

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 98P-0683]

Food Labeling: Health Claims; Soy Protein and Coronary Heart Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is authorizing the use, on food labels and in food labeling, of health claims on the association between soy protein and reduced risk of coronary heart disease (CHD). Based on its review of evidence submitted with comments to the proposed rule, as well as evidence described in the proposed rule, the agency has concluded that soy protein included in a diet low in saturated fat and cholesterol may reduce the risk of CHD by lowering blood cholesterol levels.

DATES: This regulation is effective October 26, 1999, except for § 101.82(c)(2)(ii)(B), which contains information collection requirements that have not been approved by the Office of Management and Budget (OMB). Upon approval, the FDA will publish a document in the **Federal Register** announcing the effective date of those requirements.

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SUPPLEMENTARY INFORMATION:

I. Background Information

On November 8, 1990, the President signed into law the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) (Public Law 101-535). This new law amended the Federal Food, Drug, and Cosmetic Act (the act) in a number of important ways. One notable aspect of the 1990 amendments was that they provided procedures whereby FDA is to regulate health claims on food labels and in food labeling.

In the **Federal Register** of January 6, 1993 (58 FR 2478), FDA issued a final rule that implemented the health claim provisions of the act (hereinafter referred to as the 1993 health claims final rule). In that final rule, FDA adopted § 101.14 (21 CFR 101.14), which sets out rules for the authorization and use of health claims by regulation. Additionally, § 101.70 (21

CFR 101.70) establishes a process for petitioning the agency to authorize by regulation the use of health claims about a substance-disease relationship (§ 101.70(a)) and sets out the types of information that any such petition must include (§ 101.70(f)).

In response to the 1990 amendments, FDA also conducted an extensive review of the evidence on 10 substance-disease relationships. As a result of its review, FDA has authorized claims for 8 of these 10 relationships, one of which focused on the relationship between dietary saturated fat and cholesterol and reduced risk of CHD. CHD is the most common, most frequently reported, and most serious form of cardiovascular disease (CVD) (58 FR 2739, January 6, 1993). Further, although the agency denied the use on food labeling of health claims relating dietary fiber to reduced risk of CVD (58 FR 2552), it authorized a health claim relating diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products that contain dietary fiber (particularly soluble fiber) to a reduced risk of CHD.

In the proposed rule entitled "Health Claims and Label Statements; Lipids and Cardiovascular Disease" (56 FR 60727, November 27, 1991) (hereinafter referred to as the saturated fat/cholesterol proposed rule), FDA set out criteria for evaluating evidence on diet and CVD relationships. The agency focused on those aspects of the dietary lipid and CVD relationship for which the strongest scientific evidence and agreement existed. FDA noted that, because of the public health importance of CHD, identification of "modifiable" risk factors for CHD had been the subject of considerable research and public policy attention. The agency also noted that there is general agreement that elevated blood cholesterol levels are one of the major "modifiable" risk factors in the development of CHD. FDA cited Federal Government and other reviews that concluded that there is substantial epidemiologic and clinical evidence that high blood levels of total and low density lipoprotein (LDL)-cholesterol are a cause of atherosclerosis and represent major contributors to CHD. Further, factors that decrease total blood cholesterol and LDL-cholesterol will also decrease the risk of CHD. FDA concluded that it is generally accepted that blood total and LDL-cholesterol levels are major risk factors for CHD, and that dietary factors affecting blood cholesterol levels affect the risk of CHD. High intakes of dietary saturated fat and, to a lesser degree, of dietary cholesterol are consistently associated with elevated blood cholesterol levels. FDA

tentatively concluded that the publicly available data supported an association between diets low in saturated fat and cholesterol and reduced risk of CHD (56 FR 60727 at 60737), and it confirmed that conclusion in the saturated fat/cholesterol final rule (58 FR 2739 at 2751).

Based on its review using the stated criteria, and on its consideration of comments received in response to the proposed rule entitled "Health Claims; Dietary Fiber and Cardiovascular Disease" (56 FR 60582), FDA concluded that the publicly available scientific information supported an association between diets low in saturated fat and cholesterol and high in fruits, vegetables, and grain products (*i.e.*, foods that are low in saturated fat and cholesterol and that are good sources of dietary fiber) and reduced risk of heart disease (58 FR 2552 at 2572). In the 1993 dietary fiber and CVD final rule, in response to a comment regarding the apparent hypocholesterolemic properties of specific food fibers, FDA again articulated its criteria for evaluating diet and CHD relationships (58 FR 2552 at 2567). FDA agreed that the effectiveness of naturally occurring fibers in foods in reducing the risk of CHD may be documented for specific food products. Further, the agency indicated that if manufacturers could document, through appropriate studies, that dietary consumption of the soluble fiber in a particular food has a beneficial effect on blood lipids predictive of CHD risk, they should petition for a health claim for that particular product. In response to two petitions that documented such evidence, FDA has authorized health claims for soluble fiber from certain foods and reduced risk of CHD in § 101.81 (21 CFR 101.81) (62 FR 3600, January 23, 1997, and amended at 62 FR 15344, March 31, 1997, and 62 FR 8119, February 18, 1998).

In the **Federal Register** of November 10, 1998 (63 FR 62977), and in response to a petition from Protein Technologies International, Inc. (Ref. 1 and Ref. 2), the agency proposed § 101.82 to provide for health claims on the relationship of soy protein and reduced risk of CHD (hereinafter referred to as the soy protein proposed rule). In the soy protein proposed rule, FDA considered the relevant scientific studies and data presented in the petition as part of its review of the scientific literature on soy protein and CHD. The agency summarized this evidence in the soy protein proposed rule and presented the rationale for a health claim on this food-disease relationship as provided for under the significant scientific

agreement standard in section 403(r)(3)(B)(i) of the act and § 101.14(c) of FDA's regulations.

Proposed § 101.82(c)(2)(ii)(A) identified the substance that is the subject of the proposed claim as soy protein from the legume seed *Glycine max*. The soy protein proposed rule included qualifying criteria for the purpose of identifying soy protein-containing foods eligible to bear the proposed health claim. The proposal also specified mandatory content for health claim statements; identified additional, optional information for such statements; and provided model health claims.

In its evaluation of the scientific evidence for a relationship between consumption of soy protein and blood total and LDL-cholesterol levels, the agency found the data suggestive but not sufficient to establish a dose-response for this relationship. However, the agency did find consistent, clinically significant reductions of total and LDL-cholesterol levels in controlled trials that used at least 25 grams (g) of soy protein per day. Thus, the agency proposed to base the qualifying level of soy protein on a total daily intake of 25 g, as suggested by the petitioner.

Therefore, in § 101.82(c)(2)(iii)(A), FDA proposed the qualifying criterion for a food to bear the claim as 6.25 g of soy protein per reference amount customarily consumed (RACC) (i.e., 25 g divided by 4 eating occasions per day).

In the soy protein proposed rule, FDA had tentatively indicated its intention to use a specific analytical method to measure soy protein for assessing compliance with the qualifying criterion. Comments persuaded the agency that the method would be inadequate for many products.

Therefore, in the **Federal Register** of August 23, 1999 (64 FR 45932), FDA issued a proposed rule to provide for an alternative procedure for assessing compliance (hereinafter referred to as the soy protein reproposal). In the soy protein reproposal, in § 101.82(c)(2)(ii)(B) FDA proposed that it would rely on measurement of total protein and require manufacturers, when soy is not the sole source of protein in foods, to maintain records that document the amount of soy protein in products and to make these records available to appropriate regulatory officials for inspection and copying upon request.

II. Summary of Comments and the Agency's Responses

In response to the soy protein proposed rule, the agency received approximately 130 submissions, each

containing one or more comments, from consumers, consumer organizations, professional organizations, government agencies, industry, trade associations, health care professionals, and research scientists.

About half of these submissions supported the proposed rule without providing grounds for this support other than those provided by FDA in the preamble to the soy protein proposed rule. The majority of the remaining comments were generally supportive, but requested modification of one or more provisions of the proposed rule. Some comments provided additional data on the relationship between soy protein and CHD, including one submission, originally submitted as a health claim petition and converted to a comment on the soy protein proposed rule (Ref. 3), that included a comprehensive review of available scientific evidence about the relationship. Some of the comments that disagreed with the soy protein proposed rule provided specific support for their positions. Some of the comments were received after the date for submitting comments had passed. Although the agency is not obligated to respond to late comments, in the interest of assessing the totality of the available data, it has considered each of these comments to the extent that it provided complete information for review or references accessible to the agency and addressed issues not raised in earlier comments. The agency has summarized and addressed the relevant issues raised in the comments in the sections of this document that follow.

In response to the soy protein reproposal, the Agency received approximately 10 submissions, each containing one or more comments. The agency has summarized and addressed these comments in section II.C.2 of this document.

A. Eligibility of Soy Protein as the Subject of a Health Claim

In the soy protein proposed rule, the agency assessed whether soy protein satisfied the preliminary requirement that a substance that is the subject of a health claim is associated with a disease for which the U.S. population is at risk (63 FR 62977 at 62978). Based on analyses presented in earlier rulemakings and its review of data on the mortality, morbidity, and costs of CHD and prevalence of "high risk" and "borderline high" total and LDL-cholesterol levels in the United States (Refs. 4 through 8), the agency tentatively concluded that, as required in § 101.14(b)(1), CHD is a disease for which the U.S. population is at risk.

One comment reviewed additional sources of information and reached the same conclusion.

In the soy protein proposed rule, FDA also tentatively concluded that soy protein from *Glycine max* satisfied the preliminary requirement of § 101.14(b)(3)(i) that the substance be a food that contributes taste, aroma, or nutritive value (63 FR 62977 at 62978). Sources of soy protein identified in the soy protein proposed rule included foods composed of or derived from whole soybeans and foods that contain processed soy protein ingredients: Isolated soy protein (ISP), soy protein concentrate (SPC), soy flour (SF), texturized soy protein, or texturized vegetable protein (TVP). In addition to protein, these foods and ingredients contain other naturally occurring soy constituents, such as isoflavones, fiber, and saponins. The specific processing steps employed determine the extent of retention of such naturally occurring constituents in the final product.

In assessing whether the petitioner had demonstrated that soy protein is safe and lawful at the level necessary to justify the claim, FDA noted that the petitioner stated that soy protein ingredients were in common use in food before January 1, 1958, and that they are generally recognized as safe (GRAS) by self-determination (63 FR 62977 at 62978). Because the fractionation procedures used to convert vegetable flours to vegetable protein isolates and concentrates were commonplace prior to 1958, the petitioner also asserted that ISP and SPC can be defined as soy flour "subject only to conventional processing as practiced prior to January 1, 1958." In addition, FDA reviewed information submitted by the petitioner about potential risks of consuming soy products: allergenicity (Refs. 9 and 10), exposure to trypsin inhibitors (Refs. 11 through 16), reduced bioavailability of minerals (Refs. 13, 17, 18, 19, and 20), and hormonal disturbances due to soy isoflavones (Refs. 21 through 26). Based on the totality of the evidence and, in particular, its common use in food, the agency did not take issue with the petitioner's view that the use of soy protein is safe and lawful as required in § 101.14(b)(3)(i). Thus, FDA tentatively concluded that the petitioner provided evidence that satisfied the requirement in § 101.14(b)(3)(ii) that use of soy protein at the levels necessary to justify a claim is safe and lawful under the applicable food safety provisions of the act (63 FR 62977 at 62979).

Several comments agreed with the agency's conclusion and some provided the rationale for their support. A number of comments disputed the

petitioner's assertion of GRAS status for soy protein and raised questions about the safety of soy protein-containing foods. The specific aspects of disagreement are summarized and discussed in the following sections of this document.

1. Concerns About the Safety of Soy Protein-Based Infant Formulas

(Comment 1). Many of the comments that raised concerns about the safety of consuming soy protein-containing foods addressed the safety of soy protein-based infant formulas. The observed or hypothesized detrimental effects of such formulas discussed in these comments included: hormonal disturbances due to estrogenic effects of soy isoflavones; thyroid abnormalities; altered mineral balance, especially for zinc; and diabetogenic effects in infants.

