of Cholestin, stating that the agency had "no reason to view the regulatory status of Cholestin any differently than it did when

[4] Obviously, Pharmanex believes that a Citizen Petition process is unnecessary in that the dietary supplement status of Cholestin is clear, and would prefer that the agency immediately reverse its September 30 determination and confirm the lawful nature of the product.

[5] FDA September 30 Letter at 9.

the agency detained a shipment of bulk Cholestin product on June 11, 1997."[6] Thus, Pharmanex's ability to manufacture sufficient quantities of Cholestin is being severely curtailed by FDA's import detention.

2. FDA's Actions Have Had Serious Practical Effects and Legal Consequences for Pharmanex.

By declaring that Cholestin is a drug, not a dietary supplement, FDA's letter and other actions are designed to force Pharmanex to cease marketing Cholestin as authorized under DSHEA. A court would "not be blind to the practical effects of these letters and other statements." *Washington Legal Foundation v. Kessler*, 880 F. Supp. 26, 35 (D.D.C. 1995). The agency's own characterization of its position as tentative is not determinative; "it is the effect of the agency's conduct which is most important in determining whether [it] has adopted a final policy."[7] Here, FDA's position, actions and impacts are unequivocal: FDA has made a conclusive judgment that Cholestin cannot be marketed as a lawful dietary supplement and the raw material for the product cannot be imported.

FDA has prevented Pharmanex from importing the supplies that it needs to produce Cholestin and it has forced Pharmanex to choose between complying with FDA's onerous "new drug" premarket approval requirements outside of the DSHEA legal regime, or face potentially devastating consequences, including the range of enforcement actions available to the agency under the FFDCA.

FDA's position would preclude Pharmanex from making truthful, substantiated statements about the effect of Cholestin on the structure or function of the body as it relates to the production of cholesterol by the liver. FDA's position that DSHEA does not apply to Cholestin is also creating significant uncertainty in the marketplace among wholesale and retail customers. The practical effect of these actions is to injure Pharmanex directly by diminishing its sales of Cholestin as well as impairing the good will of its product. *Cf. Pharmacia & Upjohn Company v. Generation Health d/b/a Pharmanex, Inc.*, 44 USPQ 2d 1091, 1103. ("Cholestin is a beneficial product" and forcing Pharmanex to recall or abandon its product or its Cholestin trademark would cause not only harm to the Pharmanex's reputation, "but also possible destruction of its corporate existence.").

Although Pharmanex believes that the primary and irreparable harm resulting from FDA's position on Cholestin is to consumers deprived of access to Cholestin and other dietary supplements for the reduction of cholesterol, the agency should consider the serious harm to Pharmanex that has resulted from the agency's decision on Cholestin. As documented in the

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[6] Letter from Neal Parker, Associate Chief Counsel, FDA to Stuart M. Pape, Patton Boggs, L.L.P. (September 2, 1997).

[7] *Id.* at 34. Indeed, FDA's behavior with regard to Cholestin represents an improper effort "to implement de facto regulatory policies without formally adopting final agency positions." *Id.* at 36. The court in *Washington Legal Foundation* found this practice to be "disturbing" and "intolerable." *Id.*

attached affidavit from the President of Pharmanex (Attachment 4), FDA's actions have already resulted in significant losses in sales of Cholestin and other Pharmanex products due to reduced acceptance by consumers, pharmacists and health care providers. As a result of FDA's detention of red yeast rice for use in Cholestin, the company has been forced to forego pursuing certain marketing efforts, as the company's supply of product is insufficient to meet a heightened demand. Overall, the harm caused to Pharmanex is substantial and continuing.

Under the applicable case law, FDA's actions constitute final agency action under the Administrative Procedures Act and for purposes of possible judicial review. *See Washington Legal Foundation, supra*, 880 F. Supp. at 32-36 (aggregate effect of agency pronouncements is presumptively reviewable because affected person is confronted with dilemma of choosing between disadvantageous compliance or risking imposition of serious penalties); *Ciba-Geigy Corp. v. EPA*, 801 F.2d 430, 434 (D.C. Cir. 1986)(same); *Den-Mat Corp. v. U.S.*, Food Drug Cosm. L. Rep. (CCH) ¶ 38,273 (D. Md. Apr. 24, 1992)(FDA "warning letter" not tentative because resulted in direct harm to company).

3. FDA Action Is Final Because the Agency Is Attempting to Impose a Non-DSHEA Statutory Regime on Pharmanex.

The Supreme Court recently reaffirmed that "finality" must be judged in a pragmatic manner based on the effects or consequences of the agency action, rather than its form. *See Bennett v. Spear*, 117 S.Ct. 1154, 1168 (1997). As in *Bennett*, FDA's action on Cholestin is final because it has "altered the legal regime to which [Pharmanex] is subject." *Id.* at 1168.

Moreover, by refusing to give effect to the terms, provisions, and authorizations of DSHEA, FDA has exceeded its statutory authority. "Agency action taken in excess of delegated powers" can be reviewed in court immediately. *Leedom v. Kyne*, 358 U.S. 184, 190 (1958). By attempting to exercise power over Cholestin that has been withheld in DSHEA, FDA's actions are *ultra vires* and, thus, unlawful. *See Chamber of Commerce v. Reich*, 74 F.3d 1322, 1338 (D.C. Cir. 1996).

B. FDA's Suggestion for Citizen Petition.

FDA's September 30 Letter invites Pharmanex to file a Citizen Petition in order to obtain a change in the agency's position. Given the agency's clear ruling that Cholestin is a drug and not a dietary supplement, filing a Citizen Petition may well be futile (FDA basically suggests as much by stating that "[g]iven the attention FDA has already given to this matter, the agency expects it would be in a position to rule on your citizens petition in a[n] expeditious manner.")[8] Of course, FDA could also permit the Citizen Petition (and thereby Pharmanex) to languish for years. Indeed, FDA specifically declined to provide Pharmanex with a date by which it would respond to a Citizen Petition.[9] The significant delays in FDA's responses to Citizen Petitions are

[8] September 30 Letter at 10.

[9] Letter from Neal Parker, Associate Chief Counsel, FDA to Stuart M. Pape, Patton Boggs, L.L.P. (October 2, 1997).

a matter of public record, and are in fact the subject of an ongoing investigation by the Inspector General of the Department of Health and Human Services.[10]

In any event, the Citizen Petition process is non-statutory, and is not required by law or regulation. *See Washington Legal Foundation*, 880 F. Supp. at 33. Since the Citizen Petition is not a statutory or regulatory prerequisite for final agency action, Pharmanex is not required to "exhaust" this administrative remedy suggested by FDA. *Id. See also Darby v. Cisneros*, 509 U.S. 137, 153-54 (1993)(courts may not impose exhaustion requirements not required by statute or regulation).

C. Pharmanex Has Pursued This Matter With the Agency in Good Faith.

From the very beginning, Pharmanex pursued this matter in good faith. Prior to marketing, the Company obtained a legal opinion that Cholestin was lawfully a dietary supplement. Upon learning of FDA 's concerns, Pharmanex requested meetings with the agency to discuss the issues (which the agency initially declined). Thereafter, Pharmanex revised Cholestin's label to reflect the agency's objections, temporarily suspended shipment of product at the request of FDA, and suspended pursuit of a lawsuit (brought after FDA told Pharmanex unequivocally that it believed the product was a drug) for a further opportunity for discussion. Pharmanex also responded to a series of agency requests for further information. Nevertheless, the agency has responded by prohibiting the importation by Pharmanex of red yeast rice for use in Cholestin, and by issuing a ruling that, while expressing a final agency determination that Cholestin is unlawful, asks Pharmanex to engage in a voluntary Citizen Petition process. In yet another sign of good faith, Pharmanex is willing to accede to the agency's request -- if the company is not placed at risk of further enforcement action during the period such a Citizen Petition is pending.

D. Sound Public Policy and Public Health Grounds Support the Requested Stay

DSHEA is fundamentally a public health statute. In signing DSHEA, President Clinton stated that "[i]n an era of greater consciousness among people about the impact of what they eat on how they live, indeed, how long they live, it is appropriate that we have finally reformed the way Government treats consumers and these supplements in a way that encourages good health."[11] The statutory findings are also replete with Congressional recognition of the potentially important role that supplements could play in promoting the health of Americans, particularly with regard to cardiovascular health. Indeed, in enacting DSHEA, Congress made findings that seem to be written with Cholestin in mind --

> (1) improving the health status of United States citizens ranks at the top of the national priorities of the Federal Government;

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[10] *See* "The Pink Sheet" at T&G - 3, *FDC Reports* (October 20, 1997).

[11] Statement by President William J. Clinton, The White House (October 26, 1994).

(2) the importance of nutrition and the benefits of dietary supplements to health promotion and disease prevention have been documented increasingly in scientific studies;

(3)(A) there is a link between the ingestion of certain nutrients or dietary supplements and the prevention of chronic diseases such as cancer, heart disease, and osteoporosis; and

(B) clinical research has shown that several chronic diseases can be prevented simply with a healthful diet, such as a diet that is low in fat, saturated fat, cholesterol, and sodium, with a high proportion of plant-based foods;

(4) healthful diets may mitigate the need for expensive medical procedures, such as coronary by-pass surgery or angioplasty;

(5) preventive health measures, including education, good nutrition, and appropriate use of safe nutritional supplements will limit the incidence of chronic diseases, and reduce long-term health care expenditures;

(6)(A) promotion of good health and healthy lifestyles improves and extends lives while reducing health care expenditures; and

(B) reduction in health care expenditures is of paramount importance to the future of the country and the economic well-being of the country;

(7) there is growing need for emphasis on the dissemination of information linking nutrition and long-term good health;

(8) consumers should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements . . . .

(13) although the Federal Government should take swift action against products that are unsafe or adulterated, the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers;

(14) dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare; and

(15)(A) legislative action that protects the right to access of consumers and safe dietary supplements is necessary in order to promote wellness; and

(B) a rational Federal framework must be established to supersede the current ad hoc, patchwork regulatory policy on dietary supplements.

Congress knew what it was doing when it enacted DSHEA, and FDA's position on Cholestin severely undermines the framework that it constructed. For example --

- Under the agency's September 30 Letter, if a company advertises -- or even simply recognizes -- a natural beneficial constituent in a dietary supplement, FDA may deem the constituent, not the herb or food, to be the "article" at issue. This potentially threatens all dietary supplement constituents that are being studied for pharmaceutical use.

- FDA's decision sends the message that steps taken to standardize a product to ensure functionality, or research efforts to substantiate statements of nutritional support, may be considered evidence of an intent to market a drug product. This creates an incentive for industry to know *less* about its production processes, product content, and supplement functionality.

- FDA's position that the name "Cholestin" alone is an implied disease claim turns every mention of a body part or function on a dietary supplement into a potential implied drug claim for the prevention of a disease.