FDA is aware of concerns raised about the safety of soy infant formulas, but notes that these are speculative at this time, pending the results of definitive research. FDA also notes that the American Academy of Pediatrics (Ref. 73) and the New Zealand Ministry of Health (Ref. 74) have recently issued guidelines for the safe and suitable use of soy-based infant formulas. Some issues regarding effects of infant formula are unique because infants may be entirely dependent on formula as a sole source of nutrition and the relevance of such issues for soy protein consumed as part of a mixed diet by the general U.S. population is not clear.

In any case, concerns about effects of soy protein specific to infant formulas are beyond the scope of the current rule, which authorizes a health claim about the relationship of soy protein and CHD for foods intended for use by the general population. Health claims are not permitted on foods represented or purported for use by infants and toddlers less than 2 years of age unless specifically provided for in the authorizing regulation (21 CFR 101.14(e)(5)). Diets restricted in fat, saturated fat, and cholesterol are not recommended for infants and young children, and the current rule (§ 101.82) contains no provisions for use of the health claim about the relationship between soy protein and CHD on foods for infants and toddlers.

2. Comments on Petitioner's Self-Determination of GRAS Status for Soy Protein

(Comment 2). One comment specifically agreed with the petitioner's assertion that soy protein-containing food ingredients are generally recognized as safe (GRAS) by self-determination and based on common

use in food before January 1, 1958, in conformance with § 201(s) of the act. The comment also noted that, although soy protein is not listed as GRAS or prior sanctioned in Title 21 of the CFR, FDA has noted that these lists "do not include all substances generally recognized as safe for their intended use" and, as stated at 21 CFR 182.1, "[i]t is impracticable [for FDA] to list all substances that are GRAS for their intended use." This comment also agreed with the petitioner's conclusion that fractionation procedures used to convert vegetable flours to vegetable protein concentrates and isolates were commonplace in various sectors of the grain industry, such as corn processing, well before 1958. Therefore, SPC and ISP can be defined as soy flour "subject only to conventional processing as practiced prior to January 1, 1958." The comment concluded that SF (including steam-treated SF), SPC, and ISP all fall within the category of ingredients that are GRAS through experience based on their common use. Several comments objected to the petitioner's self-determination of GRAS status, citing a variety of reasons. As stated previously, FDA does not take issue with the petitioner's self-determination of GRAS status, and the comments, discussed below, have not convinced the agency to change that conclusion.

(Comment 3). Some comments raised objections on the basis that FDA has not approved the GRAS status of soy protein.

Although FDA has not ruled formally on the GRAS status of soy protein ingredients, it has not challenged determinations that soy's use as dietary protein is GRAS. Food ingredients whose use is generally recognized as safe by qualified experts are not required by law to receive FDA approval. Under the health claim petition process, FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the act (§ 101.14(b)(3)(ii)). As discussed in greater detail below, FDA did not receive sufficient evidence from comments to challenge the petitioner's assertion that soy protein ingredients are GRAS by self-determination. The petitioner met the showing required by § 101.14(b)(3)(ii) that the substance be "safe and lawful."

(Comment 4). One comment claimed that the Center for Food Safety and Applied Nutrition recently returned a petition requesting GRAS recognition for soy protein.

The document referred to by the comment was a notification by Archer Daniels Midland Company (GRN 000001), rather than a petition for FDA

action, and the subject of the notification was soy isoflavone extract, rather than soy protein. At the company's request, FDA ceased evaluation of the GRAS Notification pending the company's updating of the file (Ref. 75). Thus, this comment was incorrect.

(Comment 5). A comment asserted that petitioner's basis for GRAS self-determination of the use of soy protein as a dietary protein ingredient (*i.e.*, common use in food before January 1, 1958) was incorrect. Because the 1979 Select Committee on GRAS Substances (SCOGS) report (Ref. 76) determined that, at the time of the report, likely average dietary exposure to soy protein isolate was only about 150 milligrams (mg) from food items, the comment asserted that soy protein isolates could not have been in common use before 1958.

FDA finds that this comment is groundless and inaccurately characterizes the findings of the SCOGS. The 1979 SCOGS report includes the background statement "Edible soy protein isolates for food uses appeared about 1957 as a major article of commerce." The 1979 SCOGS Report also cited a 1972 National Research Council survey of GRAS ingredients that listed 14 food categories in which soy protein isolates were used and calculated an average daily intake of several grams. Soy protein isolates represent only one of several possible sources of soy protein in foods. In addition, for purposes of determining if a substance is GRAS, common use is not restricted to common use in the United States.

(Comment 6). A comment supporting the petitioner's self-determination of GRAS status noted that use of soy as a food dates to about the 11th century BC in the eastern half of north China. From about the first century AD to the 15th-16th century, soybeans were introduced in Korea, Japan, Indonesia, the Philippines, Vietnam, Thailand, Malaysia, Burma, Nepal, and northern India. Soybeans first grew in the United States in 1765 and were used then to manufacture soy sauce and vermicelli (soybean paste) (Ref. 77). A comment that disputed the petitioner's self-determination of GRAS status speculated that the species of soybean grown early in its history in Asia may have differed significantly in its content of nutrients and other active components from the modern species that is cultivated in this country.

FDA does not find this comment compelling. Although the composition of soybeans has likely changed over time, modern soybean species and

cultivars are, in any case, encompassed within the period of common use of soy and soy protein in food.

(Comment 7). One comment questioned whether the Asian experience could provide assurance that soy is safe. Drawing parallels with herbal medicine in terms of attitudes, monitoring deficiencies, and the general difficulty in detecting toxicities with long latency, this comment concluded that the long history of apparent safe use of soy products cannot assure they are without risk (Ref. 78).

The comment did not provide evidence to document that soy products, consumed at levels necessary to justify the claim, are not generally recognized as safe. Moreover, considerable research is underway at this time because of the hypothesized benefits of the historical use of soy products by certain population groups. FDA supports the ongoing research to clarify the effects, both potentially beneficial and potentially adverse, of soy and agrees that any effects due to changes in the conditions of use should be monitored. However, the information currently available does not lead FDA to object to the petitioner's self-determination of GRAS status of soy protein.

(Comment 8). Several other comments asserted that the proposal did not adequately establish the GRAS status of soy protein food ingredients in that the proposal did not include a thorough evaluation of the safety of potentially harmful components, *e.g.*, lysinoalanine, nitrites and nitrosamines, trypsin inhibitors, phytate, and isoflavones.

FDA notes that the 1979 SCOGS report (Ref. 76) discussed several of these components extensively and recommended that it would be prudent to develop food grade specifications for soy protein isolates that would set acceptable limits on the levels of lysinoalanine, nitrites, and nitrosamines. But, the possible presence of these components in soy protein isolates did not lead the SCOGS panel to recommend against GRAS status of soy protein isolates.

As noted above, the agency finds the petitioner met the showing required by § 101.14(b)(3)(ii) that soy protein is "safe and lawful." The agency lacks documented evidence of adverse effects in humans and has received no information about actual levels of potentially harmful components or about threshold levels for adverse effects in humans. Accordingly, the agency has no basis to conclude that soy protein is not safe and lawful. The specific comments about potentially

harmful components of soy are discussed below.

3. Lysinoalanine: Potential Toxic Effects

(Comment 9). A few comments noted concerns about the presence of lysinoalanine in soy protein isolates and cited the SCOGS report (Ref. 76), which indicated that lysinoalanine was implicated as a renal toxic factor in rats.

FDA finds that the comments inaccurately reflected the findings of the SCOGS report. The SCOGS report noted that the relatively severe alkali treatment used to modify viscosity and adhesive properties of soy protein isolates used as sizing and coating adhesives in the production of paper and paperboard products can cause formation of lysinoalanine. The report evaluated the risk of lysinoalanine exposure from soy protein adhesives and binders used in paper and paperboard food packaging. The 1979 SCOGS report noted that, "For edible isolated protein production, extraction is usually carried out at a pH below 9 to avoid hydrolytic or rheological changes" and concluded that, while relatively low levels of lysinoalanine had been reported in some samples of food grade soy protein isolate, available information indicated that the levels of lysinoalanine in food grade soy protein isolates pose no hazard to the consumer (Ref. 76).

FDA notes that the comments that expressed concern about lysinoalanine in soy protein ingredients did not provide any information about lysinoalanine levels in food grade soy protein ingredients nor about use of alkali-processed soy protein as a food ingredient. FDA finds that the potential presence of lysinoalanine in soy protein isolates used for sizing and coating adhesives in paper and paperboard products is not relevant to the safe and lawful use of soy protein in food. FDA also notes that the production of small amounts of lysinoalanine during alkali processing has also been documented with casein and lactalbumin, so it is not unique to soy. Good manufacturing practices are and should be employed to minimize the production of lysinoalanine because of its deleterious effects on protein quality.

4. Nitrites and Nitrosamines: Potential Carcinogenic Effects

(Comment 10). Some comments expressed concerns about the potential presence of nitrites in soy protein and the potential their presence poses for the *in vivo* formation of nitrosamines, which have been shown to be carcinogenic in experimental animals.

FDA notes that many natural and processed foods contribute to the total human intake of nitrite. In an appendix titled "Health Aspects of Nitrites in Soy Protein Isolates," the SCOGS report (Ref. 76) presented an estimate of the consumer exposure to nitrite contributed by soy protein in perspective to nitrite from other dietary sources and that formed in the gastrointestinal tract by reduction of salivary and dietary nitrate. The SCOGS report estimated the maximum daily nitrite consumption for a vegetarian eating meat alternatives prepared from soy protein to be 0.04 mg/kilogram (kg) body weight (or 2.8 mg for a 70-kg person). The report estimated daily per capita intake of nitrite from other foods of plant origin and cured meats to be about 2.4 mg and daily exposure to nitrite from saliva to be 15 mg. The report estimated that nitrite formed in the intestine from reduction of ammonia or organic nitrogen compounds contributed about 90 mg/day. Given the relatively minor potential contribution of soy protein to total nitrite exposure, and the fact that no data were submitted to document the current levels of nitrites or nitrosamines in soy protein isolates, FDA is not persuaded of the necessity for establishing specifications for acceptable levels of these compounds.

5. Trypsin Inhibitors: Potential Effects on Pancreatic Function

(Comment 11). A number of comments presented evidence that modern heat treatment and other processing do not entirely eliminate the activity of trypsin inhibitors in soy protein-containing products. Additional references provided in comments (Refs. 79, 80, 81, and 82) suggested that the mechanism of feedback regulation of pancreatic enzyme secretion may be responsible for deleterious effects on the pancreas—hyperplasia and formation of nodules—seen in animal studies. Further, Leiner (Ref. 80) demonstrated that infusion of high levels of isolated trypsin inhibitor in humans can evoke this mechanism but noted that further research was needed to assess whether frequent exposures to low levels of trypsin inhibitors consumed in the diet could have the same effect. Other comments cited evidence for potential anticarcinogenic effects of these and other protease inhibitors (Ref. 83). Leiner (Ref. 82) hypothesized that any anticarcinogenic effect of protease inhibitors would likely be manifested at levels too low to evoke their adverse effects on the pancreas.

FDA notes that the observed adverse effects have been limited to animal

studies. To date, deleterious effects of consumption of low levels of soybean trypsin inhibitors have not been documented in humans. For example, Mills *et al.* (Ref. 84) conducted a prospective study of fatal pancreas cancer among 34,000 California Seventh-day Adventists, a group with high soy consumption. Compared to all U.S. whites, Adventists experienced decreased risk from pancreas cancer death, which was not statistically significant. Although there was a suggestive relationship between increasing meat, egg, and coffee consumption and increased pancreatic cancer risk, these variables were not significantly related to risk after controlling for cigarette smoking. However, increasing consumption of vegetarian protein products, beans, lentils, and peas as well as dried fruit was associated with highly significant protective relationships to pancreas cancer risk.

Therefore, FDA finds that the information presented in these comments has not documented deleterious effects of dietary intake of trypsin inhibitors from soy in humans and, thus, does not lead the agency to take issue with the petitioner's conclusion that the use of soy protein is safe and lawful as required by § 101.14(b)(3)(iii).

6. Phytate: Effects on Mineral Balance

Comments raised concerns about the potential deleterious effect of soy protein and its phytate content on mineral status. Phytate, the salt of phytic acid or inositol hexaphosphate, is a natural plant constituent containing six negatively charged phosphate groups that can form strong complexes with divalent cations such as calcium, magnesium, iron, zinc, and copper. Concerns relative to soy have concentrated mainly on iron and zinc, based primarily on studies of the absorption and bioavailability of these minerals.

(Comment 12). One comment cited a study in which a soy protein-based purified diet induced iron deficiency in monkeys (Ref. 85). The same comment also noted two studies in humans—one that found inhibition of the absorption of nonheme iron from both semisynthetic meals and meals comprising conventional foods by various soy protein-containing ingredients (Ref. 86), and one that found increasing inhibition of nonheme iron absorption with increasing amounts of phytate in liquid formula meals that contained soy protein isolates (Ref. 87). In a study cited in another comment, the substitution of some meat in a mixed

meal by soy protein caused a decrease in the absorption of nonheme iron and an increase in the absorption of heme iron (Ref. 88), so that overall iron absorption was not compromised. Another comment reported that human feeding studies with soy protein that have examined measures of iron status have not shown detrimental effects (Ref. 89).

A comment raised concerns about the effect of soy protein on zinc status based on studies of absorption of zinc from soy infant formula (Ref. 90) and a study that showed decreased serum thymulin in subjects fed a low-zinc, soy protein-based experimental diet designed to produce mild zinc deficiency (Ref. 91). As noted earlier, issues specific to infant formula are outside the scope of this rulemaking and the experimental diet in the latter study (Ref. 91) is of limited relevance to the likely conditions of consumption of soy protein in the population that is the target of the health claim. Another comment cited two studies (Refs. 92 and 93) showing no adverse effects of soy protein on absorption of zinc from meals in subjects with adequate zinc status.

One comment provided additional information on the mechanism of phytate interference with zinc homeostasis (Ref. 94) and characterized the problem as more than a matter of decreased bioavailability of the zinc consumed in a meal. The comment noted that phytate can remove from the duodenum zinc that is mainly derived from pancreatic secretions, that is, zinc that may have been consumed 1–2 weeks earlier. Although these data are derived from animal studies, the comment indicated that the physiology of zinc homeostasis is not qualitatively different across species.

This comment expressed concern that high consumption of soy protein might exacerbate marginal zinc deficiency, which is difficult to diagnose, and suggested that labeling should include the content of both zinc and phytate so consumers can be educated that a molar ratio of phytate:zinc of less than 10 is needed to avoid detrimental effects on zinc status, as suggested by research in animals (including Ref. 95). The comment acknowledged that education would be needed for the public to utilize such labeling. The agency recognizes that adequacy of iron and zinc status in largely plant-based diets is a legitimate concern.

FDA finds that the evidence of potential adverse effects of soy protein on iron and zinc status is equivocal. Interpretation of the evidence is difficult because findings in human studies are often inconsistent with results of animal

studies. Moreover, many factors affect the absorption of these minerals, including the amount consumed in a meal, the enhancing and inhibiting effects of other components of the meal, and the nutritional status of the subject. Animal studies suggest that zinc status is a strong determinant of effects of phytate/soy on zinc absorption: zinc absorption is more impaired with zinc deficiency, in contrast to the effect of low iron status, which enhances iron absorption. However, given the lack of documented evidence for impaired iron and zinc status in humans consuming soy protein as part of a mixed diet, FDA is not persuaded of the necessity for the suggested labeling with respect to the phytate: zinc molar ratio. Nor is it persuaded that many consumers would find the suggested information, which is highly technical, useful at this time.

7. Soy Isoflavones: Estrogenic Effects

Many comments addressed concerns about the possible deleterious consequences of phytoestrogen effects of the soy isoflavones, genistein and daidzein. Most of these addressed proliferative (and potentially carcinogenic) effects on estrogen-sensitive tissues, effects on circulating hormone levels and potential deleterious effects on fertility, and potentially adverse effects on sexual development.

a. *Proliferative effects.* (Comment 13). Several comments cited a number of studies of in vitro effects of individual isoflavones on proliferation of estrogen-sensitive cells. For example, Dees *et al.* (Ref. 96) found that genistein increased a number of indices for proliferative activity in MCF-7 human breast cancer cells. As the authors noted, these findings are consistent with the conclusion that dietary estrogens at low concentrations do not act as antiestrogens, but act like estradiol to stimulate human breast cancer cells to enter the cell cycle. However, many other studies (reviewed in Refs. 97 and 98) have found that the phytoestrogens present in soybeans inhibit breast cancer cell proliferation in vitro (at lower concentrations, closer to physiological levels) and inhibit mammary cancer development in various animal models. FDA concludes that studies in transformed cells cannot predict with certainty whether effects will be beneficial or detrimental in humans consuming soy protein.

(Comment 14). Comments argued that two reports showed effects of dietary intake of soy isoflavones on breast tissue in women. Petrakis *et al.* (Ref. 99) studied 24 normal pre- and postmenopausal white women, ages 30

to 58 years, who underwent monthly nipple aspiration of breast fluid and gave blood and 24-hour urine samples for biochemical studies. The women consumed no soy in months 1–3 and 10–12. During months 4–9 the women ingested daily 38 grams (g) of soy protein isolate containing 38 mg of genistein (daidzein content was not reported). This study's findings indicated that prolonged consumption of soy protein isolate had a stimulatory effect on the breast of premenopausal women, characterized by increased secretion of breast fluid and elevated levels of plasma estradiol. The study also detected evidence of epithelial proliferation (hyperplasia) in 7 of the 24 subjects during consumption of soy. McMichael-Phillips *et al.* (Ref. 100) examined the effects of dietary soy supplementation on the proliferation rate of premenopausal, histologically normal breast epithelium and the expression of progesterone receptor. Women ($n = 48$) with benign or malignant breast disease were randomly assigned to receive their normal diet either alone or with a 60-g soy supplement (containing 45 mg isoflavones) taken daily for 14 days. Serum concentrations of the isoflavones genistein and daidzein increased in the soy group at 14 days. The proliferation rate of breast lobular epithelium significantly increased after soy supplementation when both the day of menstrual cycle and the age of patient were accounted for. Progesterone receptor expression increased significantly in the soy group. The authors concluded that further studies are required to determine whether the short-term stimulation of breast proliferation is due to estrogen agonist activity and to examine the long-term effects of soy on both the pituitary gland and breast.

FDA finds that the detection of proliferative effects in these two studies suggests the need for additional research. The findings do not, however, establish that the observed effects are detrimental and are not supported by the findings of epidemiologic studies of soy intake and risk of premenopausal breast cancer (Ref. 101).

b. *Fertility and Hormone Levels.* (Comment 15). Some comments referenced a number of studies that reported reduced fertility in animals exposed to phytoestrogens (including Refs. 102, 103, and 104). Some of these studies involved phytoestrogens other than those found in soy or consumption of soy under extreme or unusual conditions. FDA is not convinced of the relevance of these studies to human consumption of soy protein.

(Comment 16). Comments cited the study of Cassidy *et al.* 1994 (Ref. 105) as suggesting the potential for deleterious effects on human fertility. These investigators examined the influence of a diet containing soy protein on the hormonal status and regulation of the menstrual cycle in six premenopausal women. Soy protein (60 g containing 45 mg isoflavones) given daily for 1 month significantly ($p < 0.01$) increased follicular phase length and/or delayed menstruation. Midcycle surges of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were significantly suppressed during dietary intervention with soy protein. Plasma estradiol concentrations increased in the follicular phase and cholesterol concentrations decreased 9.6 percent. The authors concluded that responses to soy protein are potentially beneficial with respect to risk factors for breast cancer and may in part explain the low incidence of breast cancer and its correlation with a high soy intake in Japanese and Chinese women. One of the comments that cited this study acknowledged that it is unclear whether these soy effects are beneficial or adverse. FDA notes that the study found that soy did not interfere with ovulation and the study did not assess effects on fertility.

In a similar study with a longer duration, Duncan *et al.* (Ref. 106) studied effects of isoflavone consumption in 14 premenopausal women. The women consumed isoflavones in soy protein powders (control diet, 10; low isoflavone diet, 64; high isoflavone diet, 128 mg/day) for three menstrual cycles plus 9 days in a randomized cross-over design. The low isoflavone diet decreased LH and FSH levels during the periovulatory phase. The high isoflavone diet decreased free T3 and dehydroepiandrosterone sulfate levels during the early follicular phase and estrone levels during the midfollicular phase. No other significant changes were observed in hormone concentrations or in the length of the menstrual cycle, follicular phase, or luteal phase. Endometrial biopsies performed in the luteal phase of cycle 3 of each diet period revealed no effect of isoflavone consumption on histological dating. FDA notes that although this study's findings varied somewhat from those of Cassidy *et al.* (Ref. 105), it also did not directly address the effect of soy on human fertility. FDA finds that these two studies do not provide sufficient evidence to address the effect of soy protein on human fertility.

c. *Developmental Effects.* (Comment 17). One comment cited the study of

Faber and Hughes, 1993 (Ref. 107) as showing alterations in LH regulation following developmental treatment with genistein, suggesting that during pregnancy in humans, isoflavones could be a risk factor for abnormal brain and reproductive tract development. This study involved injection of 0, 1, 10, 100, 200, 400, 500, or 1,000 micrograms of genistein into neonatal rats on days 1–10. Because of the differences in developmental stages between rodents and humans, this type of experiment is used as a model for prenatal (third trimester) effects of diethylstilbestrol (DES). Increased exposure to genistein led to decreased LH secretion; the volume of the sexually dimorphic nucleus of the preoptic area increased compared to controls only in animals that received the two highest doses of genistein. An earlier paper by Faber and Hughes 1991 (Ref. 108) showed that effects elicited by neonatal injections of 1000 micrograms of genistein were similar to those of 0.1 micrograms of DES. The comment also cited studies using a similar experimental model by Medlock *et al.* (Refs. 109 and 110) as demonstrating that equol (a metabolite of daidzein in some individuals) acts as an endocrine disruptor during development. FDA finds that the relevance of these studies to an assessment of potential prenatal effects of dietary soy protein during pregnancy is uncertain.

(Comment 18). One comment cited the study of Harrison *et al.* (Ref. 111) that showed pregnant Rhesus monkeys fed genistein had serum estradiol levels 50 to 100 percent higher than the controls in three different areas of the maternal circulation. The comment also noted the finding that the fetuses of genistein fed monkeys had a 70 percent higher serum estradiol level than did the controls. In this study, five monkeys were fed genistein (amount not specified) during pregnancy and compared to five controls. No differences were reported in maternal weight gain, fetal weights at delivery, or placental weights. Significant differences in estradiol levels (but not progesterone) were noted at delivery in maternal peripheral blood, uterine veins, ovarian veins, and the fetus, and in maternal blood during pregnancy, but values were not reported. FDA received only an abstract describing this study. Without more complete documentation, the merits or weaknesses of this study cannot be evaluated. Therefore, FDA has not used this study to evaluate the concerns raised in this comment.

FDA notes that, in another study that examined dietary effects, Fritz *et al.* (Ref. 112) fed female rats genistein from

conception to day 21 postpartum in the diet at concentrations of 0, 25 and 250 mg genistein/kg diet. They found that genistein in the diet at "physiological levels" (equivalent to those in Asians consuming a traditional high soy diet) enhances cell differentiation, resulting in programming of mammary gland cells for reduced susceptibility to chemically induced mammary cancer, with no observed toxicity to the fertility of dams or the reproductive tract of female offspring. FDA finds that these dietary studies in animals do not provide evidence for detrimental developmental effects in humans.

(Comment 19). Another comment raised the possibility that soy phytoestrogens could be responsible for inducing premature puberty and cited the case-control study of estrogenic exposures by Freni-Titulaer *et al.* (Ref. 113) of patients with premature thelarche seen in Puerto Rico between 1978 and 1981. In subjects 2 years of age or older at the onset of thelarche, the study found no statistically significant associations. In subjects with onset before 2 years of age, statistically significant positive associations were found with a maternal history of ovarian cysts, consumption of soy-based formula, and consumption of various meat products. A statistically significant negative association was found with consumption of corn products. The authors concluded that these statistical associations were not sufficient to explain the reported increase in premature thelarche because in over 50 percent of the case subjects there was no exposure to any of the risk factors for which statistical associations were found.