Clearly, the impact of FDA's decision on Congress's DSHEA framework, and thus the dietary supplement industry as a whole, could be devastating.

1. Cholestin is a Lawful Dietary Supplement Product.

As documented below, Cholestin meets all statutory requirements for a dietary supplement product under DSHEA.

a. Cholestin Meets All Compositional Requirements for a Dietary Supplement.

Food fermentation is an ancient science, and many cultures and civilizations have used fermentation to expand their dietary options.[12] Some well-documented fermentation processes include the making of cheeses, bread, and alcohol, all of which utilize yeast as a major ingredient. Red yeast rice is a traditional fermented food consumed in many Asian countries including China, Japan, Philippines, Indonesia, Malaysia, Thailand and Vietnam, as well as in the United States. Its food value is well known, and dates back more than a thousand years to the first century A.D.[13] In China, it is a common staple of the daily diet in southern coastal provinces such as Guangdong, Fujian, Zhejiang and Jiangsu.

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[12] C.W. Hesseltine, A millennium of Fungi, Food, and Fermentation Mycologia, Vol. LVII, No.2. P. 149-197. H.L. Wang and C.W. Hesseltine (U.S.D.A.), "Glossary of Indigenous Fermented Foods" Mycologia Memoir No. 1 1, Indigenous Fermented Foods of Non-Western Origin", eds. C.W. Hesseltine and H. L. Wang, Ch. 18, p.317-344. C.W. Hesseltine, "The future of fermented foods," Nutrition Reviews, 1983 Oct. 41(10):293-301. Attachment 5 is a compilation of historical and scientific literature on red yeast rice and mevinolin.

[13] H.-G. Meyer., Diplomarbeit, Saarbrucken.

The first document describing the use of red yeast fermented rice dates from 800 A.D. during the T'ang Dynasty of China. Several names, including Hung-Chu, Hong Qu, Ang-kak, Ankak rice, and Beni-Koji, are used as synonyms for this food product. Because of its flavor, aromatic fragrance, color and beneficial properties, red yeast rice is frequently used as a flavoring agent for a variety of Chinese dishes. Examples of recipes using red yeast rice are roast pork, roast duck, fermented bean curd, preserved dry fish and vegetable pork stew. Red yeast is also used widely for making Shioxing and Beni-Koji rice wine, and its ability to preserve the freshness of meat and fish is highly valued by Chinese chefs.

The traditional method of making red yeast rice is solid state fermentation[14] on cooked or uncooked non-glutinous whole rice kernel. The laborious traditional method for making red yeast rice was described in 1590 in the ancient Chinese Pharmacopoeia, "Ben Cao Gang Mu (Li Shi-Zhen, 1590) - Dan Shi Bu Yi" which also noted its health-promoting properties, such as improved blood circulation.[15] The following description of the ancient process is from T'IEN-KUNG K'Al -WU[16] (Chinese Technology in the Seventeenth Century):

> Grains of the common (i.e. non-glutinous) rice, whether of the early or late variety, are pounded and hulled to the most excellent whiteness and then soaked in water for seven days. When the odor has become unbearable, the grains are taken to a river and rinsed clean with the free flowing water (only the running water of mountain streams should be used; water from large rivers will not do).
>
> After washing, the odor still remains, but when the material is steamed in a pot it will change and give off a most fragrant aroma. When half cooked, the rice is taken out of the pot and quickly immersed in cold water. When the rice has cooled off, it is steamed again; this time being allowed to cook thoroughly.
>
> The cooked rice is placed together, several *tan* to a heap, for the addition of leaven. For making red yeast, the leaven must be manufactured from the best red colored wine mash at a proportion of one peck of mash to three pints of the natural juice of smartweed mixed in alum water. Two catties of this leaven are added to every tan of steamed rice while the latter is still hot, then mixed quickly by several pairs of hands until it has cooled. The mixture is allowed to stand for a considerable length of time under constant observation, so that the rice can be definitely fermented by the leaven. The occurrence of the fermentation in the mixture is indicated by a slight rise in its temperature. (In actual preparation), the steamed rice, mixing with leaven, is put in large bamboo baskets and washed once with an aqueous alum solution. The mixture is then divided into separate woven bamboo trays and placed on shelves in order to catch the breeze. From now on, the air will be the determining factor for culturing the yeast, fire and water exerting practically no influence. Each bamboo tray contains about five pints of the steamed rice. The room (in which

[14] C. W. Hesseltine., Solid State Fermentation-An Overview, International Biodeterioration 23 (1987) p. 79-89.

[15] G.A. Stuart., Chinese Materia Medica-Vegetable Kingdom. Southern Materials Center, Inc. (1979), P.233-234.

[16] Ying-Hsing Sung., T"IEN-KUNG K'Al-WU-Chinese Technology In The Seventeenth Century. The Penn. State Univ. Press. (1966) P.292-294.

> the trays are shelved) should be large and high-ceilinged, so as to keep the pressure of heat from the roof, and the room should face south so as to escape the (strong) afternoon sun. The material is stirred about three times in every two-hour period. For seven days, the people tending the yeast will stay constantly near the trays, never daring to sleep soundly and rising several times during the night.
>
> At first, the rice is snowy white, but after one or two days the color turns pitch black. From black it turns to brown, from brown to rust, from rust to red, and at brightest the red color again changes into a light yellow. With the help of air currents, the substance will go through all these stages of change right before one's eye, and this process is called "cultivation of yellow yeast." The yeast produced through such a process is twice as valuable and potent as ordinary yeast. The rice is washed once with water between the black and brown stages, and once more between the brown and red states. After it has turned red, however, it is not washed again.
>
> In making this yeast, it is necessary that the workers' hands, the trays and mats used, be absolutely clean. The slightest bit of dirt will bring the entire operation to ruin.

The *Monascus* yeast widely used in the production of red yeast rice first became known in Western society in the nineteen century through the work of Dutch scientists. When traveling in Java, these scientists observed the use of a red powder (*i.e.*, red yeast rice) for food preservation by the local population. They brought specimens back to Europe and found that the red powder contained a new species of fungi previously unidentified by Western botanists. Subsequent research led to the isolation and classification of various *Monascus* strains.[17] The first species of the genus *Monascus* was isolated, and the genus named, in 1884. In 1895, the species used to produce Cholestin, *Monascus purpureus* Went, was isolated from red yeast rice and described by F.A.F.C. Went. The pigments from this red yeast rice give certain Chinese foods their characteristic color.[18] Today there are more than 31 *Monascus* strains deposited in the American Type Culture Collection, of which 17 strains are reported as *Monascus purpureus* Went.

Monascus, a mold characterized by slow growth, has been demonstrated to be the predominant microorganism in red yeast rice. However, in ancient times, successful fermentation of *Monascus* was often problematic. Contamination by other fast-growing molds such as *Aspergillus* and *Rhizopus* was frequent and difficult to eliminate. Indeed, preservation and isolation of an optimal *Monascus* culture was impossible before this century. However, after extensive research and with the advent of modern analytical techniques to track fermentation procedures, scientists at Beijing University developed a thorough understanding of the ancient

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[17] F.A. F.C. Went., Le champignon de I'ang-quac. Une nouvelle the'le'bole'e. Ann. Sci. Nat. Bot. Ser. 8, 1: (1895) P.1-18. H. Nishikawa., Biochemistry of filamentous fungi. 1. Colouring matters of *Monascus purpureus* Went. J. Agricult. Chem. Soc. Jpn. 8 (1932), P. 10071015.

[18] A.D.G. Wowell, A. Robertson, and W.B. Whalley. Azaphilones, a general survey. Chem. Soc. Symp.(Spec. Publ.No.5) Chem. Soc. London. (1956) P. 27-35.

fermentation process and identified previously unrecognized factors that limit yield. They determined that red yeast rice yield is highly dependent on the following factors:

- Exposed surface area of the rice kernel;
- Air supply to the fermentation mixture;
- The type of selected pure *Monascus purpureus* Went strain used;
- Internal acidity of the rice kernel;
- The concentration of the amylase enzyme;
- The temperature of the mixture; and
- Contamination factors.

Although Pharmanex has learned from these insights, the process for making Cholestin, which uses a natural non-bioengineered single pure strain of *Monascus purpureus* Went yeast combined with non-glutinous rice, is remarkably similar to that employed for hundreds of years. The fermentation is carried out under strictly controlled conditions; and the absence of any competing contaminants greatly increases the yield. Through superior quality control, *but without deviating from traditional methodologies*, higher levels of red yeast per gram of rice than that produced in mixed strain ferments are obtained.

The Cholestin manufacturing process consists of the following steps, undertaken under quality-controlled conditions common to the food industry:

- Selected non-glutinous rice is first highly polished.
- Polished rice is crushed to 2 mm (approximate diameter) pieces.
- Rice is soaked in vinegar water (7 days) to reach an optimal internal pH.
- Rice is thoroughly rinsed to remove the acidic solution.
- Rice is semi-cooked and spread on a stainless steel tray.
- *Monascus purpureus* Went yeast, fortified with nutrients for rapid growth, is added to the rice.
- Air is pumped through the mixture, which is washed everyday to maintain a constant moisture level and to remove contaminants.
- Samples are tested on the seventh day for yeast levels and the density of the rice kernel.
- When the appropriate yeast level and rice kernel density are reached, the product is subject to final rinse and sterilization, then drying and milling.

As noted, until recently, making red yeast rice with the traditional benefits associated with the product was an art form. There were no quality control methods other than to measure the rice kernel density and visually to inspect the inside of the kernel to determine the yield of red yeast from a batch of fermentation product. However, the discovery of HMG-CoA reductase

inhibitors in red yeast rice provided a biochemical marker with which to monitor the level of yeast, including all of its beneficial constituents, in the manufacturing process. Thus, *total* HMG-CoA reductase inhibitors are used as a production measure to provide a standardized, high quality product.

Notwithstanding these refinements, Cholestin's components are neither concentrated by any method of extraction nor manipulated by any chemical procedure to increase the concentration of any particular natural constituent. It has been Pharmanex's purpose to produce, in a modern production setting, a traditional and beneficial Chinese food product, and to offer it as a dietary supplement. The end product is simply that Chinese food; the production methods and measurements ensure that the consumer gets a consistent, known product.

In the attached *Statement of Sanford A Miller, Ph.D.,* the former Director of FDA's Center for Food Safety and Applied Nutrition confirms that the fermentation process used by Pharmanex is a modern version of a traditional food processing technique, and that the quality control measures introduced by Pharmanex are common to the food industry. (Attachment 6).

In light of the above facts, Pharmanex's Cholestin product meets all statutory requirements for a dietary supplement under DSHEA --

- The red yeast rice in Cholestin is a "product . . . intended to supplement the diet" in that it is clearly labeled and marketed as a dietary supplement, and does not purport to be a drug. 21 U.S.C. § 321(ff)(1).

- Red yeast rice is a traditional "dietary substance for use by man to supplement [the] diet by increasing the total dietary intake" 21 U.S.C. § 321(ff)(1)(E).

- The presence of metabolites in a dietary supplement, or the use of such metabolites as a marker for yeast levels, does not alter the regulatory status of the product. Indeed, the definition of "dietary supplement" encompasses dietary ingredients that are "a concentrate, metabolite, constituent, extract, or combination of" any of the other specifically sanctioned categories of dietary supplement ingredients. 21 U.S.C. §321(ff)(1)(F).

- Consistent with Pharmanex's standardization efforts, DSHEA specifically requires greater standardization and application of more stringent specifications in the processing of dietary supplements by incorporating provisions relating to compliance with quality, purity and compositional representations. 21 U.S.C. § 343(r)(2)(F). The statute also permits specific percentage level claims for dietary ingredients. 21 U.S.C. § 343(s)(2)(D)-(E)

- Nothing in DSHEA prohibits dietary supplement companies from optimizing the manufacturing process for a product to maximize quality and functionality, and the introduction of modern food processing methods to an ancient food production process does not forfeit dietary supplement status. Indeed, DSHEA specifically permits the agency to promulgate good manufacturing practices (GMPs) for dietary supplements based upon current GMPs for food, and

the agency's Advance Notice of Proposed Rulemaking on dietary supplement GMPs is completely consistent with Pharmanex's quality control efforts.[19]

- From a food processing standpoint, there is really no difference between the use of the single, *Monascus purpureus* Went strain in Cholestin and the selection of a particular culture, from among a range of available cultures, to make yogurt. The selection of the *Monascus purpureus* Went strain certainly does not chemically alter traditional red yeast rice, and does not change the food status of the product. Moreover, the *Monascus purpureus* Went strain is just one of a number of strains used in red yeast foods that produce HMG-CoA reductase inhibitors.

- Even with respect to "new dietary ingredients" DSHEA specifically provides that a dietary supplement is not adulterated if it "contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered." 21 U.S.C. § 350b(a)(1). The legislative history of DSHEA specifically excludes from the term "chemically altered" "the following physical modifications: minor loss of volatile components, dehydration, lyophilization, milling, tincture or solution in water, slurry powder, or solid in suspension."[20] This exclusion clearly contemplates that even new dietary ingredients (which red yeast rice made with *Monascus purpureus* Went yeast is <u>not</u> because red yeast rice has always contained this and other *Monascus* strains) can be marketed if they represent a non-chemical alteration of a dietary ingredient present in the food supply.

In sum, Pharmanex's Cholestin product meets every legal parameter for a dietary supplement product.

b. Cholestin is Not Barred by Section 201(ff)(3) (21 U.S.C. § 321 (ff)(3)).

FDA, in apparent recognition that traditional red yeast rice naturally containing mevinolin satisfies all of the basic definitional parameters for a dietary supplement, has based its ruling on a strained reading of Section 201(ff)(3) of the FFDCA that in turn relies upon a selective review of the facts placed before the agency. Section 201(ff)(3) provides that the term "dietary supplement" --

> (3) does-
>
> "(A) 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 unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 402(f); and
>
> "(B) not include-

[19] 62 Fed. Reg. 5700 (February 6, 1997).

[20] 140 Cong. Rec. H11,179 (Oct. 6, 1994).

> "(i) an article that is approved as a new drug under section 505...or (ii) an article authorized for investigation as a new drug, antibiotic, or biological 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...marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this Act.

The agency's September 30 Letter states that, "in marketing Cholestin, Pharmanex intends to market, and in fact is marketing, "lovastatin," an article approved in 1987 pursuant to FFDCA Section 505 as the prescription drug "Mevacor."[21] The agency notes that Cholestin contains mevinolin levels -- which it equates chemically with lovastatin -- "that will result in significant administration of lovastatin." The agency also finds of importance the fact that "while not all strains of red rice yeast can produce lovastatin, Pharmanex uses one of the few strains that does to make Cholestin." The agency views these factors, and the fact that Pharmanex applies quality control measures to the traditional process, as evidencing the marketing of "lovastatin." The agency further states that "lovastatin" was not marketed as a food or dietary supplement in the United States prior to the approval of Merck's Mevacor™ in 1987, and thus is barred from dietary supplement status under DSHEA.

i. Pharmanex is Not Marketing Lovastatin

The agency approaches the issue with an inappropriate prescription drug orientation. Even if Pharmanex accepted the proposition that mevinolin is the same as lovastatin, Pharmanex has not marketed a lovastatin product. Pharmanex has consistently marketed Cholestin as containing a range of naturally occurring HMG-CoA reductase inhibitors, unsaturated fatty acids, and other constituents which provide the product's functionality. Moreover, rather than marketing a lovastatin drug product, Pharmanex has presented the product as providing a natural way to lower cholesterol *without drugs* and in the context of a healthy diet and exercise regimen. This is precisely what Congress envisioned when it framed DSHEA.

Where Pharmanex has used the term lovastatin, it was used to refer to the analogous -- *but not identical* -- natural substance, known as mevinolin. Moreover, it has usually been referenced in the context of a warning. Given that mevinolin and lovastatin are chemically similar, it is useful for consumers, pharmacists and physicians to understand that Cholestin contains HMG-CoA reductase inhibitors. As the agency is well aware, DSHEA specifically provides that the presence of directions, conditions of use and warnings on the label or in

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[21] FDA September 30 Letter at 3. In an argument worthy of a Kafka novel, the agency notes that Pharmanex provided the agency with tests documenting the presence of mevinolin in red yeast rice found on the U.S. market, and thus "the company recognizes lovastatin as the relevant compound." As noted in Pharmanex's August 5 letter to the agency, these samples and test results were submitted in response to the agency's statement that it could not locate red yeast rice products that naturally contained mevinolin.

labeling of a dietary supplement do not transform the product into a drug. 21 U.S.C. § 343(s). Surely the agency would not want to dissuade dietary supplement companies from providing such warnings. Indeed, FDA's Foods Advisory Committee has recommended the use of a warning for dietary supplements containing senna, which is also widely sold as an over-the-counter drug. The agency has also warned that willow bark dietary supplements containing salicylates may be unsuitable for children because of aspirin's link with Reye's syndrome. However, the agency has not contended that either of these dietary supplement ingredients are drug products because of such warnings.

The "article" Pharmanex is selling is red yeast rice containing its natural, beneficial constituents. Section 201(ff)(3) does not apply to Cholestin because the article -- red yeast rice -- has never been approved (or investigated) as a new drug. Pharmanex does not manufacture or sell isolated mevinolin or any other isolated constituent of red yeast rice. As noted, a Cholestin capsule is composed of red yeast rice made from the traditional method. Pharmanex applies quality control and efficiency measures to standardize the product, but no chemical alteration takes place.

The use of the term "article" to include an overall product rather than its components is common in the definitional sections of the FDCA. Section 201(k) defines a device as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related *article*." (emphasis added). This definition refers unmistakably to finished products. Similarly, cosmetics are defined in § 201(i) as "*articles* intended to be rubbed, poured, sprinkled or sprayed on, introduced into, or otherwise applied to the human body . . . " The terms "label" and "labeling" are defined as written, printed, or graphic matter that is either "upon the immediate container of any article," upon "any of its containers or wrappers," or "accompanying such article."[22] Again, these provisions can be read to encompass overall products. The FDCA routinely contemplates the use of the term "article" for that purpose.

FDA's attempt to read the term "article" Section 201 (ff)(3) as including "components" is without effect -- red yeast rice is in fact the only "component" in Cholestin dietary supplement. Mevinolin is not an isolated product. Rather, it is a natural constituent that is part of the supplement -- it is not the "article" itself. FDA has likewise recognized a distinction in the food context between ingredients -- such as food additives -- and constituents of such ingredients.[23]

The agency's September 30 Letter argues that because "finished drug products always contain inactive ingredients, excipients, and other substances other than the approved active ingredient...then manufacturers of purported dietary supplements could always avoid the constraints imposed by FDCA 201(ff)(3) by ensuring that their article differs from an approved

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[22] 21 U.S.C. § 201 §§ (k),(m).

[23] *See, e.g., Scott v. Food and Drug Administration,* 728 F.2d 322 (6th Cir., 1984) (affirming FDA's determination that the color additive Delaney Clause did not apply to constituents).

drug product by one or more inactive ingredients or excipients."[24] This statement is indicative of FDA's failure to consider carefully the nature of the Cholestin product. Simply put, Pharmanex is not arguing that FDA could not take action against ground Mevacor™ added to an herbal base -- but that is not the Cholestin product. Mevinolin is just one of a number of *natural* constituents in red yeast rice/Cholestin -- including at least nine other HMG-CoA reductase inhibitors. It is not an isolated substance to which inactives and/or excipients have been added. Any other interpretation would be nonsensical and leave any biologically active substance in the food supply potentially subject to being considered a drug by FDA.

The agency cites L-carnitine for the proposition that a dietary supplement marketed prior to the approval of a pharmaceutical version of the same substance is lawfully a dietary supplement under Section 201(ff)(3).[25] Pharmanex agrees. However, L-carnitine marketed alone as a dietary supplement or as an ingredient in a multi-ingredient supplement is not the proper analogy. Rather, the agency's position on Cholestin is the equivalent of objecting to a protein supplement that naturally contains L-carnitine as a constituent because a drug containing L-carnitine as an active ingredient has obtained FDA approval.

Even if mevinolin were a separable "article" for purposes of Section 201(ff)(3), it is not the same "article" as the drug Mevacor™. Mevinolin is a substance found in nature, without manipulation such as isolation, purification and crystallization. This natural metabolite must be distinguished from the isolated, purified, and crystallized compound identified as lovastatin and marketed as the drug Mevacor™. As noted in the attached letter from Dennis J. McKenna, Ph.D., a prominent pharmacognosist --

> ...The fact that Cholestin™ contains HMG-CoA reductase inhibitors, of which mevinolin is one of approximately ten similar compounds, does not make it "equivalent" to the prescription pharmaceutical, lovastatin. Cholestin™ also contains a variety of other compounds with biological activity, such as carotenoids, vitamins, minerals, essential fatty acids, etc. Some of these constituents exist in significantly greater quantities than mevinolin. Cholestin™ therefore cannot be construed to be identical to lovastatin.
>
> Many commonly consumed foods contain biologically active substances that have activities that are similar to prescription medicines. Examples include the estrogenic flavonoids genistein and diadzein, found in soy products and many other foods, anticoagulant coumarin derivatives similar to the prescription medication Warfarin, curcumin and other antiinflammatory curcuminoids found in turmeric, the analgesic capsaicin from cayenne peppers, the antibiotic quinic acid found in cranberry juice. All of these biologically active compounds occur in common foods at physiologically active levels. Many of them have actions on the body that are similar to prescription medications....