Thus, FDA concludes that this study provides no convincing evidence that soy was responsible for premature thelarche. Moreover, FDA notes that the study documents no deleterious effects of consuming soy protein at the levels necessary to justify the health claim in population groups that are the target of the claim.

d. *Other.* (Comment 20). One comment cited a study associating intake of tofu in mid-life by Japanese-American men in Hawaii with vascular dementia and brain atrophy in old age (Ref. 114). This comment hypothesized that isoflavone inhibition of aromatase, which catalyzes the conversion of testosterone to estradiol, may provide a mechanistic explanation for this finding. The report cited (Ref. 116) is an abstract that indicates the researchers found an association of high tofu intake with low cognitive test scores and with Alzheimer's disease, rather than vascular dementia.

FDA finds that this abstract does not provide a sufficient basis to evaluate the merits and weaknesses of this study. As such, it is not useful in evaluating the safety concerns at issue. Moreover, the report does not provide information on total soy intake or what variables were controlled in the analysis. If tofu or soy were implicated in Alzheimer's disease, its prevalence would be expected to be higher in Japan than in Hawaii, but White *et al.* (Ref. 115) found the prevalence of Alzheimer's disease was higher in Hawaii than in Japan. Therefore, FDA is not persuaded by the comment raising concerns about potential adverse effects of soy protein in dementia and brain atrophy in older persons.

(Comment 21). One comment addressed the general issue of threshold effects for estrogenic compounds, citing a study (Ref. 116) that showed no threshold dose for estradiol-induced sex reversal of turtle embryos. It also cited a study (Ref. 117), available in abstract form, that reviewed 31 dose-response curves for hormone-mimicking chemicals that also failed to show a threshold. The report of this study did not include mention of soy isoflavones and did not specify the estrogenic effects examined. FDA does not find this evidence particularly useful. The relevance of the turtle model to humans is uncertain and the other cited evidence was available only in abstract form.

e. *Conclusion.* Soy isoflavones and other dietary phytoestrogens are known to exert hormonal effects—both estrogenic and antiestrogenic—depending on the amount and type consumed and endogenous hormonal status of the organism studied; they are much less potent than endogenous estrogen or synthetic estrogens such as DES. There is considerable variability from person to person in the absorption, metabolism, and disposition of the soy isoflavones, genistein and daidzein (Ref. 118), and researchers have found that their metabolism and excretion depend on the duration of ingestion and the subject's sex (Ref. 119).

Overall, the evidence for proliferative effects, effects on fertility and hormone levels, and developmental and other effects in humans due to the estrogenic effects of soy isoflavones is very limited. Both possible beneficial effects and possible detrimental effects are still hypothetical. FDA finds that the information presented in the comments has not adequately documented deleterious effects of dietary intake of soy isoflavones in humans.

8. Soy Isoflavones: Goitrogenic Effects

(Comment 22). Comments noted that isoflavones are inhibitors of the enzyme thyroid peroxidase (TPO), which produces the thyroid hormones T3 and T4, and indicated that its inhibition can be expected to generate thyroid abnormalities. Other comments, however, noted the lack of evidence for consequential effects of TPO inhibition (*i.e.*, high prevalence of goiter) in populations with high soy consumption.

One comment noted that there exists a body of animal data that demonstrates goitrogenic and even carcinogenic effects of soy products and cited the study by Kimura *et al.* (Ref. 120). These researchers developed malignant goiter in rats by feeding diets containing 40 percent defatted soybean and no iodine. No deleterious effects were seen in controls fed the same diet with iodine added.

Comments noted the existence of a number of case reports in the older literature of soy inducing goiter in infants (Refs. 121 through 125). Van Wyk *et al.* (Ref. 121) studied one infant who developed goiter on a soybean formula and tested the same product in 12 adults. In adults, the product did not interfere with iodine absorption, impair iodine uptake, interfere with oxidation of iodine in the thyroid, or (in most subjects) interfere with the release of protein-bound iodine into the blood. Hydovitz (Ref. 12) provided a single case report; Shepard *et al.* (Ref. 123) described three cases and presented evidence that soybean goiter was caused by iodine deficiency. Pinchera *et al.* (Ref. 124) reported on a case of a congenitally hypothyroid infant and found high fecal losses of thyroxine. Addition of adequate iodine to soy-based infant formulas in the 1960's generally resolved or prevented goiter. However, Chorazy *et al.* (Ref. 125) more recently reported on a hypothyroid infant who was semi-refractory to thyroid hormone therapy while consuming soy formula.

Several comments cited the study of Ishizuki *et al.* (Ref. 126) as evidence for goitrogenic effects of soy in adults. This study is published in Japanese and the available English abstract is poorly translated. As described in that abstract, the design and findings are unclear: goiters were said to occur in half the subjects eating 30 g soybeans daily for 3 months, though "various parameters of serum thyroid hormones remained unchanged by taking soybeans." The soybean preparation used (reported in some comments to be roasted, pickled soybeans), iodine intake, and other dietary changes were not reported.

In one comment, researchers indicated that they had identified genistein and daidzein as the goitrogenic isoflavonoid components of soy and defined the mechanisms for inhibition of TPO-catalyzed thyroid hormone synthesis using *in vitro* studies of the pure isoflavones (Refs. 127 and 128). The comment noted that the observed irreversible inactivation of TPO by isoflavones, through covalent binding to TPO, raises the possibility of neoantigen formation. The comment also noted that anti-TPO is the principal autoantibody present in autoimmune thyroid disease and proposed that this hypothetical mechanism is consistent with the reports of Fort *et al.* (Refs. 129 and 130) of a doubling of risk for autoimmune thyroiditis in children who had received soy formulas as infants compared to infants receiving other forms of milk. However, the studies of Fort *et al.* were retrospective case-control analyses of early feeding practices in children with diabetes (Ref. 129) or autoimmune thyroid disease (Ref. 130). The studies did not establish a cause-and-effect relationship or assess medical indications for use of soy formula in these children.

FDA notes that no data or other information presented in the comments documents deleterious effects on thyroid function of consuming soy protein at the levels necessary to justify the health claim in population groups that are the target of the claim.

9. Allergenicity of Soy Protein

(Comment 23). One comment disputed the statement in the soy protein proposed rule that soy allergies are often outgrown. FDA finds that the comment cited data that did not directly address this issue but documented the following with respect to soy: a case report of an anaphylactic reaction to soy in an adult (131); severe reactions to soy in several Swedish children and adolescents, who had known severe reactions to peanuts and asthma but had not reacted previously to soy (Refs. 132 and 133); cross reactivity of some soy and peanut allergens (Ref. 134); and an outbreak of gastrointestinal illness associated with consumption of an improperly processed soy protein tuna salad extender in which only a few individuals exhibited signs of true hypersensitivity reactions (Ref. 135).

(Comment 24). One comment noted that use of soy protein health claims will highlight the presence of soy protein in foods. Another comment noted that any food protein can stimulate a food allergy and that such allergies are commonly due to milk, egg, and nut proteins. This comment noted

that infants who develop cow's milk allergies or intolerance are frequently prescribed soy substitutes and a small subset of these high-risk children also develop soy protein allergy.

FDA finds that the comments that noted concerns about the allergenicity of soy protein cited these concerns as evidence that consumption of soy is unsafe, but did not propose that any particular action be taken by the agency as a consequence to protect consumers with soy allergies. FDA does not believe that, because some persons may have allergic reactions to a food, it is unsafe. FDA has previously stated that the declaration of an allergenic substance in the ingredient statement on the food label provides adequate information for consumers regarding the presence of the allergenic ingredient in the product (63 FR 8103 at 8113), and sees no reason to change this view with respect to soy. FDA notes, in agreement with one of the comments received, that authorization of a health claim for soy protein and CHD will highlight the presence of soy protein in those food products that bear the claim. The agency, therefore, anticipates that persons with known soy allergies will be able more easily to avoid soy protein based products.

B. Updated Review of Scientific Evidence and Issues Related to the Evidence

In the soy protein proposed rule, FDA conducted a comprehensive review of the human studies submitted in the petition (Refs. 27 through 66) (63 FR 62977 at 62980). Of these, the agency gave particular weight to 14 clinical trials (Refs. 27, 28, 30 (1 trial), 31, 36, 37 (1 trial), 40 (2 trials), 44, 49, 51, 54, 58, and 59). These 14 trials met the criteria for selection set out by the agency (63 FR 62977 at 62980): they included subjects representative of the general U.S. population; were well controlled; reported information on intakes of saturated fat and cholesterol; and avoided problems associated with small sample size, lack of a placebo, and other design problems. The agency summarized these studies in Table 1 of the soy protein proposed rule (63 FR 62977 at 62998). The agency also summarized seven clinical trials in adults (Refs. 33, 35, 46, 55, 56, 60, and 64) and three trials in children (Refs. 34, 42/45, and 63) with type II or familial hypercholesterolemia in Table 2 of the soy protein proposed rule (63 FR 62977 at 63011). In addition, FDA reviewed the results of one epidemiological study (Ref. 65 and 63 FR 62977 at 62986) and a meta-analysis (Ref. 66 and 63 FR 62977 at 62987) that included a number

of the soy protein studies submitted in the petition.

Based on these studies, FDA concluded there was scientific evidence for a consistent, clinically significant effect of soy protein on blood total and LDL-cholesterol levels (63 FR 62977 at 62989). The hypocholesterolemic effect of soy protein was seen in addition to the effects of a low saturated fat and low cholesterol diet. The degree of lowering of blood total and LDL-cholesterol was consistently and highly dependent on initial levels, within and across studies of subjects with normal, moderately elevated, and severely elevated blood lipid levels, with persons having higher blood lipid levels showing greater effects. Soy protein consistently caused only statistically nonsignificant effects or slight elevations in high density lipoprotein (HDL)-cholesterol levels. The intervention studies indicated that a minimum level of approximately 25 g of soy protein was needed to have a clinically significant effect on total and LDL-cholesterol levels.

1. Additional Data Submitted With Comments and New Studies

(Comment 25). Several comments included submissions of additional studies of the effects of soy protein on total and LDL-cholesterol or directed FDA to studies published since it issued the soy protein proposed rule. FDA reviewed these studies and found that two (Refs. 136 and 137) meet its criteria for consideration.

One comment included an unpublished paper by Teixeira *et al.*, 1999 (Ref. 136) that examined the effects of feeding four graded levels of soy protein in moderately hypercholesterolemic men. After a three-week lead-in on a National Cholesterol Education Program (NCEP) Step 1 diet, subjects were randomly assigned to one of five experimental groups. Each group received 50 g protein daily, provided in a variety of baked goods and ready-to-mix beverages, from ISP or casein in different proportions for 6 weeks. The proportions of protein were 50, 40, 30, 20, and 0 g (for control) as ISP and 0, 10, 20, 30, and 50 g as casein, respectively. At 3 weeks, statistically significant ($p < 0.05$) reductions in total and non-HDL-cholesterol were seen only in the groups consuming 40 and 50 g of soy protein. At 6 weeks, statistically significant reductions ($p < 0.05$) from baseline were found for non-HDL cholesterol levels in all soy protein-consuming groups and, in all except the 40 g soy protein group, for total cholesterol level. Although a reduction in total cholesterol was noted in this

latter group, it was non-significant ($p=0.07$). The authors noted that neither non-compliance with the diet nor alterations in blood isoflavone content could account for this result. The study also showed that levels of HDL-cholesterol were not affected by dietary treatment at any soy consumption level investigated.

FDA also noted the recently published study by Wong *et al.*, 1998 (Ref. 137), who conducted a well designed and controlled trial using NCEP Step 1 diets with most protein provided by soy (50 g/day of soy protein) or animal protein. Subjects were 13 normocholesterolemic and 13 hypercholesterolemic men aged 20–50 years and the trial was a randomized, 2-part, crossover study. Subjects were fed either an NCEP Step I soy protein-containing diet or an NCEP Step I animal protein diet for 5 weeks. After a washout period of 10–15 weeks, the subjects were fed the alternate diet for 5 weeks. The study found the hypocholesterolemic effect of soy protein to be independent of age, body weight, pretreatment plasma lipid concentrations, and sequence of dietary treatment. Regardless of plasma lipid status, the soy protein diet was associated with a statistically significant decrease in the plasma concentrations of LDL cholesterol ($p=0.029$). FDA finds these two studies supportive of the relationship of soy protein to reduced risk of CHD.