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24 FDA September 30 Letter at 6-7.

25 FDA September 30 Letter at 4 n. 5.

> Another example could be cited in L-DOPA (1-3,4-dihydroxyphenylalanine), the active ingredient in several prescription anti-Parkinson's medications (*e.g.*, Dopar, Larodopa). L-DOPA is also a common constituent of many leguminous vegetables (Mucuna species, Vicia species, Astragalus species etc.) as well as bananas (Musa species). The recommended dose for pharmaceutical preparations of L-DOPA (500 to 1000 mg/day) is comparable to the daily intake that one might receive, for example, from a hearty serving of broad beans. Vicia faba has been reported to contain up to 25, 000 ppm of L-DOPA, so a serving of as little as 20 grams could be equivalent to the minimum recommended dose of L-DOPA...

Letter from Dennis J. McKenna, Ph.D. to Dr. Michael Chang, Chief Scientific Officer, Pharmanex, Inc. (October 19, 1997) (Attachment 7).

Pharmanex has attached letters and affidavits from the following world-renowned experts in the field of chemistry, all stating that mevinolin and lovostatin are very different compounds --

- **Carl Djerassi, Ph.D.**, Professor of Chemistry, Stanford University, Awarded the National Medal of Science and the Priestley Award (the highest award of the American Chemical Society) (Pharmanex founder and Scientific Advisory Board Chair) (Attachment 8)

- **Lester A. Mitscher, Ph.D.**, Distinguished Professor, Kansas University Department of Medicinal Chemistry (Member, Pharmanex Scientific Advisory Board) (Attachment 9)

- **Koji Nakanishi, Ph.D.**, Centennial Professor of Chemistry, Columbia University (Member, Pharmanex Scientific Advisory Board) (Attachment 10)

- **Chi-Huey Wong, Ph.D.**, Professor and Ernest W. Hahn Chair in Chemistry, The Scripps Research Institute (Attachment 11)

As Drs. Djerassi and Mitscher note, the agency's distinction with respect to the term "article" would appear to contradict its own policies in the drug context. In particular, the agency's reasoning on Cholestin runs directly contrary to the position the agency took when it decided to prevent the approval of generic forms of Premarin. In that case, FDA decided that because the drug Premarin was a complex amalgam of naturally occurring estrogens from mares' urine, purer, synthetic forms of estrogens could not be considered the equivalent product.[26]

Even if Section 201(ff)(3) were applicable, Cholestin™ would clearly qualify as a dietary supplement because red yeast rice -- including red yeast rice naturally containing mevinolin -- was marketed as a food and a dietary supplement (in light of the long-recognized benefits of red

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[26] Memorandum from Janet Woodcock, M.D., Director, FDA Center for Drug Evaluation and Research, to Douglas L. Sporn, Director, FDA Office of Generic Drugs, "Approvability of Synthetic Generic Version of Premarin" (May 5, 1997).

yeast rice consumption), both in the United States and abroad -- long before Mevacor™ was approved as a drug.

Indeed, it appears that the earliest reported attempt to manufacture red yeast rice in the United States -- in 1920 -- was undertaken by Margaret B. Church, an employee of the Bureau of Chemistry, U.S. Department of Agriculture -- **the direct predecessor to the Food and Drug Administration.** Moreover, the fungus species used in the production of Cholestin, *Monascus purpureus* Went, is specifically referenced in this 1920 study, entitled *Laboratory Experiments on the Manufacture of Chinese Ang-Khak* [red yeast rice] *in the United States,* as the fungus used to produce red yeast rice in China, and it is the strain employed in Church's production efforts.[27] The article notes that "[n]otwithstanding the competing organisms, *Monascus purpureus* has always been successfully isolated from Chinese red cheeses, which are colored with red rice." Upon successful completion of a batch of red yeast rice, Church notes that the result "may without hesitation be called American-made Chinese ang-khak." The scientific literature independently documents that the strain used in this 1920 effort, *Monascus purpureus* Went, produces mevinolin.[28]

In addition to the market information on red yeast rice discussed below, this 1920 study is only one example of a compelling body of scientific literature indicating that mevinolin has always been in red yeast rice (and other foods) in significant quantities. For example --

- In a 1986 study entitled *Productivity of Monacolin K (Mevinolin) in the Genus Monascus*[29], the authors tested 124 strains of the genus *Monascus* for production of mevinolin. Three of the nine strains of *Monascus purpureus* tested were found to produce mevinolin. Virtually all of the species tested -- including *Monascus purpureus* -- are strains long used in food. The authors specifically note that of the 18 species tested, "all 16 species other than *Monascus ruber* and *Monascus pazi* were isolated by Nobuyoshi Sato in the 1930s, mainly from red koji-related food products in China, Hong Kong, and Taiwan" and that "[f]rom a mycological standpoint, *M. purpureus* is similar to *M. anka*, and is a typical koji mold that has been used in China since ancient times."

- The ability to produce HMG-CoA reductase inhibitors has been found to be "wide-spread among fungi originating from different taxonomic groups and habitats."[30] In a 1993 study which screened 380 fungal strains of 50 different genera and 143 species, at least

[27] Church, M.B. (1920). "Laboratory Experiments on the Manufacture of Chinese ang-Khak in the United States." The Journal of Industrial and Engineering Chemistry 12(1): 45-46. (Attachment 12)

[28] *See, e.g.*, Juzlova, P., L. Martinkova, and V. Kren. (1996). "Secondary metabolites of the fungus *Monascus*: a review." Journal of Industrial Microbiology 16: 163-170. (Attachment 13)

[29] Negishi, S., et al. (1986), "Productivity of Monacolin K (Mevinolin) in the Genus *Monascus*" Fermentation Engineering 64:509-512. (Attachment 14)

[30] Gunde-Cimerman, et al. (1995) "A hydroxymethylglutaryl-CoA reductase inhibitor synthesized by yeasts." FEMS Microbiology Letters 132:39-43, 39. (Attachment 15)

22 percent tested positive by HPLC analysis for the presence of mevinolin.[31] In another study, mevinolin was found in the fruiting bodies of a widely consumed mushroom at very high levels.[32]

Nevertheless, FDA attempts to counter the fact that Pharmanex previously produced two samples of red yeast rice with mevinolin for the agency by producing affidavits that purportedly undermine Pharmanex's position. In fact, the agency's affidavits are ambiguous and do not support the agency's position. One, from Maypro Industries, a supplier of bulk nutritional supplements, confirms that in 1994 Maypro marketed red yeast rice containing mevinolin, albeit without great success, at trade shows in the United States. (Attachment 1). Moreover, Maypro's brochure specifically notes the broad use of red yeast rice ("Beni-Koji") -- including red yeast rice from *Monascus purpureus* yeast strains -- in Asian foods, and the fact that "it is well known that Beni-Koji fungi such as M. Pilosis produces Monacolin [another term for mevinolin], which disturbs the synthesis of cholesterol." (Attachment 18)

The other affidavit obtained by FDA, from Kamwo Herb & Tea Company, Inc. (formerly Kamwo Trading Company, Inc.), in essence states that Kamwo had red yeast rice available and readily quoted a price to a customer. (Attachment 1) The letter confirms that Tom Leung of Kamwo sent a letter noting that the product could legally be sold. Although the affidavit states that red yeast rice is "not a normal stock item", the affidavit does not address the fact that the letter in question, dated October 16, 1996, stated that Kamwo Trading Company had been selling red yeast rice made with *Monascus purpureus* "to ethnic food shops and other herbal product customers" for at least seven years, "primarily for the purpose of supplementing the diet." This letter was provided to the agency on August 5, 1997. The agency attempts to undermine this letter as merely stating that "Kamwo can get [red yeast rice] if someone wants it." However, FDA's September 30 Letter does not address the fact that Pharmanex readily obtained a sample from Kamwo, a part of which was also provided to FDA on August 5, 1997.

Despite the fact that the agency's affidavits actually support Pharmanex, FDA attempts to use the affidavits to counter the ample evidence that red yeast rice with mevinolin was marketed well before Mevacor™. It is important to note that the samples provided to the agency were submitted to document the availability of red yeast rice containing mevinolin on the current U.S. market, even though the agency had failed in its attempt to find it. However, these samples are merely two trees in a forest of information submitted by Pharmanex indicating that mevinolin has naturally been present at significant levels in red yeast rice -- and a range of other food products sold in the United States -- for decades before 1987.

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[31] Gunde-Cimerman, J., J. Friedrich, et al. (1993), "Screening fungi for the production of an inhibitor of HMG CoA reductase: Production of mevinolin by the fungi of the genus Pleurotus." FEMS Microbiology Letters 111: 203-206. (Attachment 16)

[32] Gunde-Cimerman, N., A. Plemenitas, *et al.* (1993). "Pleurotus fruiting bodies contain the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase-lovastatin." Exp Mycol 19(1): 1-6. (Attachment 17)

Nevertheless, we have attached additional documentation as to the long history of exportation of red yeast rice containing mevinolin to the United States. This documentation includes --

- Statements from two of the largest manufacturers of red yeast rice in China, Fujian Province Gutian County Red Yeast Factory and Yiwu Natural Pigment Industrial Corporation (Attachment 19), both of which produce red yeast rice containing mevinolin (analyses included in Attachment 19). The Fujian Province statement notes that "[s]ince 1965" their red yeast rice "has been sold in Japan, Canada, U.S.A., many countries in Southeast Asia, and Hong Kong, Macao, and Taiwan." The Yiwu Natural Pigment Industrial Corporation statement notes that "[s]ince 1984, we have exported our products to the United States and European countries." The quantity of red yeast pigment, red yeast rice, and red yeast powder we export each year is over 1,600 tons." Both statements note that their products are known for blood circulation/cholesterol lowering effects.

- Tests of red yeast rice from four other companies in Asia, indicating significant levels of mevinolin. (Attachment 20).

- Additional tests demonstrating the mevinolin content of seven brands of red yeast rice currently on the market in the United States, along with a copy of the receipts for product purchases and the product labels. (Attachment 21).

- Statements of four retailers/importers/exporters of red yeast rice in the United States. (Attachment 22).

- Importation records indicating significant shipments of red yeast rice into U.S. ports. (Attachment 23).

- Analyses of mevinolin content of brands of oyster mushrooms long marketed in the United States, with labels and receipts. (Attachment 24).

- A statement of the Beijing Science and Technology Commission noting the long history of traditional red yeast rice production and the fact that some red yeast strains used by Chinese manufacturers produce HMG-CoA reductase inhibitors. (Attachment 25) The statement also notes that the beneficial health effects of red yeast rice come from many different classes of compounds in the product.