(Comment 26). One comment cited two metabolic ward studies by Fumagalli *et al.* 1982 (Ref. 138), designed to examine fecal steroid excretion in adults with familial type II hypercholesterolemia, that had not been reviewed by FDA in the soy protein proposed rule, as supportive of the ability of soy protein to lower total cholesterol levels. However, FDA finds these studies had a very small number of subjects, short duration of treatment, and reported insufficient information to determine the amounts of soy protein in the diets consumed. These studies failed to meet FDA's selection criteria for review and, so, FDA has not considered them further.

(Comment 27). Comments included information on two studies by Jenkins *et al.* 1999 (Refs. 139 and 140) that assessed the effects of inclusion of soy protein and soluble dietary fiber in an NCEP Step II diet in hypercholesterolemic subjects in a randomized crossover design. Dietary saturated fat (less than 7 percent of energy) and cholesterol (less than 80 mg/day) did not differ in the test and control metabolic diets (Ref. 139). Compared with the control diet, the test

diet (which provided 33 grams of soy protein from a variety of commercially available foods) resulted in a 6 percent decrease in total cholesterol and a 7 percent decrease in LDL-cholesterol levels. The second study (Ref. 140) used a similar design but was only available as an abstract that contained too little detail for the agency to evaluate it.

FDA finds that neither of these studies can provide support for a hypocholesterolemic effect of soy protein per se because both soy protein and soluble fiber were varied concurrently. However, these studies do suggest that inclusion of these specific components can further enhance the lipid-lowering effect of a low saturated fat, low cholesterol diet.

(Comment 28). A comment also submitted the recent study by Washburn *et al.*, 1999 (Ref. 141) for consideration. In this randomized, double-blind crossover trial, 51

normocholesterolemic, perimenopausal women consumed supplements for 6-week periods of 20 g of complex carbohydrate, 20 g of soy protein containing 34 mg of phytoestrogens given in a single dose, and 20 g of soy protein containing 34 mg of phytoestrogens split into two doses. Significant declines in total cholesterol level (6 percent lower) and LDL-cholesterol level (7 percent lower) were observed with both soy treatments compared to the carbohydrate placebo control. However, no dietary assessments were performed; thus, FDA cannot determine whether the women may have modified their usual dietary intake in response to the supplements and whether and how intake of dietary constituents may have differed among the treatment groups.

FDA identified two additional recently published studies for consideration. Nilausen and Meinertz, 1998 (Ref. 142) employed liquid formula diets containing a very high level of protein (150 g/day) with soy or casein as the sole protein source to examine individual variability in lipemic response in a small metabolic study of normocholesterolemic men. In most subjects effects of soy protein on both LDL- and HDL-cholesterol levels were favorable, but considerable variability in response was observed. Duane, 1999 (Ref. 143) also conducted a small metabolic ward study in normocholesterolemic men that compared effects of (1) a control diet with "standard" amounts of dietary cholesterol, (2) a diet with essentially no dietary cholesterol and all animal sources of protein substituted by TVP, and (3) a diet similar to the second one with eggs isocalorically substituted for

protein and fat to bring dietary cholesterol levels to the moderate range. Diets containing soy protein decreased LDL-cholesterol but the effect was of borderline statistical significance. FDA notes that the small number of subjects and the unusual dietary conditions employed in these two studies limit their usefulness in adding to the body of evidence about the effects of soy protein on circulating lipid levels.

In summary, although most of the new studies considered had flawed or unusual designs that compromised their evaluation, the two better designed and controlled studies (Ref. 136 and Ref. 137) provide additional support for the cholesterol lowering effects of inclusion of reasonable amounts of soy protein in diets low in saturated fat and cholesterol.

2. Interpretation of the Clinical Trial Data for Soy Protein

(Comment 29). One comment raised concerns about the apparent inconsistency in FDA's application of its review selection criteria, especially with respect to giving the greatest weight in evaluation of the health claim to those studies that reported information about the dietary intake of constituents known to have the greatest influence on total and LDL-cholesterol levels. The comment noted that values for dietary saturated fat and cholesterol were not reported for some studies and that an outmoded description of polyunsaturated fatty acid to saturated fatty acid ratio was reported for some studies.

FDA agrees that values for these dietary constituents were not reported explicitly in all of the studies selected for review. In such cases, FDA relied upon other documentation contained in the study publications regarding the contents of the test and control diets, such as sample menus and reported manipulations of sources of saturated fat and cholesterol, for assurance that dietary saturated fat and cholesterol did not differ significantly in the test conditions.

(Comment 30). One comment questioned the appropriateness of including studies in which only total cholesterol levels were measured.

As noted above, in earlier rulemakings on diet and CHD relationships, FDA concluded that it is generally accepted that blood total and LDL-cholesterol levels are major risk factors for CHD, and that dietary factors affecting blood cholesterol levels affect the risk of CHD. FDA notes that a few of the older studies that it considered and reviewed in the soy protein proposed rule, and in previous

rulemakings, measured only total cholesterol levels. FDA concluded that inclusion of these studies for review was desirable in order to assess the totality of the publicly available scientific evidence on the relationship of soy protein and risk of CHD, even though LDL-cholesterol levels are now considered to be a more powerful risk factor than total cholesterol levels.

(Comment 31). A few comments disagreed with FDA's tentative decision to authorize a health claim for the relationship between soy protein and CHD because not all of the studies reviewed in the soy protein proposed rule showed significant reductions of total and plasma cholesterol levels.

A recent review and meta-analysis of the effectiveness of NCEP Step 1 and Step 2 dietary interventions in free-living subjects by Yu-Poth *et al.* (Ref. 144) noted an appreciable range of response to the dietary interventions with the maximal effect being more than twice the average response reported in controlled feeding studies with Step 1 diets. The interventions reviewed were designed to achieve reduction of dietary saturated fat and cholesterol and weight reduction, factors known to have a major impact on circulating cholesterol levels. (The hypocholesterolemic effects of soy protein, like those of soluble fiber from whole oats and psyllium seed, are of a lesser magnitude than those of reduced dietary saturated fat and cholesterol.) Denke (Ref. 145), in an editorial comment on the study by Yu-Poth *et al.*, notes that cholesterol-lowering dietary therapy is subject to profound individual variation in response. In metabolic ward studies of subjects with unselected cholesterol levels, 5 percent of individuals had no cholesterol-lowering response to dietary modification and the percentage of nonresponders increased to 10–25 percent in outpatient studies (Denke, 1995, Ref. 146). Such nonresponse can result in a significant underestimation of the effectiveness of dietary intervention when only the mean response is considered. The small metabolic ward study of Nilausen and Meinertz (Ref. 142), described above, documented evidence for considerable inter-individual variability in the response of cholesterol levels to diets containing soy protein.

Based on the studies reviewed in the soy protein proposed rule and the new studies reviewed in this document, FDA concludes that the totality of the available scientific evidence supports a consistent, if not universal, hypocholesterolemic effect of soy protein included in a low saturated fat and low cholesterol diet. The degree of

consistency is notable in light of the different experimental designs and diets studied, the different forms and amounts of soy protein tested, and the variability in initial cholesterol levels of the subjects. The modest lowering of total and LDL-cholesterol levels generally observed in these studies can effect a significant reduction in CHD risk.

(Comment 32). Other comments reviewed various possible mechanisms for the cholesterol-lowering effects of soy protein and some argued that until the mechanism of action of soy protein is clearly established, no health claim should be authorized. FDA notes, however, that such knowledge is not necessarily required for authorization of a health claim.

3. Role of Soy Isoflavones in and Effect of Processing on the Hypocholesterolemic Effect of Soy Protein

In the soy protein proposed rule, FDA examined the limited evidence that addressed whether the hypocholesterolemic effects of soy protein intake were dependent, as suggested by the petitioner, on concomitant intake of a specified level of naturally occurring soy isoflavones, *i.e.*, 2 mg isoflavones per g of soy protein (Refs. 22, 28, 31, 70, and 71). FDA also took note of a letter to the editor from Sirtori *et al.* (Ref. 72), who conducted a number of trials in which soy protein exhibited hypocholesterolemic effects and asserted that the products used in those trials were essentially devoid of isoflavones. Given the limited number of studies and the contradictory outcomes, FDA was not persuaded that the isoflavone component of soy protein was a relevant factor to the diet-disease relationship. Rather, FDA tentatively concluded that the evidence from a wide range of studies using differently processed soy protein was supportive of a relationship between soy protein per se and reduced risk of CHD.

(Comment 33). Several comments reviewed and discussed the animal and human studies that examined effects of isoflavones directly or that compared the effects of ISP processed with and without alcohol extraction that can remove essentially all isoflavones. Some of these studies examined effects on parameters in addition to cholesterol levels, such as measures of lipid-related gene expression, atherosclerosis, and vascular reactivity. Because the health claim for soy protein and CHD is based on the hypocholesterolemic effect of soy protein, only that aspect of the studies is summarized below.

In one study, Balmir *et al.* (Ref. 147) fed male rats diets containing protein from ethanol-acetone extracted ISP, nonextracted ISP, casein, or casein to which the ethanol-acetone extract was added. Rats fed either ISP diet had lower serum total cholesterol concentrations compared with those fed either casein diet. Lower serum LDL-cholesterol concentrations were found in rats fed either ISP diet and in rats fed casein plus extract compared with those fed casein. Sugano and Koba (Ref. 148) found that a methanol-extracted soy fraction was not as effective as the unextracted fraction in maintaining low plasma cholesterol levels in rats. Kirk *et al.* (Ref. 149) showed that a soy protein-based isoflavone-containing diet resulted in a reduction in cholesterol levels in C57BL/6 mice compared to a diet containing alcohol-washed soy protein, although it had no effect on cholesterol levels in transgenic mice that lacked the LDL receptor. In another study, Balmir *et al.* (Ref. 147) fed male Golden Syrian hamsters diets containing protein from ISP, ISP with added ethanol-acetone extract, casein, or casein with added extract. Lower serum total cholesterol and LDL cholesterol concentrations were observed in hamsters fed ISP, ISP with extract, or casein with extract compared with those fed casein. Addition of the extract to casein at higher levels did not lower serum lipids relative to casein. Tovar-Palacio *et al.* (Ref. 150) fed gerbils one of five experimental diets containing either casein or alcohol-washed ISP provided alone, or ISP supplemented with one of three different levels of an alcohol extract of isolated soy protein contributing either 2.1, 3.6 or 6.2 mg isoflavones/g protein. Gerbils fed all of the soy-based diets had significantly lower total and LDL + very low density lipoprotein (VLDL)-cholesterol levels than those fed casein. The additions of the alcohol extract to ISP did not reduce serum cholesterol levels any further. This study suggests that, in gerbils, consumption of an isoflavone-containing extract does not contribute to the hypocholesterolemic effect of alcohol-extracted soy protein. These reports did not characterize the nature of the extracts used in the studies. Overall, FDA finds that studies in these animal models do not clarify the role of isoflavones in the hypocholesterolemic effect of soy protein.

Comments noted a series of studies conducted in monkeys that examined the effect of removal of isoflavones and other alcohol-extractable compounds from soy protein on its cholesterol-lowering activity. Anthony *et al.* (Ref.

22) fed peripubertal male and female rhesus monkeys moderately atherogenic diets in which the source of dietary protein was a soy protein isolate, either containing isoflavones or with the isoflavones removed by alcohol extraction, in a crossover design with each period lasting for 6 months. The intact soy protein (compared with the extracted soy protein) significantly reduced LDL+VLDL-cholesterol levels in both males and females and significantly increased HDL-cholesterol levels for females. Honoré *et al.* (Ref. 23) fed young adult rhesus monkeys with pre-existing diet-induced atherosclerosis one of two soy-based diets, which were identical in composition except that the isoflavones were extracted from one and intact in the other, for 6 months. Total and LDL-cholesterol levels were significantly lower in females fed the intact soy protein than in those fed the extracted soy protein. The same trend was seen in males, but the difference was not statistically significant for total cholesterol. Anthony *et al.* (Ref. 70) studied young male cynomolgus macaques fed one of three moderately atherogenic diets for 14 months. The groups differed only in the source of dietary protein, which was either casein/lactalbumin, soy protein with the isoflavones intact, or soy protein with the isoflavones mostly extracted. Animals fed intact soy protein had significantly lower total and LDL+VLDL-cholesterol levels compared with the other two groups. The animals fed intact soy protein had the highest HDL-cholesterol level, the casein group had the lowest level, and the group fed the extracted soy protein was intermediate. Anthony *et al.* (Ref. 151) randomized male and female macaques to groups fed a casein-containing diet or diets with soy protein with the isoflavones intact or extracted. Fat and cholesterol were identical in all diets. The LDL+VLDL-cholesterol levels were highest in the casein group, slightly lower in the group fed extracted soy protein, and significantly lower in the group fed intact soy protein. The HDL-cholesterol levels were significantly higher in both soy protein groups than in the casein group. FDA notes that the alcohol extraction procedure used by these researchers, which was not characterized in the study reports, appeared to diminish the hypocholesterolemic effect of ISP.

Comments submitted three human studies of isolated isoflavones that examined their role in cholesterol lowering. In a study published only as an abstract, Colquhoun *et al.* (Ref. 152)

administered daidzein and genistein to 23 male and female subjects with an average cholesterol level of 243 mg/deciliter (dL) in a blinded crossover design. Nestel *et al.* (Ref. 52) studied 21 women in a randomized cross-over design with two active treatment periods (80 mg of isolated soy isoflavones) and one 5-week placebo period, while they consumed a soy-free diet. Hodgson *et al.* (Ref. 153) conducted a randomized, blinded, placebo-controlled trial of 8 weeks duration and a two-way parallel design that tested the administration of 55 mg of soy isoflavones to 46 men and 13 postmenopausal women. Plasma lipid levels were not affected by soy isoflavones in any of these studies. FDA notes that these studies do not support a role for isolated isoflavones in cholesterol lowering.

Three studies submitted in comments examined the effects of variation of isoflavone content in soy protein-containing diets in human subjects. Cassidy *et al.* (Ref. 154) conducted metabolic ward studies of the effects of various soy products with and without isoflavones in small numbers of healthy, nonvegetarian, premenopausal women. During one (control) menstrual cycle, the women ate a constant diet containing no soy products. Then, over a second complete cycle six subjects consumed a similar diet into which 60 g TVP/day, containing 45 mg conjugated isoflavones, was incorporated. Three participants had 50 g miso, containing 25 mg unconjugated isoflavones, added daily to their diet over a menstrual cycle, and six others consumed 28 g TVP/day, containing 23 mg conjugated isoflavones. Five participants completed a third diet period in which they were randomly assigned to consume either the control diet over a cycle, or a similar diet incorporating 60 g of a ISP from which the isoflavones had been chemically extracted. A significant reduction in total cholesterol was found with 45 mg conjugated isoflavones, but not with 23 mg conjugated isoflavones or isoflavone-free ISP.

As previously reviewed in the soy protein proposed rule (63 FR 62977 at 62988), the study of Baum *et al.* (Ref. 28) investigated the impact of soy protein as ISP containing different levels of isoflavones in hypercholesterolemic, postmenopausal women. Adjusted mean differences in the change from baseline for total serum cholesterol level did not differ in the two soy groups and the control group. However, there was a statistically significant reduction of 8–9 percent in non-HDL (LDL+VLDL)-cholesterol in both of the ISP treatment groups ($p < 0.05$) compared to the control

group. HDL-cholesterol was also significantly increased ($p < 0.05$) in both soy groups compared to the control. The level of isoflavones did not affect any of the blood lipid levels measured.

FDA also previously reviewed the unpublished study by Crouse *et al.*, which was subsequently accepted and published (Ref. 31), in the soy protein proposed rule (63 FR 62977 at 62987). This study examined the effect of soy protein containing different levels of isoflavones in hypercholesterolemic men and women. Subjects with qualifying serum lipid levels (LDL-cholesterol greater than 140 mg/dL) after one month and who were compliant with the study regimen were randomized into one of five treatment groups. The treatment groups received 25 g protein from ISP prepared from soy with different levels of isoflavones (either 1.0, 1.6, or 2.5 mg total aglycone isoflavones/g protein), or 25 g protein from alcohol-washed ISP that contained essentially no isoflavones (0.2 mg total aglycone isoflavones/g protein) or 25 g protein from casein (no isoflavones) in beverages for 9 weeks. Results indicated that compared to casein the ISP containing the highest level of isoflavones significantly lowered total ($p < 0.05$) and LDL-cholesterol ($p < 0.05$), by 4 percent and 6 percent, respectively, while HDL-cholesterol was not altered. In subjects with LDL-cholesterol in the top half of the study population, serum total and LDL-cholesterol were reduced by 9 percent ($p < 0.03$) and 12 percent ($p < 0.03$), respectively, by the ISP with the highest isoflavone content, and by 8 percent ($p < 0.03$) and 9 percent ($p < 0.03$), respectively by the ISP with the second highest isoflavone content, while HDL-cholesterol concentrations were maintained. The authors reported a dose-response effect of increasing amounts of isoflavones on total and LDL cholesterol level. One comment included a reanalysis of the dose-response data that did not include data for the casein diet, in order to control for an independent effect from soy protein itself, and found no significant effect based on isoflavone content. A comment from the petitioner disagreed with this analysis. It also indicated that the study did not eliminate the possibility that isolated soy protein per se has cholesterol-lowering properties, but rather suggested that soy protein with higher levels of isoflavones might have even greater effects. FDA finds that the disparity in these comments does not clarify the equivocal nature of the available evidence. FDA finds that these studies do not provide sufficiently consistent results to cause the agency to

change the conclusion reached in the soy protein proposed rule.

(Comment 34). One comment objected to FDA's consideration of the letter to the editor by Sirtori et al. (Ref. 72) because the reference substantiating the technique for processing the soy protein product was missing from the letter, the products were not tested for isoflavone content at the time of the studies, different soy products (isolate and flour) were used to manufacture the textured soy protein used in the studies, and the references for studies cited in the letter did not match the ones cited by FDA in the soy protein proposed rule. FDA agrees that the reference for the patented procedure for the production of the TVP, described as making use of rapid heating under high pressure, was omitted in the letter by Sirtori et al. (Ref. 72) and that the isoflavone content of the products reported (Cholsoy and Croksoy) was not measured at the time the studies in which they were used were conducted.

The letter by Sirtori et al. (Ref. 72) cites two older studies—Sirtori et al., 1979 (Ref. 55) and Sirtori et al., 1979 (Ref. 155)—as well more recent studies—Sirtori et al., 1995 (Ref. 156)—conducted by their group. The five studies of Sirtori's group that FDA reviewed and cited in the soy protein proposed rule as using products that contained essentially no isoflavones (Refs. 33, 34, 35, 46, and 56) are included in the reference list of Sirtori et al., 1995 (Ref. 156), which is a review article. The agency did not review Sirtori et al., 1979 (Ref. 155) in the soy protein proposed rule, and it did not cite Sirtori et al., 1977 (Ref. 55) because it specifically indicated use of a soy protein product different from those tested for isoflavone content. FDA gives

some credence to the knowledge of the investigator about the products used in his studies, but agrees that the letter to the editor does not provide sufficient documentation to permit an unequivocal conclusion that the products found to be devoid of isoflavones were identical to those used in the clinical studies.

(Comment 35). One comment asserted that most of the studies reported by Sirtori's group were performed using a textured soy protein based on steam-treated soy flour; this treatment would be expected to remove isoflavones. The comment also included a letter from Sirtori (Ref. 157) stating that essentially all of his group's studies beginning in 1980 were with products without isoflavones. However, the patent referenced in this letter was not included with this submission. Thus, FDA cannot verify that the process used to produce the products used in Sirtori's studies over time was the same used to produce the products analyzed recently for isoflavone content.

(Comment 36). The interpretation of the data available on the role of soy isoflavones in and the effects of processing on the hypocholesterolemic effect of soy protein varied widely in the comments. Several comments agreed with FDA's conclusion that the evidence did not support a significant role for soy isoflavones in cholesterol-lowering effects of soy protein. One comment supported the petitioner's original conclusion that a level of 2 mg aglycone isoflavones per g soy protein was necessary for cholesterol lowering. In a comment, the petitioner agreed with FDA "that a relationship exists between soy protein per se and reduced risk of CHD."

The additional evidence about the role of isoflavones is contradictory and inconclusive and has not persuaded FDA to alter its original conclusion about the inability to identify a specific contribution of soy isoflavones to the cholesterol-lowering effects of soy protein. At the same time, the evidence shows a clear relationship between soy protein and reduced risk of CHD despite lack of a clearly defined mechanism for its effect.

(Comment 37). Several comments interpreted the evidence as showing that alcohol extraction used in the processing of certain soy protein ingredients (to the extent that they are rendered essentially devoid of isoflavones) impairs or eliminates the hypocholesterolemic effects of soy protein and recommended that the health claim not be allowed for alcohol-washed products. Comments also raised some questions about the extent to which extensively alcohol-washed products, such as those used in the animal studies, are available commercially. One comment asserted that some of ISP products used in the primate studies were subjected to additional alcohol extraction by the investigators, but the agency could not independently verify this assertion. This comment also stated that all commercial sources of soy protein contain some isoflavones.

FDA examined the recently compiled USDA-Iowa State University Isoflavone Database (Ref. 158), which documents the following ranges of total isoflavone content for various soy protein-containing ingredients, and found that most, but not all, contained levels of isoflavones higher than those that would result from harsh alcohol extraction procedures:

TABLE 1

Product	Aglycone isoflavones (mg/100 g edible portion)
Soy flour, textured	4.40–295.55
Soy flour, defatted	73.72–168.09
Soy flour, full-fat, raw	59.80–264.84
Soy flour, full-fat, roasted	131.70–260.50
Soy protein concentrate, aqueous washed	61.23–167.00
Soy protein concentrate produced by alcohol extraction	2.08–31.82
Soy protein isolate	46.50–199.25
Instant beverage, soy powder	100.10–125.00

FDA agrees that the data from the animal studies reviewed suggest that alcohol washing of soy protein can reduce its hypocholesterolemic effects. With respect to human studies, FDA finds the available evidence is

insufficient to permit any conclusions about the impact of processing by alcohol extraction on the hypocholesterolemic effect of soy protein. Thus, FDA concludes it would be premature to exclude alcohol-washed

products from eligibility to bear the health claim.

(Comment 38). One comment noted that several clinical trials designed to resolve questions about the impact of processing and isoflavone content are

currently in progress. Many of the comments on these issues urged that FDA proceed with the health claim regulation as proposed, but monitor research developments and make changes in the regulation as warranted by the results.

As noted above, FDA finds that, in light of the evidence that soy protein processed in various ways, containing unknown amounts of isoflavones, has hypocholesterolemic effects, FDA is not applying any criteria for inclusion of naturally occurring isoflavones or excluding alcohol-washed products from eligibility to bear the health claim on soy protein and CHD.

(Comment 39). A few comments suggested that, regardless of the conclusions about the significance of soy isoflavones to the reduction of CHD risk, food products that bear the soy protein health claim be allowed or required to state the isoflavone content of the product on the label. The comments did not provide any evidence that persuaded the agency that consumers would find this information helpful in making healthful dietary choices. Accordingly, the agency is not adopting this suggestion.

4. Amount of Soy Protein Required for Significant Effect on Cholesterol Levels

Based on the limited data reviewed that supported a dose-response and the data that showed clinically significant reductions in total and LDL-cholesterol with soy protein ingestion in the range of 17–31 g/day, and recognizing that the hypocholesterolemic effects of soy protein were dependent on initial blood lipid levels, the agency tentatively concluded that 25 g/day represented a reasonable, effective amount of soy protein (63 FR 62977 at 62992). In addition, the agency noted that an amount of 25 g/day of soy protein represents half of the Reference Daily Intake (RDI) of 50 g for protein and is a reasonable level of consumption in the context of the total daily diet. Thus, FDA tentatively concluded that the amount of soy protein associated with reduction in total and LDL-cholesterol levels and, thus, with reduced risk of CHD was 25 g or more of soy protein per day (63 FR 62977 at 62992).

(Comment 40). Many comments agreed with the agency's conclusion that 25 g or more of soy protein per day was associated with reduction in total and LDL-cholesterol levels. Several comments raised concerns about the adequacy of the available data to support an assessment of dose-response. One comment expressed concern that higher levels of soy protein are needed to modify cholesterol levels in

normocholesterolemic individuals and that this should be indicated as part of the claim.