FDA cannot dismiss this presence of mevinolin in the food supply -- including in red yeast rice -- prior to 1987 as "*de minimis*." If one looked only at mevinolin content, which Pharmanex did at agency's request, the levels of mevinolin found in red yeast rice in this country are far from *de minimis*. As Pharmanex noted in its July 18 letter to the agency, it is likely that many persons in parts of Asia -- and likely some consumers in this country -- regularly consume much *more* mevinolin as a constituent of red yeast rice than would a U.S. consumer from Cholestin dietary supplement consumption. This is particularly likely if one considers that there are other significant natural dietary sources of mevinolin. Given its fairly widespread occurence

in the food supply and significant levels of consumption in the large U.S. Asian community,[33] it is likely that mevinolin and other natural HMG-CoA reductase inhibitors in red yeast rice have been consumed for decades in the United States at levels far exceeding that of constituents in many dietary supplements found on shelves throughout this country. (*See* Statements of John Fieschko, Ph.D., Keith H. Steinkraus, Ph.D., and Henry C. Lim, Ph.D. (Attachment 26)).

Nevertheless, in its September 30 Letter, FDA suggests that such a *de minimis* proviso could apply under Sections 201(ff)(3) in that no red yeast rice has been marketed with the levels of mevinolin found in Cholestin. To support this interpretation, the agency cites the decision of the D.C. Circuit in *Public Citizen v. Young*, 831 F.2d 1108 (1987) *cert denied* 485 U.S. 1006 (1988). This reference is puzzling in that the court in *Public Citizen* ruled that the statutory provision then in question -- the Delaney Clause -- does *not* contain a *de minimis* exception.

The language of § 201(ff)(3) does not admit itself of a *de minimis* exception. There is nothing in either its plain meaning or its limited legislative history to indicate that FDA was given discretion in applying the definition that it set forth. The relevant language merely states that a product was, prior to approval by FDA as a drug or biologic, "marketed as a dietary supplement or as a food." 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."

While the *Public Citizen* case does not support the position that FDA claims, it is nonetheless instructive on this point. The court articulated two considerations in determining whether a statute contains a *de minimis* exception: the language and plain meaning of the statute, and the purpose of the act and whether the application of its literal terms would lead to absurd, futile or inconsistent results. The court found the language of the Delaney Clause to be unyielding -- if FDA found that a substance might induce cancer, it could not list it for use in cosmetics. Congress made no provision for agency discretion. The language of Section 201(ff)(3) is similar in that there is no indication that agency discretion is to apply. Indeed, if it were, Congress presumably would have identified some principle or standard upon which it is to be based.

Perhaps most significant, the court in *Public Citizen* articulated the conditions under which the *de minimis* exception is not to apply. "[T]he doctrine obviously is not available to thwart a statutory command; it must be interpreted with a view to 'implementing the legislative design.'" *Id.* at 1113. The plain statutory command of DSHEA is to make the benefits of foods previously used by only a small portion of the population more broadly available to American consumers. FDA's suggestion that it can carve out a *de minimis* exception would thwart that command.

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[33] The Asian-American community in the United States (including Pacific Islanders), was 9.2 million in 1995, including 1.65 million Chinese-Americans. *1996 World Book Almanac*, p. 386, Funk & Wagnalls, New Jersey (1995).

ii. Section 201(ff)(3) Includes No Geographical Limitation

Although Pharmanex has documented a long history of marketing of red yeast rice in the United States, the standard for satisfaction of Section 201(ff)(3) requires only that an article be "marketed as a dietary supplement or a food" prior to the drug product in question. Unlike in the new dietary ingredient provision of DSHEA, the statute does not specify U.S. marketing, and the centuries of marketing of red yeast rice containing mevinolin in Asia are fully relevant. Even in the case of a statutory provision which required a finding of "common use" in food -- a much higher burden than in Section 201(ff)(3) -- FDA has been prohibited from writing a geographical limitation into the FFDCA.[34]

iii. Pharmanex Does Not Add Lovastatin to Cholestin

In Pharmanex's discussions with FDA regarding Cholestin, the agency has periodically suggested that the company somehow "spikes" Cholestin by adding mevinolin to the product. That allegation is simply wrong. The scientific literature documents that mevinolin is naturally present in a variety of foods, including red yeast rice made by the traditional process with *Monascus purpureus* Went, and Pharmanex has provided extensive evidence of its presence at significant levels in the U.S. food supply. If these facts are not sufficient, Pharmanex would gladly permit agency representatives to witness the production of the Cholestin red yeast rice at our facility in China, and the end result can be tested for mevinolin content. In lieu of such a visit, we have attached a sworn *Affidavit of Michael Chang* that "no mevinolin or any substance other than those traditionally used to produce red yeast rice (*Monascus purpureus* Went yeast, rice, vinegar, nutrients, and water) is added in the process for making Cholestin" and "[a]ll of the constituents of the red yeast rice, to the full extent present in the product, are a natural result of the red yeast rice fermentation process." (Attachment 27).

iv. Pharmanex Is Entitled to Standardize its Product Under DSHEA.

FDA's September 30 Letter finds that Cholestin can be deprived of its status as a dietary supplement because Pharmanex has standardized its manufacturing process.[35] This position on standardization is fundamentally at odds with the terms of DSHEA.

In DSHEA, Congress specifically authorized dietary supplements to make "percentage level claims" regarding the percentage of a nutrient or ingredient contained in the product. 21 U.S.C. 343(r)(2)(F). In order to make truthful percentage level claims, a manufacturer must standardize its manufacturing process. Without standardization, it would not be possible to attain the stated percentage levels consistently and uniformly. Section 403(a) prohibits any false or misleading statements on food or dietary supplement labels. As such, any percentage level claim

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[34] *Fmali Herb v. Heckler*, 715 F.2d 1385, 1390 (9th Cir. 1983).

[35] *See* FDA September 30 Letter at 4.

made under Section 403(r)(2)(F) is subject to substantiation. The only way to substantiate a percentage level claim is standardization.

As stated by Judge Miles in the Cholestin trademark litigation "[T]he HMG-CoA reductase inhibitors, or statins, present in Cholestin are natural by-products."[36] FDA's September 30 Letter never disputes this fact, and it would be impossible for the agency to do so. As Judge Miles found, all of the constituents of Cholestin are naturally occurring. Pharmanex engages in no chemical alteration, isolation or crystallization in producing Cholestin.

However, under DSHEA, Pharmanex could manufacture a dietary supplement that was "a concentrate, metabolite, constituent, [or] extract" of any herb, botanical or other dietary substance. 21 U.S.C. 321(ff)(1)(F). In other words, DSHEA allows Pharmanex to manufacture dietary supplements by "concentrating" or "extracting" the naturally occurring statins or other ingredients in red yeast rice, or by isolating particular "metabolites" and "constituents" in the dietary substance. But Pharmanex does not go nearly as far as the law allows. Instead of concentrating, extracting or isolating any of the naturally occurring constituents of red yeast rice, the Company merely standardizes its production process so that a consistent level of yeast -- including all beneficial constituents -- is found on the rice. Accordingly, FDA's cannot disqualify Cholestin as a dietary supplement based on Pharmanex's manufacturing process.

c. Cholestin is Safe

Cholestin's safety and functionality has been the subject of extensive research. In particular, the cholesterol-related statements of nutritional support for Cholestin are substantiated by a total of 17 clinical studies in China, including 8 controlled and 9 open-label trials, each measuring changes in total cholesterol, triglycerides, and HDL cholesterol. In the United States, a double-blind, placebo-controlled study recently conducted at the University of California at Los Angeles School of Medicine further substantiates the product's safety and functionality. The UCLA study report has been submitted for publication and thus cannot be submitted to the agency at this time.

Given this level of research, it is perhaps not surprising that the agency has never directly called into question the safety of the Cholestin product. Nevertheless, FDA's September 30 Letter states that the agency believes that any dietary supplement product for cholesterol-lowering is unsafe for over-the-counter sale due to lack of active physician supervision. Such an assertion cannot satisfy FDA's specific statutory burden under DSHEA with respect to dietary supplement safety --

- DSHEA amended the FFDCA to provide, *inter alia*, that a dietary supplement product is "adulterated" if "it is a dietary supplement or contains a dietary ingredient that presents a significant or unreasonable risk of illness or injury under conditions of use recommended

[36] *Pharmacia & Upjohn Company v. Generation Health d/b/a Pharmanex, Inc.*, 44 USPQ 2d 1091, 1098.

or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use[.]" *See* FFDCA Section 402(f)(1)(A)(i-ii), codified at 21 U.S.C. §342(f)(1)(A)(i-ii). Thus, the plain language of this provision requires the FDA to consider whether the *particular product* when used *as recommended* presents a "significant or unreasonable risk of illness or injury." A vague concern regarding physician supervision will not suffice.

- Although FDA may continue to regulate adulterated dietary supplements under the general adulteration provision Section 402(a)(1), it may do so only under the conditions set out at FFDCA Section 402(f)(1)(D), codified at 21 U.S.C. § 343(f)(1)(D), which require the agency to meet this burden with respect to the uses recommended on the label of a particular dietary supplement product, not merely as to a conceivable range of uses.

- Finally, in relevant part, FFDCA Section 402(f)(1)(D), codified at 21 U.S.C. § 342(f)(1)(D),[37] provides that in any adulteration action, the FDA "shall bear the burden of proof in each element to show that a dietary supplement is adulterated." This provision charges the FDA with the burden of proving that a particular dietary supplement product is adulterated, thereby requiring the government to prove each element of the adulteration provision before taking action against a particular dietary supplement product. Id.; see also SENATE REPORT 103-410 (October 8, 1994) (emphasizing that a primary objective of DSHEA is "to make clear that the FDA bears the burden of proving that a dietary supplement product is not safe before removing it from the marketplace").

Given the extensive information documenting the safety of Cholestin, as well as Pharmanex's responsible practices with respect to product labeling, FDA simply cannot find Cholestin unsafe under the FFDCA.

d. A Federal Court Has Already Determined That Cholestin is a Lawful Product

On July 11, 1997, Judge Wendell A. Miles of the United States District Court, Western District of Michigan, carefully considered the dietary supplement status of Cholestin in the context of the Pharmacia & Upjohn Company's claim that the Cholestin trademark infringed Upjohn's Colestid™ mark. (Attachment 3) In denying Pharmacia & Upjohn's Motion for Preliminary Injunction, the Court determined "[t]hat Colestid and Cholestin are not direct competitors is confirmed not only by their differing compositions and appeal to consumers, but also by their indications and recommended usage." After hearing extensive testimony on Cholestin's regulatory status, composition and labeling, the court stated --

[37] This section also provides that "The court shall decide any issue under this paragraph on a de novo basis." Thus in a judicial proceeding involving an FDA challenge to the safety of a dietary supplement, a reviewing court can no longer defer to the administrative record, but must decide each issue on the basis of the evidence presented in court.

> Upjohn argues that because Pharmanex's product claims for Cholestin "look and sound like drug claims," the product is actually a drug which competes with Colestid. However, Pharmanex's promotional materials for Cholestin do not tout the product as a drug; to the contrary, they characterize it as natural and drug-free. Upjohn points to other factors which it argues suggest that Pharmanex is promoting Cholestin as a drug, including prominent product warnings, in particular a warning that Cholestin contains "HMG-CoA reductase inhibitors e.g., lovastatin" which "have been associated with some rare but serious side effects, including serious diseases of the liver and skeletal muscle." However, the HMG-CoA reductase inhibitors, or statins, present in Cholestin are natural by-products. They are not the isolated, crystallized lovastatin present as the active ingredient in the prescription drug Mevacor. Moreover, the placement of product warnings on packaging materials is a prudent practice which does not transform a dietary supplement into a dangerous drug.[38]

Overall, this opinion provides an important confirmation that Cholestin is properly marketed as a dietary supplement, and has a legitimate and important role that clearly differs from drug products intended for treatment of hypercholesterolemia and heart disease.

2. Congress Recognized and Intended that Dietary Supplements Such as Cholestin Should Play an Important Role to Promote and Maintain Health.

As noted, when Congress enacted DSHEA, it found that certain dietary supplements could prevent chronic diseases such as heart disease. *See* 21 U.S.C. 321 note. In addition, Congress recognized that preventive health measures, including appropriate use of safe nutritional supplements, would limit the incidence of chronic diseases and reduce long-term health care expenditures. For these reasons, among others reflected in DSHEA, Congress intended that consumers should be empowered to make health care choices based on information about the health benefits of particular dietary supplements. Indeed, Cholestin's natural cholesterol-lowering function meshes perfectly with the letter and spirit of DSHEA.

FDA, on the other hand, appears to be penalizing Cholestin because it actually lowers cholesterol levels. If so, FDA is frustrating the purposes of DSHEA. As stated in DSHEA, "the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers." While the public must be protected from unsafe or adulterated products, DSHEA clearly authorized the sale of dietary supplements, such as Cholestin, that are made under quality-controlled conditions to ensure a standardized, beneficial product.

Moreover, DSHEA plainly intended to promote a scientific approach to the manufacture and sale of dietary supplements. For example, it authorized manufacturers to describe or characterize the role of a dietary supplement in affecting the structure or function of the human body. It authorized manufacturers to state -- right on the label -- what percentage of a nutrient or ingredient is contained in their products. Obviously, a manufacturer cannot make a truthful

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[38] 44 USPQ 2d 1091, 1098..

claim about the percentage levels of nutrient content unless the manufacturer can standardize its manufacturing process to uniformly achieve such levels. Similarly, Congress indicated that dietary supplement manufacturers should follow scientific methods and procedures by authorizing FDA to prescribe good manufacturing practices for supplements.

FDA, again, appears to be penalizing Pharmanex's science-based approach to dietary supplements. This contradicts the intent of Congress to promote a more scientific and rational regulatory regime for dietary supplements. Perhaps most significantly, FDA is penalizing the public, which could certainly benefit from having access to an all natural, relatively inexpensive cholesterol-lowering dietary supplement.

3. DSHEA Permits Statements of Nutritional Support Regarding the Maintenance and Promotion of Healthy Cholesterol Levels.

Pharmanex makes no claims that are prohibited by the FFDCA. To the contrary, Cholestin's claims are well within the parameters of DSHEA's amendments to the FFDCA. The vast majority of the scientific and medical community believes that the promotion and maintenance of healthy cholesterol levels is an important public health goal. In achieving that goal, it is essential that consumers have available a broad range of approaches, including diet, exercise, lifestyle changes and, when necessary, drug therapy. However, the approval of drug therapies for cholesterol reduction in individuals with a disease state does not preclude a legitimate role for dietary supplements that affect, and are labeled as affecting, the structure or functions of the body relating to cholesterol.

In fact, the current scientific knowledge and public health recommendations regarding cholesterol -- including the recommendations of the National Cholesterol Education Program (NCEP) of the National Heart, Lung and Blood Institute of the National Institutes of Health -- are wholly consistent with properly substantiated statements of nutritional support on dietary supplement products relating to the reduction of cholesterol. Under the NCEP recommendations, total cholesterol levels below 200 mg/dL are classified as "desirable blood cholesterol." Total cholesterol levels between 200 and 239 mg/dL are classified as "borderline-high blood cholesterol," and total cholesterol levels above 240 mg/dL are classified as "high blood cholesterol." The primary recommendation for individuals with borderline-high blood cholesterol is dietary modification (which implicitly can include the consumption of dietary supplements), to promote and maintain normal cholesterol levels. Insofar as cholesterol levels in the 200-239 mg/dL range can be considered "normal" in millions of Americans, drug therapy is not indicated for most of that population.

Thus, the current scientific understanding of cholesterol levels, and the methods recommended for evaluating and lowering them, indicate that there is a distinction between individuals with borderline-high blood cholesterol levels and high blood cholesterol levels (both in terms of total blood cholesterol and lipoprotein composition). The latter have cholesterol levels that are sufficiently high that they present a disease state that should, in many cases, be addressed by drug therapy. The former group is treated as a matter of nutrition, not unlike a weight level that should be lowered but is not a disease.

In support of its position on cholesterol-related statements of nutritional support for dietary supplements, Pharmanex has attached the statements and *Curricula Vitae* of three prominent experts in the area of cholesterol. (Attachment 28).

- **David Heber, M.D. , Ph.D., FACP, FACN**, Professor of Medicine and Public Health and Director, UCLA Center for Human Nutrition, UCLA School of Medicine. (Member, Pharmanex Scientific Advisory Board)

- **James M. Rippe, M.D.**, Professor of Medicine, Tufts University School of Medicine, Director of the Center for Clinical and Lifestyle Research in Shrewsbury Massachusetts. (Member, Pharmanex Scientific Advisory Board)

- **David Maron, M.D.**, Director, Preventive Cardiology, Assistant Professor of Medicine, Vanderbilt University Medical Center

These experts all conclude that there is an appropriate role for dietary supplements in the promotion and maintenance of healthy cholesterol levels, particularly with respect to the many Americans who do not have hypercholesterolemia or heart disease and for whom drug treatment is not indicated.

Consistent with these views, Pharmanex does not claim that Cholestin prevents or mitigates heart disease or hypercholesterolemia. Rather, Pharmanex truthfully claims that Cholestin promotes healthy cholesterol levels as part of a program of prudent diet and exercise. *This is clearly a claim about Cholestin's affect on the structure or function of the human body, which is expressly authorized by DSHEA.* Cholestin is not marketed as a substitute or alternative to drug therapy. It is targeted only to individuals whose cholesterol levels are under 240 mg/dL. People with cholesterol levels in this range are not considered to have a disease; rather, they are outside of the "ideal" range. Nothing in FDA's September 30 Letter, or the relevant medical literature, supports the proposition that a regimen which moves individuals from a borderline high cholesterol level down to an ideal level would be the "mitigation or prevention" of a disease. In any case, people with cholesterol levels under 240 mg/dL -- Cholestin's target consumers -- are not suffering from hypercholesterolemia as implied in FDA's September 30 Letter.

FDA argues in its September 30 Letter, at 9-10, that cholesterol reduction claims are inherently implied claims to mitigate or prevent hypercholesterolemia and arterial build-up because "the ability to remove a substance that could cause disease . . . from the body, is a disease prevention claim." *Id.* This argument is also off base. It flies in the face of the provision in DSHEA authorizing dietary supplement manufacturers to make claims "describing the role of a nutrient or dietary ingredient intended to affect the structure or function in humans." 21 U.S.C. 343(r)(6)(A). A statement about the health of any organ can be twisted into an implied prevention claim, but this is not what Congress said.

The FFDCA provides the statutory framework for FDA's authority to regulate product claims. The statute, as amended by such laws as the Nutrition Labeling and Education Act (NLEA) and DSHEA, allows different categories of claims for foods, drugs and supplements. There are three basic types of claims relevant to the analysis here: (i) drug or "disease" claims; (ii) health claims; and (iii) statements of nutritional support. The category into which product claims are placed is an important factor in determining whether the product will be regulated as a food, drug or dietary supplement.

a. Drug, Disease and Health Claims

Since its enactment, the FDCA has defined "drug" to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man..."[39] It is from this part of the definition that the term "disease claim" is taken. If a "disease claim" is made for a product, that product is, by definition, a drug. Pre-DSHEA, disease claims, and thus the scope of the "drug" category, were interpreted fairly broadly. For instance, FDA prevailed in categorizing garlic tablets as drugs on the strength of claims that "two or three tablets a day offer a convenient method" for including garlic in the diet, despite the fact that no therapeutic value was claimed and no disease connection was mentioned.[40]

Health claims are so called because they describe the relationship between a nutrient and a specific "disease or health-related condition."[41] The NLEA, enacted in 1990, formalized the health claims definition and established that "health claims" are authorized only if pre-approved by the FDA and authorized in a regulation.[42] Health claims are significant in that they allow communication of a product-disease connection without forcing the product into the "drug" category. Essentially, health claims state that an article reduces the risk of chronic disease.

Given the process required for health claim approval, however, it is not surprising that relatively few such claims have been FDA-approved. In order for FDA to authorize a health claim, it must first determine that there is "significant scientific agreement" among experts qualified by training and experience to evaluate the validity of the claim. Despite controversy surrounding the issue for several years, FDA ultimately promulgated final regulations in 1994 which applied the same approval standard for health claims to supplements as that for foods.[43]

b. Structure/Function Claims

The term "structure/function" claim as it is currently used originates in the DSHEA "statements of nutritional support" ("SNS") provisions for dietary supplements: statements may

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39 21 U.S.C. §321(g)(1)(B).

40 *United States v. 150 Packages. . . Bush Mulso Tablets*, 83 F. Supp. 875 (E.D.Mo. 1947).

41 Id. at §343(r)(1).

42 Pub. Law No. 101-535, 104 Stat 2353 (1990).

43 59 Fed. Reg. 395 (1994).

be made for supplements if they "describe the role of a nutrient or dietary ingredient intended to affect the *structure or function* in humans. . .."[44] The FDCA drug definition has included similar language for decades, however, which meant that "articles (other than food) intended to affect the structure or function of the body of man" were to be regulated pre-DSHEA as drugs. *The essential difference between a SNS and a health claim is the mention of disease.*

There are many pre-DSHEA federal cases which confirmed the status of various products as drugs based to some degree on structure or function claims.[45] A 1960's case, *Vitasafe*, illustrates the how broadly drug "structure or function" claims were interpreted. In that case, vitamin and mineral capsules were held to be misbranded in part because of "lipotropic factors" claims which purported to affect the mobilization of fat in the liver.[46] Such claims were held to affect the "structure or function" of part of the body and therefore qualified the products as drugs under the FDCA drug definition.[47]

Because that prong of the FDCA drug definition applied to "articles (other than food),"[48] industry argued that, by implication, such claims could be made for foods as long as diseases were not mentioned.[49] Courts never fully confirmed this position, however, and undermined the argument for supplements by holding that foods were limited to products with "taste, aroma and nutritive value."[50] Herbal products and other supplements were subject to inconsistent court decisions and FDA determinations for many years, and existed until 1994 in an ambiguous legal state.