FDA agrees that the available data on the hypocholesterolemic effects of soy protein do not permit a dose-response assessment. However, FDA notes that dose-response data are not required to establish the qualifying criteria for a substance that is the subject of a health claim. Under § 101.70, which describes the requirements for health claim petitions, the petition must address whether there is an optimum level of the particular substance to be consumed beyond which no benefit would be expected (§ 101.70(f)(B)(1)). This information may or may not be based on dose-response data. For example, in its evaluation of the scientific evidence for a relationship between consumption of soluble fiber from psyllium seed husk and blood total and LDL-cholesterol levels, the agency found no reliable data to establish a dose-response for this relationship (62 FR 28234 at 28240). However, the agency did find that, in placebo-controlled studies that tested an intake of 10.2 g of psyllium seed husk per day as a part of a diet low in saturated fat and cholesterol, there were consistently significant effects of psyllium husk on blood total and LDL-cholesterol levels. Therefore, the agency based the qualifying level of soluble fiber from psyllium seed husk on a total daily intake of 10.2 g husk or about 7 g of soluble fiber.

The qualifying level of 25 g/day has been demonstrated to have a consistent, clinically significant effect on total and LDL-cholesterol levels. This 25 g/day level of intake for cholesterol lowering is confirmed by the new study of Teixeira et al. (Ref. 136), which showed significant hypocholesterolemic effects of 20 g/day of soy protein. Therefore, the agency disagrees with the comments suggesting that dose-response data are needed before the agency can authorize a health claim. The totality of scientific data, which establish a clinically significant reduction in blood cholesterol based on an intake of at least 25 g/day of soy protein, provides an adequate basis for establishing a qualifying level for soy protein-containing products.

The agency agrees that the available data indicate that the hypocholesterolemic effect of soy protein may be dependent on initial cholesterol levels, but notes that moderately hypercholesterolemic individuals are generally more responsive to dietary interventions than normocholesterolemic individuals. As the leading cause of death in this country, CHD is a disease for which the

general U.S. population is at risk. The risk of dying from CHD is related to serum cholesterol levels in a continuous and positive manner, increasing slowly for levels between 150 mg/dL and 200 mg/dL and more rapidly when the cholesterol level exceeds 200 mg/dL (Ref. 37). The public health policy articulated by the NCEP, National Heart, Lung, and Blood Institute, is to extend the benefits of cholesterol lowering to the population as a whole by promoting adoption of eating patterns that can help lower the blood cholesterol levels of most Americans (Ref. 67). A dietary intervention that lowers blood cholesterol levels only in persons with high levels would, like an intervention that lowers cholesterol levels across the entire population range, cause a shift in the population distribution of blood cholesterol levels resulting in a decrease in the mean value for the blood cholesterol level in the general population (Ref. 67). The anticipated effect of such a shift would be to reduce the morbidity from CHD and to produce a continued or accelerated decline in the CHD mortality rate in the United States. The agency is persuaded by the evidence it has reviewed in this rulemaking that the consumption of soy protein, as part of a low saturated fat and cholesterol diet, can be a useful public health measure to assist in the national policy of promoting eating patterns that will help in achieving or maintaining desirable blood cholesterol levels in the general population. Therefore, it concludes that the health claim need not indicate that hypercholesterolemic individuals may be more responsive to consumption of soy protein than normocholesterolemic individuals. In addition, consistent with the agency's conclusions in rulemaking on the dietary saturated fat and cholesterol/CHD claim (58 FR 2739 at 2745, January 6, 1993), the wording of the health claim as "may" or "might" reduce the risk of heart disease" adequately represents the fact that not all persons will realize the same magnitude of benefit from adopting the dietary change.

5. Summary of the Scientific Evidence

FDA reviewed human studies submitted by the petitioner and in comments that evaluated the effects on serum cholesterol and LDL-cholesterol levels of dietary interventions with soy protein in subjects with normal to elevated serum cholesterol levels and that met the agency's criteria for selection.

Most intervention trials in subjects with total cholesterol levels less than 300 mg/dL found that soy protein

reduced total and/or LDL-cholesterol levels to a clinically significant degree (Refs. 31, 28, 27, 51, 44, 37, 49, 30, 58, 29, 43, 136, and 137). Moreover, HDL-cholesterol levels were unchanged (Refs. 31, 27, 51, 40, 37, 49, 36, 53, 136, and 137) or slightly increased (Refs. 28, 44, 58, and 59). In some cases (Refs. 27, 44, and 49), decreases in total and LDL-cholesterol were statistically significant only in subsets of subjects with the higher initial blood lipid levels. Results in normocholesterolemic subjects (Refs. 30, 36, 58, 59, and 53) were more variable than those in hypercholesterolemic subjects (Refs. 31, 28, 27, 51, 44, 40, 37, 49, 54, 29, 43, and 136) except in the study of Wong et al. (Ref. 137), in which normocholesterolemic and moderately hypercholesterolemic subjects were equally responsive. The outcome of an epidemiologic study (Ref. 65) also supported a relationship between higher levels of soy protein intake and lower blood lipid levels.

Most of the studies in subjects with total cholesterol levels less than 300 mg/dL used low saturated fat and low cholesterol diets (Refs. 31, 28, 27, 51, 44, 30, 36, 53, 29, 43, 136, and 137), but some used "usual" diets (Refs. 37, 49, 54, 36, 58, and 59). Although soy protein was found to lower blood lipid levels in some of the studies using "usual" diets, hypocholesterolemic effects of soy protein were more consistently observed with diets low in saturated fat and cholesterol. Given the variability of amounts and forms in which soy protein was provided in the diets, the response of blood lipid levels appears robust and notably consistent, particularly in subjects with moderate hypercholesterolemia.

Data from studies of adults with type II and familial forms of hypercholesterolemia (and total cholesterol levels in excess of 300 mg/dL) (Refs. 55, 33, 64, 56, 64, 46, and 35) were also consistent in showing large and statistically significant decreases in total and LDL-cholesterol, accompanied by no changes or slight increases in HDL-cholesterol levels. Nearly all of the subjects in these trials consumed low saturated fat and low cholesterol diets during the studies and had consumed such diets prior to studies with soy protein. Soy protein was tested in a variety of foods but produced fairly consistent results regardless of the food form fed and apparent differences in processing techniques.

The FDA concludes, based on the evidence submitted and reviewed, that soy protein, included in a diet low in saturated fat and cholesterol, can lower blood total and LDL-cholesterol levels,

without adversely affecting HDL-cholesterol levels. The agency also concludes that the effect is due to soy protein per se and is not consistently related to the presence or absence of isoflavones. The evidence currently available, as reviewed in section II.B.3 of this document, does not permit a conclusion regarding how significantly alcohol processing may affect the hypocholesterolemic effects of soy protein. The intervention studies reviewed indicate that a minimum level of approximately 25 g of soy protein per day results in a clinically significant effect on total and LDL-cholesterol levels.

With respect to the scientific data and information about the relationship of soy protein and CHD, the relevant data are provided by well controlled and well designed studies. Soy protein, the food substance that is the subject of the claim, is measured in those studies. The relationship of the biomarkers evaluated—total and LDL-cholesterol—to the risk of CHD is validated and the studies measured the biomarkers appropriately. Finally, a consistent body of evidence from a variety of studies is available. Accordingly, the agency is able to conclude, based on the totality of the publicly available scientific evidence, that there is significant scientific agreement that soy protein, included at a level of 25 g/day in a diet low in saturated fat and cholesterol, can help reduce total and LDL-cholesterol levels, and that such reductions may reduce the risk of CHD.

C. Nature of the Food Eligible to Bear the Claim

1. The Qualifying Amount of Soy Protein

Using 25 g of soy protein as the qualifying amount for a CHD claim, the petitioner suggested that a single serving of a soy protein-containing product (*i.e.*, one RACC) should provide $\frac{1}{4}$ of this amount (based on four servings a day). Thus, a soy protein-containing product would have to contain at least 6.25 g soy protein ($\frac{1}{4} \times 25$ g) per RACC. The petitioner stated that this approach was reasonable because it would permit a wide variety of low fat, soy protein-containing products to bear the health claim. The petitioner provided a list of products on the market that currently meet the proposed requirements and a list of products that could be modified to meet them (Ref. 1, Appendix V). The agency has generally made the assumption that a daily food consumption pattern includes three meals and a snack (see 58 FR 2302 at 2379, January 6, 1993). The agency

tentatively concluded in the soy protein proposed rule that the assumption of four servings per day of soy protein-containing foods was reasonable. Therefore, the agency found that use of the qualifying criterion set forth in the petition would be appropriate (63 FR 62977 at 62992).

Most comments agreed that the qualifying level of 6.25 g soy protein per RACC was appropriate. Many of these comments also indicated that a sufficient number and variety of soy protein-containing foods are available to enable consumers to select suitable products to consume a total of 25 g soy protein per day.

(Comment 41). Several comments suggested rounding the qualifying level to 6 or 7 g of soy protein per RACC, in keeping with the requirements for the labeling of protein in the Nutrition Facts panel.

FDA, however, notes that the Nutrition Facts panel contains the amount of total protein per serving of the product, regardless of the source ingredient. For many products that may bear the claim, soy protein may not be the sole contributor to total protein. Therefore, FDA finds that the amount of soy protein in a serving of a food that may bear the health claim will neither be required nor permitted to appear in the Nutrition Facts panel. The qualifying level need not conform to requirements specific to the Nutrition Facts Panel.

(Comment 42). One comment received in response to the soy protein reproposal indicated that food processors will be required to declare the corrected amount of protein and the percent Daily Value of protein on the Nutrition Facts panel, in accordance with 21 CFR 101.9(c)(7)(i). This comment noted that, in nearly all cases, the amount of protein declared will be lower than the quantity of protein present in the product and may, in some instances, be lower than the qualifying amount of soy protein.

FDA notes that compliance with the requirements of this regulation will be based on the actual amount of soy protein present in the food and not on the amount of protein declared on the nutrition label.

(Comment 43). One comment suggested that the qualifying level should be increased to 12.5 g soy protein per RACC because of concerns that consumers would not choose soy protein-containing foods frequently enough during a day to reach a total of 25 g and might believe that the health benefit may be attained by eating a single serving of a food that provided no more than 6.25 g soy protein. Several

other comments also raised concerns that consuming soy protein-containing foods up to four times daily would represent a significant change from the typical American diet that might not be selected by many consumers.

FDA cannot assess how many consumers would be interested in making such a change, but it is persuaded that it will be feasible for motivated consumers to do so. Doubling the qualifying level of soy protein per RACC would greatly and unnecessarily restrict the number of foods potentially eligible to bear the health claim. Because § 101.82(c)(2)(i)(G) requires that the claim specify both the daily dietary intake of soy protein that is necessary to reduce the risk of coronary heart disease and the contribution that one serving of the product makes to the specified daily dietary intake, consumers will not be misled about the amount of soy protein needed for the health effect.

(Comment 44). A number of comments suggested that greater flexibility in meeting the recommended total daily intake of 25 g soy protein per day could be achieved by permitting a lower qualifying level on the basis of increasing the number of servings or eating occasions per day from four to five or six or more. Several of these comments proposed that the qualifying level of soy protein should be reduced to 4 g per RACC; one suggested lowering the qualifying level to 2.5 g per RACC. Most of these comments indicated that 4 g soy protein per RACC is the maximum amount of soy protein from soy flour that can be incorporated in baked products that consumers find palatable and acceptable. These comments suggested that lowering the qualifying level would stimulate manufacturers to develop a wider range of products and indicated that use of ISP in baked products would be prohibitively expensive. One comment challenged FDA's assertion that consumers would be able to consume an effective amount of soy protein from a variety of products, including baked goods. FDA based the assertion on its observation that baked products had been used to provide soy protein in some studies the agency relied upon to justify authorization of the health claim (Refs. 27, 28, and 51); in one study (Ref. 27), the authors indicated that 25 g soy protein daily was provided in four muffins. ISP was the source of soy protein in the baked products used in these studies. Some comments stated that FDA need not base the qualifying level on four eating occasions per day as the agency had done for other health claims for substances (beta-glucan

soluble fiber from whole oats and soluble fiber from psyllium seed husks).