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[44] 21 U.S.C. §343(r)(6)(A)(emphasis added).

[45] *See United States v. An Article . . . Labeled In Part "Line Away, Temporary Wrinkle Smoother"*, 284 F. Supp. 107 (1968)(holding "temporary wrinkle smoother" is a claim showing the product is intended to affect the structure of the body and is therefore a drug); *United States v. Articles of Drug . . . Silogen and Zymaferm*, 1975-1977 FDLI Jud. Rec. 79 (D. Neb. 1976)(holding products designed to improve animal digestion and milk production were drugs in that they were designed to affect the function -- digestion -- of animals); and *United States v. an Undetermined Number... Vitasafe Formula M*1*, 226 F. Supp. 266, 279 (D.N.J. 1964); *remanded on other grounds, United States v. Vitasafe Corp.*, 345 F.2d 864 (3d Cir. 1965); *cert. denied, Vitasafe Corp. v. United States*, 382 U.S. 918 (1965).

[46] *Vitasafe Formula M*1*, 226 F. Supp. 266, 279.

[47] *Id. citing* 21 U.S.C. §321(g)(1)(C).

[48] §321(g)(1)(C)(emphasis added).

[49] I. Scott Bass and Anthony L. Young, *Dietary Supplement Health and Education Act: A Legislative History and Analysis*, 4 (1996).

[50] *Nutrilab v. Schweiker*, 713 F.2d 335, 338 (7th Cir. 1983); *See American Products Co. v. Hayes, 744 F.2d 912 (2d Cir. 1984).*

DSHEA was enacted in 1994 to create a new framework for the regulation of dietary supplements and supersede the "ad hoc patchwork regulatory policy"[51] on supplements which had been in place up to that point. DSHEA affirmed the status of dietary supplements as foods[52] (albeit a new statutory class of foods) and explicitly provided that supplement manufacturers could make statements of nutritional support, including "structure/function" claims, without causing their products to be classified automatically as drugs.[53] A "structure/function" claim may be made as long as FDA is notified within 30 days of marketing, the manufacturer possesses adequate substantiation and the product contains a disclaimer that (i) FDA has not evaluated the claim and (ii) the product is not intended to "diagnose, treat, cure, or prevent any disease."[54]

Since DSHEA confirmed dietary supplements' status as "foods," a legal distinction between drugs and supplements depends on the differences that can be drawn between "structure/function" claims and "disease" claims. The pre-DSHEA cases do not make this distinction, because there was no distinction to make with respect to most dietary supplements -- until DSHEA, structure/function and disease claims (with limited food exceptions) existed largely in the realm of drug products.

c. DSHEA Created A New Regime

DSHEA marked a different approach to the regulation of dietary supplements than the regime in existence before 1994, in part by establishing an additional category of claims which could be made for these products. The court in *Nutritional Health Alliance* understood the impact of the 1994 statute: "the mandates and tone of the DSHEA signal a shift toward *a more permissive approach to health claims* on labels."[55] The court continued, noting that the "government charged with promoting the food supply and the rights of consumers have paradoxically limited the information to make healthful choices in an area that means a great deal to over 100 million people."[56]

The legislative history of DSHEA[57] further demonstrates that the statute was intended to maximize consumer choice by allowing safe supplements to be marketed more easily. When

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51 Pub. L. 103-417, Sec 2(15)(B).

52 §§321(ff) and 411(c)(1)(B)(ii).

53 21 U.S.C. § 343(r)(6).

54 *Id.*

55 *Nutritional Health Alliance and Soo Man Shim d/b/a New Nutrisserie v. Donna Shalala, Sec'y U.S. Dept. HHS and David Kessler, Commissioner FDA*, 953 F. Supp. 526, 528 (S.D.N.Y. 1997) (emphasis added).

56 *Id.*

57 The legislative history of DSHEA officially agreed upon by Congress was limited by agreement of the bill sponsors to a one page statement. *Statement of Agreement*, P.L. 103-417, U.S.C.A.N., p. 3523. Use of the term "legislative history" in this memorandum refers more

introducing testimony on dietary supplements in 1993, Congressman Henry Waxman acknowledged that FDA had received "mixed signals" from Congress and the public on how best to regulate supplements and that it was time to formalize a consistent regulatory approach to the issue.[58] He said that his hope was to use the legislative process to "guarantee safe dietary supplements as long as they make no unproven claims."[59] DSHEA was the result of years of continued debate on House and Senate bills and testimony representing all perspectives. In passing DSHEA, Congress specifically intended to facilitate consumer access to safe dietary supplements, recognizing that "legislative action . . . is necessary to promote wellness."[60]

Senator Hatch remarked in his introduction of the Senate bill that "[i]n our free market society, consumers should be able to purchase dietary supplements and companies should be able to sell them these products so long as the labeling and advertising are truthful, nonmisleading, and there exists a reasonable scientific basis for product claims."[61] Even the inclusion of the word "Education" in the title of the Act is suggestive of DSHEA's intended function as a facilitator of increased consumer access to information. DSHEA's preamble states explicitly that "the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers,"[62] and this language was emphasized in the recent *Nutritional Health Alliance* opinion.[63]

As long as a disease state is not mentioned, DSHEA allows "structure/function" statements through which a manufacturer may claim that its products affect the structure or function of the body in a manner "linked" to health-related benefits.[64] Congress' purposes for DSHEA were undeniably to facilitate consumers' knowledge about, and access to, dietary supplements as "preventative health measures" and to limit unnecessary regulatory barriers.

FDA must now acknowledge that Congress has changed the statutory landscape and react accordingly. Substantiated statements of nutritional support for safe dietary supplements relating to both "good" bodily functions and health risk-related functions are now permitted by federal statute.

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broadly to early drafts of legislation, testimony, transcripts of Committee proceedings and the like.

58 Hearing Before the Subcommittee on Health and the Environment on H.R. 509, H.R. 1709 and S. 784 - Bills to Amend the FDCA to Establish Provisions and Standards Regrading the Composition and Labeling of Dietary Supplements, 103rd Congress, 1st Sess., July 29, 1993 (Introductory statements of Representative Henry Waxman).

59 *Id.*

60 Pub. L. 103-417, Sec 2(15)(A).

61 Remarks of Sen. Orrin Hatch, Introduction of S. 764, Cong. Rec, S 4577, April 7, 1993.

62 Pub. Law 103-417 § 2.

63 953 F. Supp. 526, 528 (S.D.N.Y. 1997).

64 Pub. Law 103-417, 108 Stat. 4325, §2.

d. FDA and Dietary Supplement Commission Support for Cholesterol Claims

FDA's September 30 Letter states, at 9-10, that cholesterol reduction claims are "disease" claims. However, the agency has not been internally consistent on this point, and the September 30 position also conflicts with the view expressed by the Dietary Supplement Commission created pursuant to DSHEA. Although FDA has sent "courtesy letters" objecting to certain cholesterol claims, in many other instances it has apparently withheld objection to similar claims. In one Courtesy Letter, the Office of Special Nutritionals made a "general comment" that "reduce blood cholesterol" may be an appropriate supplement claim when coupled with promotion of a "healthful diet useful in reducing blood cholesterol."[65] Pharmanex's claims for Cholestin have always been made in conjunction with recommendations to couple supplement use with a healthy diet. For instance, Cholestin packaging reads "Cholestin is intended for use as part of a multiple cholesterol maintenance program that includes a healthy diet that is restricted in saturated fat and cholesterol . . ."

At an industry conference on structure/function claims held in February of 1996, Dr. Elizabeth Yetley, Director of the Office of Special Nutritionals, asserted that a "cholesterol reduction" claim can be "either a food or a drug claim," depending on the context.[66] Her example of the "drug context" was a claim to treat hypercholesterolemia.[67] Pharmanex, however, has not made any such claims. Cholestin has been marketed explicitly as a supplement for individuals with blood cholesterol levels below those for which a physician would advise medication. The claims Pharmanex has made for Cholestin concern cholesterol levels in the range under 240 mg/dL. These are below any threshhold for disease and are not, therefore, the sort of claims which Dr. Yetley indicated would trigger the regulation as a drug.

In June of 1997, the Commission on Dietary Supplement Labels released its much-anticipated Draft Report.[68] The Commission was authorized by DSHEA as an independent agency within the executive branch[69], and it was convened to consider and make recommendations for the regulation of label claims for dietary supplements. The Commission is

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[65] Letter from Robert J. Moore, Office of Special Nutritionals/CFSAN, FDA to Alan B. Clemetson, M.D., December 16, 1996.

[66] Transcript of Conference Audio Recordings, "Dr. Yetley Response", NNFA Conference (February 29 - March 1, 1996).

[67] *Id.*

[68] Commission on Dietary Supplement Labels, *Commission on Dietary Supplement Labels Report to the President, the Congress, and the Secretary of the Department of Health and Human Services*, Draft for Public Comment, June 1997.

[69] Pub. Law 103-417, Sec. 12 (1994).

an expert panel, and the expectation of Congress[70], FDA and industry has been that the Commission's recommendations will be given great weight by FDA.

In the Draft Report of the Commission, members were supportive of legitimate supplement cholesterol claims, noting that:

> "FDA took the position [prior to DSHEA] that virtually any statement relating to cholesterol would be interpreted as a claim relating to the prevention of heart disease. These Commissioners believe that this position may need reconsideration in light of DSHEA and that *it would be possible to craft a statement of nutritional support regarding the maintenance of healthy blood cholesterol levels that is a statement of nutritional support and not a health or drug claim.*"[71]

This position is exactly correct: it makes no sense, post-DSHEA, to characterize all cholesterol claims as drug claims on the ground that they are implied heart disease claims when DSHEA explicitly touts the importance of lowering the incidence of chronic disease "such as. . . heart disease" through the use of supplements.[72] In attempting to strike the right balance between public protection and public access to information and safe products, DSHEA does not allow direct "disease" claims such as "Cholestin will prevent heart disease." It does, however, allow the claims Pharmanex makes for Cholestin, which describe the effect the product will have on a function of the body -- in this case, the effect of Cholestin on blood cholesterol levels.

e. Analysis of Cholestin's Claims

As discussed above, the enactment of DSHEA meant that disease claims may not be made for dietary supplements, but that supplements may incorporate claims that the product will affect bodily "structure or function." The claims Pharmanex has made for Cholestin are "structure/function" claims because they represent that the product will affect the level of cholesterol in the blood. Pharmanex has made claims that the product will "restrict production of cholesterol in the liver", where 80 percent of the body's cholesterol is produced. Cholesterol is synthesized in the body through a series of chemical reactions and is an ongoing function involving alternating increases and reductions in cholesterol levels.[73] Production of cholesterol in the liver is therefore a function of the human body and claims to affect cholesterol levels are intended to affect this function.

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[70] Congress gave the Commission the task of "evaluat[ing] how best to provide truthful, scientifically valid, and nonmisleading information to consumers so [they] may make informed and appropriate health care choices" and incorporating its findings in the Report. Id.

[71] *Id.* at p. 33, (emphasis added).

[72] Pub. Law 103-417, § 2.

[73] National Cholesterol Education Program, *Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults*, Appendix III, NIH 1993.

A federal court ruling supports the reasoning that liver processes, in particular, are a "structure or function" of the human body. When ruling on claims made for a vitamin capsules that the product would effect the "mobilization of fat . . . in the liver" the court noted that this was an effect on the structure and function of the human body.[74] Just as liver fat production is a "function" of the body, so is production of cholesterol in the liver. Because claims made for Cholestin are aimed at effecting cholesterol levels and not a disease, they are exactly the sort of claim allowed by DSHEA's structure/function provision.[75]

i. Cholestin's Claims Are Not Disease Claims

Despite FDA's assertions in the September 30 Letter, at 9-10, Pharmanex does not make marketing claims for Cholestin that state that the product will prevent, cure, treat or mitigate heart disease, heart attacks, arterial build-up, or hypercholesterolemia, and this fact is important in classifying the claims. The level of cholesterol in the blood is not a disease, but rather an ongoing function of the human body. Hypercholesterolemia describes abnormally high blood levels of cholesterol in the "high risk" range, generally considered to be above 240 mg/dL.[76] Indeed, even hypercholesterolemia, standing alone, is not defined medically as a disease, but merely describes a certain level of cholesterol in the cells and plasma of circulating blood.[77] Pharmanex has not made claims for hypercholesterolemia or any disease, but has instead positioned the product with claims to "maintain healthy cholesterol" and "reduce total cholesterol."

Because Pharmanex has not made direct disease claims, the question must be analyzed in terms of whether Pharmanex has made implicit heart disease claims for Cholestin that convert it from a lawful dietary supplement to an unapproved new drug. First, there are levels of health which are less than optimal, but are not characterized as "disease" until they reach a certain level of severity and bodily dysfunction. For instance, ten extra pounds is a nuisance, 200 extra pounds is dangerous obesity. A person who wishes to maintain optimal levels of blood cholesterol to increase the chances of prolonged health is simply not the same as one ingesting a substance to treat a disease. This distinction lies at the heart of DSHEA. DSHEA was premised on the idea that Americans could lead longer, healthier lives through the maintenance of healthy habits and safe supplement use.[78] To infer a disease (and therefore a "drug" or

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[74] *Vitasafe,* 266 F.Supp. 266, 278. The court held that the products were drugs, based in part on its pre-DSHEA classification of the structure/function claims as drug claims.

[75] 21 U.S.C. §343(r)(6).

[76] Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, National Cholesterol Education Program, pp. I-17, IA-3; Stedman's Medical Dictionary, 25th Ed. (1990). Cases of familial hypercholesterolemia may result in levels of up to 350 mg/dL.

[77] Stedman's Medical Dictionary, 25th Ed (1990).

[78] Pub. L. 103-417, §2.

unapproved "health") claim from those made by Pharmanex for cholesterol would strip DSHEA of its intended meaning and effect. Cholestin is exactly the sort of product to which DSHEA intended to give the public greater access in order to promote better health.

ii. Pharmanex Has Made No References to any Disease in its Marketing of Cholestin and this Is Legally Significant Under DSHEA

Explicit use or prohibition of particular words is important in various instances throughout the FFDCA. DSHEA allows manufacturers to market dietary supplements that are intended to affect the structure or function of the body. 21 U.S.C. 343(r)(6)(A). Prior to DSHEA, however, such a product would have fallen within the definition of drug if it did not otherwise have taste, aroma or nutritional value. Following DSHEA, a dietary supplement intended to affect the structure or function of the body will not be a "drug" (on that basis alone), so long as the manufacturer prints the statutory disclaimer on the label stating that the product is "not intended to prevent a disease." 21 U.S.C. 343(r)(6)C). But as Congress directly recognized in DSHEA, there is a "link between . . . dietary supplements and the prevention of chronic diseases such as cancer, heart disease and osteoporosis." 21 U.S.C. 321 note. Therefore, DSHEA has established a regulatory framework that permits dietary supplements to have health-related effects on the structure or function of the body, and play a role in the prevention of disease as articulated in DSHEA's preamble, provided that the product (1) expressly states that it is a dietary supplement, (2) expressly disclaims that it is intended to prevent disease, and (3) does not expressly draw the link between the supplement and the disease.

Pharmanex's claims for Cholestin do not mention or identify any disease. Rather, Cholestin's claims are permissible statements about the impact of the product on the structure or function of the body. The fact that relevant structures or functions of the body -- cholesterol production -- may be "linked" to chronic disease is fully consistent with the prescriptions of DSHEA.

f. FDA's Policies on OTC Drugs for Hypercholesterolemia Are Not Relevant to Cholestin

In support of its position that "over-the-counter products offered to prevent or reduce high cholesterol levels are drugs" FDA's September 30 Letter cites a Health Fraud Bulletin predating the enactment of DSHEA.[79] As noted, Pharmanex does not market Cholestin "for the prevention or reduction of high cholesterol levels." The Cholestin consumer has cholesterol levels that are

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[79] FDA September 30 Letter at 10 *citing FDA, Health Fraud Bulletin Number 18* (March 22, 1993) (hereinafter "Bulletin"). The agency's citation to this Bulletin makes quite clear that the agency's attempt to frame its decision as tentative cannot succeed -- the 1993 Bulletin notifies the FDA field offices that the Health Fraud Staff is "prepared to accept Warning Letter recommendations based upon documentation of the marketing of OTC products promoted to...reduce high cholesterol levels or any similar or related claim" and provides specific statutory violations to charge in such Warning Letters. Bulletin at 2.

not at a high, *i.e.*, disease, level, and Cholestin does not claim prevention of disease. The agency's citation to this pre-DSHEA policy clearly demonstrates the agency's refusal to update its policies to reflect Congress's newer DSHEA framework.

Moreover, although FDA recently decided to prohibit the over-the-counter sale of drug products for hypercholesterolemia, that judgment is not relevant to the Cholestin matter.[80] FDA cannot use a policy developed in the drug/disease context to negate Congress's clear direction that dietary supplement products meeting the DSHEA dietary supplement definition may bear statements of nutritional support that describe the role of a dietary ingredient intended to affect the structure or function in humans (*i.e.*, the body's production of cholesterol). [81]

g. The First Amendment Protects Cholestin Claims Made by Pharmanex

Not only is FDA's attempt to classify the Cholestin statements of nutritional support as "drug" claims inconsistent with current law, but FDA's suggested application of the statute raises serious First Amendment concerns. The claims in Cholestin's labels and labeling are constitutionally protected as commercial speech, and Courts have held that FDA's ability to restrict product claims is not unlimited. In *Rubin v. Coors*, the Supreme Court was unanimous in deciding that a federal regulation prohibiting the disclosure of alcohol content in malt beverage labeling violated the First Amendment.[82] The opinion rests on the idea that the government may not deprive consumers of truthful information for their own good.[83] In *Nutritional Health Alliance v. Shalala*, the court held that the First Amendment did not allow FDA to prohibit" presumptively valid, non-misleading health claims" for an indefinite period of time.[84] No federal court has addressed thus far the present question regarding the constitutional limits of supplement statements of nutritional support restriction, but the cases cited above are important in recognizing that FDA's "public health" rationale only goes so far. In classifying Cholestin's cholesterol statements of nutritional support as drug claims, when DSHEA's preamble warns against unnecessary government restriction, Cholestin clearly meets the definition of a dietary supplement, and Pharmanex provides a safe, beneficial product for public consumption, FDA is reaching too far.

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[80] FDA September 30 Letter at 5, *citing* FDA, *Guidance for Industry: OTC Treatment of Hypercholesterolemia* (September 1997).

[81] Although FDA takes the position that products for lowering cholesterol levels are inappropriate for over-the-counter use, in 1993 the agency approved a cholesterol test for home use by consumers without a prescription.

[82] *Rubin v. Coors Brewing Co.*, 115 S. Ct. 1585 (1995).

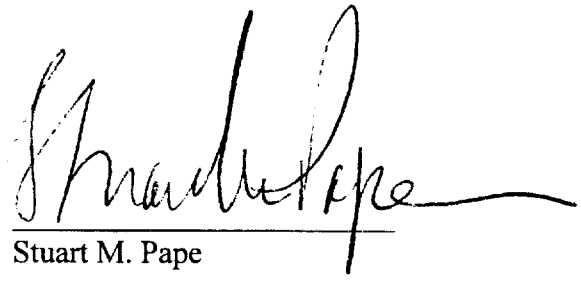
[83] *See generally* Lars Noah and Barbara Noah, *Liberating Commercial Speech: Product Labeling Controls and the First Amendment*, 47 Fla. L. Rev. 63 (1995).

[84] *Nutritional Health Alliance and Soo Man Shim d/b/a New Nutrisserie v. Shalala and Kessler*, 953 F. Supp. 526, 531 (S.D.N.Y. 1997).

FDA's attempt to classify the Cholestin claims as drug or unapproved health claims is contrary to statutory mandate, constitutionally suspect, and does not further the goal of public health protection. The claims Pharmanex has made for Cholestin are directed toward the "structure or function" of the body -- namely, the effect on blood cholesterol levels -- and, thus, these claims are permitted by DSHEA for dietary supplements. The level of cholesterol in an individual's blood is not a "disease", except in the extreme case of hypercholesterolemia. Not all people with elevated cholesterol develop hypercholesterolemia or cardiovascular disease, and Cholestin claims do not suggest the product will "diagnose, treat, cure, or prevent"[85] these conditions. The product is instead positioned as an aid in maintaining optimum cholesterol levels over time to promote good health. FDA must therefore comply with DSHEA and further the goal of public health by allowing Pharmanex to continue marketing Cholestin as a supplement with appropriate cholesterol statements of nutritional support.

Conclusion and Request for Prompt Action

FDA's decision on the regulatory status of Cholestin is contrary to law. The harm caused by the agency's decision -- harm to the public, the dietary supplement industry, and Pharmanex -- is serious and continuing. In good faith, Pharmanex asks FDA to stay all enforcement actions based on its Cholestin decision while the matter is reviewed in a voluntary Citizen Petition process. Alternatively, although we believe the agency's September 30 decision is legally final agency action, we ask FDA to recognize that the Cholestin product is lawful and a Citizen Petition process unnecessary.



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[85] Such claims are specifically prohibited by 21 U.S.C. § 343(r)(6).