FDA finds that these comments did not provide a compelling rationale for selecting an appropriate number of eating occasions on any other basis. The agency has not limited its previous determinations of an appropriate qualifying level of a substance that does not have a Daily Value in a food to be eligible to bear a health claim to consideration of the number of individual foods or classes of food products then available that might bear the claim. Rather, in determining what constitutes a level of the substance sufficiently high to justify the claim, FDA considers factors such as the number of servings likely to be consumed and the feasibility of developing a variety of foods that contain a significant proportion of the total daily intake needed for the claimed benefit. For example, when the psyllium claim was authorized, FDA was aware of only one conventional food product that would have been eligible to bear the claim and concluded that, if various psyllium-containing foods were available, consumption of four servings daily could be achieved. Based on experience with that claim and other health claims, FDA believes that manufacturers will be encouraged by the availability of a health claim for soy protein and CHD to develop new products that will be eligible to bear the claim. The agency is not persuaded by the comments received that it should abandon its assumption that a daily food consumption pattern includes three meals and a snack (see 58 FR 2302 at 2379, January 6, 1993) and that one serving of a soy protein-containing product could reasonably be consumed at each eating occasion. As noted in the discussion above of the comments that expressed concerns about the willingness of consumers to select soy protein-containing foods as many as four times a day, such an eating pattern represents a considerable change from a typical American diet. Although one of the comments included detailed menus that illustrated the possibility of consuming more than one soy protein-containing product per eating occasion, FDA has concluded that it should not lower the amount of soy protein required for a food to be eligible to bear the health claim.

(Comment 45). One comment suggested that the amount of soy protein required for eligibility to bear the health claim be permitted to be determined on the basis of serving size as well as RACC.

This comment is outside the scope of this rulemaking. Current regulations (21

CFR 101.12(g)) require that, "The reference amount [i.e., the reference amount customarily consumed] * * * shall be used in determining whether a product meets the criteria * * * for health claims." In a previous rulemaking, FDA had considered permitting this option, but comments persuaded the agency that the most reasonable approach was to base claim evaluations on the reference amount (58 FR 2229 at 2287). FDA agreed with the comments that claims should reflect the true characteristics of a product, and that those characteristics do not change if the product is packaged in a different size container. The comment received in response to the soy protein proposed rule did not provide a convincing rationale to justify a change in this decision.

2. Method for Determining Qualifying Amount of Soy Protein in Foods

In the soy protein proposed rule (63 FR 62977 at 62992), FDA proposed use of the Association of Official Analytical Chemists (AOAC) official method of analysis No. 988.10 to measure soy protein in foods. As described in the soy protein reproposal (64 FR 45932 at 45933), each of the comments on this proposed analytical method disagreed with its use and concluded that the method was unlikely to produce a reliable measure of the soy protein content in every food. The comments noted a variety of problems with the assay. These comments persuaded the agency that AOAC official method of analysis No. 988.10 was not an appropriate method for the quantitation of soy protein in many of the products that may be eligible to bear the health claim.

In the soy protein reproposal, FDA discussed the alternative approaches suggested in comments for assessing compliance with the qualifying level of soy protein in products that bear the health claim. Based on this information, the agency provided its tentative rationale for a procedure employing measurement of total protein and, for products containing sources of protein other than soy, calculation of the soy protein content based on information contained in manufacturers' records (64 FR 45932 at 45934). Thus, in the soy protein reproposal, FDA modified previously proposed § 101.82(c)(2)(ii)(B) to provide for this alternative approach for compliance assessment that relied, in some cases, on records that the agency could inspect.

The agency received approximately 10 comments in response to the soy protein reproposal. One of the comments did not address the proposed

procedure for compliance assessment but, rather, reiterated concerns raised in comments on the soy protein proposed rule about the safety of soy isoflavones. Among the materials it referenced were two documents authored by FDA staff that the comment characterized as "reports." FDA could not identify one of these documents from the citation given and the other was a letter submitted as a comment to Docket 98P-0683 in response to the soy protein proposed rule. Another comment raised concerns about the GRAS status of soy protein. FDA has addressed the issues raised in the earlier comments regarding GRAS status and safety in Section II.A of this document. In addition to commenting about the reproposal, one comment raised a technical issue about the nutrition labeling declaration of protein that is addressed in Section II.C.1.

(Comment 46). Two comments objected to the 30-day comment period allowed for the soy protein reproposal. FDA stated its rationale and authority for selecting this period in the soy protein reproposal (64 FR 45932 at 45936 and 45937) and notes that these comments were submitted and received in timely fashion. One of these comments asserted that after the comment period for the soy protein proposed rule had passed, no new submissions or evidence after that date other than that of FDA origin (or from published scientific documents accessed by FDA) was acceptable. As noted in the introduction of Section II of this document, FDA disagrees with this assertion. FDA considered comments received after the initial comment period, regardless of source, to the extent that each provided complete information for review or references accessible to the agency and addressed issues not raised in earlier comments.

(Comment 47). A comment asserted that the issue of the method FDA will use to verify that foods contain the qualifying amount of soy protein is irrelevant because FDA was required to consider and evaluate only the claims made for the substance identified in the petition, soy protein with naturally occurring isoflavones.

This comment misunderstands FDA's responsibility to review and evaluate the available scientific evidence and reach appropriately supported conclusions about the substance-disease relationship based on information provided in the petition, accessed in the public scientific literature, and received in comments. FDA notes, for example, that in response to a petition for oat bran and oatmeal, it proposed to authorize a health claim on the relationship of those foods and CHD (61

FR 296). Comments received in response to that proposal persuaded FDA to change the substance of its final rule to beta-glucan soluble fiber from whole oats (62 FR 3584). The agency has addressed the earlier comments on the role of isoflavones in the hypocholesterolemic effect of soy protein in Section II.B.3 of this document.

(Comment 48). Two comments objected to any use of recordkeeping for compliance assessment, questioning whether it could be an appropriate substitute for analytical methods to assess the truthfulness of health claims. One of these comments also reiterated objections to authorization of the health claim, because of concerns about incomplete scientific understanding of the biological activity of soy components, in terms of both safety and contribution to the protective effect of soy protein in CHD. The agency has addressed these concerns, which were raised in comments on the soy protein proposed rule, in Sections II.A and II.B.3, respectively, of this document.

The other comment asserted that an approved, scientifically accurate methodology is needed for any health claim. However, it also indicated that FDA should finalize its regulation as originally proposed, but did not propose an alternative for compliance verification other than suggesting that a manufacturer might voluntarily share analytical data with the agency if questions about compliance were raised.

FDA does not agree with the contention that an analytical method is an absolute requirement for a health claim, even though it is the preferred means for verifying compliance with the requirements of a health claim regulation and substantiating the truthfulness of all label statements.

(Comment 49). Many other comments supported continued work to develop appropriate analytical methodology for measuring the content of soy protein in foods, and urged FDA, in collaboration with other government agencies, industry, and scientific organizations, to pursue this effort. As noted in the soy protein reproposal, FDA intends to do so, to the extent that resources permit. Also, as noted in the soy protein reproposal, and as urged in a number of comments, FDA would propose to amend its regulation to provide for compliance verification based on one or more analytical methodologies when such methods have been validated.

(Comment 50). Several of the comments specifically addressed the method for assessing compliance set out in the soy protein reproposal. None of these comments objected to use of an

analytical method for measuring total protein as a measure of soy protein in foods that contain soy as the only source of protein. Absent an appropriate analytical methodology, each of these comments supported the need for manufacturers to have and keep records to substantiate the amount of soy protein in a food that bears the health claim and contains sources of protein other than soy, and to make such records available to appropriate regulatory officials upon request. These comments noted that in cases where records are needed to substantiate label claims, food manufacturers have historically provided such records voluntarily upon request to the FDA and could be expected to continue to do so in the future. They argued that FDA need not assert broad records inspection authority in order to obtain the information needed for compliance assessment. They noted 21 CFR 101.13(j)(ii)(A), which requires firms to have substantiation for the basis of nutrient reference values in comparative nutrient content claims and to make such substantiation available to appropriate regulatory officials upon request, as a model for requests of records.

FDA agrees that a manufacturer must have substantiation that a qualifying amount of soy protein is present in a product that bears the health claim and that such records can serve as the basis for substantiation of use of the health claim. FDA noted in the **Federal Register** of February 2, 1996 (61 FR 3885 at 3886) several examples of regulations that implemented the 1990 amendments in which the agency could not independently, using analytical methodology, verify the basis for statements on the food label, but instead would rely on access to a manufacturers' information supporting its labeling claims. These include access to:

(1) A detailed protocol and records of all data used to derive a density-adjusted reference amount for aerated foods (58 FR 2229 at 2272 and § 101.12(e));

(2) Information that provides the basis for deriving reference nutrient values for comparative nutrient content claims such as "light" (58 FR 2302 at 2365 and § 101.13(j)(1)(ii)(A));

(3) Specific information with respect to the caloric content of new products with reduced digestibility (58 FR 2079 at 2087 and 2111 and § 101.9(c)(1)(i)(D)); and

(4) Information supporting nutrient content claims for restaurant foods (58 FR 2302 at 2388 and § 101.13(q)(5)(ii)).

In each of these cases, verification of the truthfulness of a label claim can be assessed by FDA only with access to information known only by the manufacturer. The same is true, in the absence of a validated analytical method to measure the amount of soy protein in the presence of other proteins, for verifying that the qualifying amount of soy protein to bear the health claim is present in a food that contains sources of protein in addition to soy. Thus, the agency concludes, in agreement with these comments, that it is appropriate to require access to manufacturers' records substantiating the ratio of soy protein to total protein for foods that contain sources of protein in addition to soy to assess their compliance with this regulation. Also, in agreement with these comments, the agency concludes that it need not assert broad records inspection authority to have access to appropriate records. The agency disagrees, however, with comments that indicate that reliance on the voluntary provision of records by manufacturers is sufficient to meet the agency's need to verify compliance. Rather, the agency is taking the approach of codifying a requirement for the manufacturer to provide appropriate records, on request, as the agency has done previously.

Although most of the comments supported the use of records, in principle, for compliance assessment, they also raised concerns about the types of records that FDA might request, the circumstances under which FDA would request records, and the legal authority of the FDA to require records and records inspection.

(Comment 51). Several comments indicated that FDA had used overly broad and imprecise language in the soy protein reproposal to describe the types of records that FDA would request. They indicated that a manufacturer is best able to determine the nature of the records that would be needed to substantiate the amount of soy protein in its own products and urged that manufacturers be allowed the flexibility to determine how to document substantiation. One comment argued that a recipe-based system would be too complex and burdensome for baked goods in particular. Other comments expressed concern that FDA would, in all cases, require inspection of a wide variety of records, including nutrient data bases or analyses, recipes or formulations, purchase orders for ingredients, and others.

FDA agrees that the manufacturer will be in the best position to know which of its records provide documentation of the amount of soy protein in its products, and specifically the ratio of

soy protein to total protein. By listing the types of records that could provide such documentation in the soy protein reproposal, FDA did not intend to indicate that it would request all of these records and subject them to inspection, or even that it would specify any particular records when it requests them. Instead, FDA intended to suggest the types of records a manufacturer might use to substantiate the levels of soy protein in its foods. Accordingly, FDA has modified § 182(c)(2)(ii)(B) to clarify that the manufacturer is to identify these materials.

(Comment 52). One comment questioned whether FDA might request records for products in which soy is the only source of protein and urged FDA to specify that it would not request records for such products.

FDA agrees that, because measurement of total protein provides adequate assessment of compliance for products in which soy is the sole source of protein, that it would not, under the regulation, request records for substantiation of the amount of soy protein in such products. The agency believes that the proposed language adequately communicates this point and has made no changes to the regulatory language in response to this comment.

(Comment 53). One comment requested that FDA identify what circumstances would precipitate a request for records. Although FDA cannot specify all such circumstances, it notes, as did another of the comments, that a substantial proportion of its enforcement actions are undertaken in response to trade complaints.

(Comment 54). One comment asked that the agency specify that any records requested could be provided on site without the need for reproduction or duplication by the investigator. Another comment, however, objected to FDA making requests for information on site, arguing that most companies would have the necessary information at headquarters rather than at production facilities. This comment urged that FDA make any such requests in writing and allow the manufacturers to provide appropriate substantiation within a reasonable period of time. As FDA will not require inspection of records on site, the concern about reproduction or duplication is moot. FDA agrees that making a request for records in writing is appropriate and has modified the regulation accordingly.

(Comment 55). Some comments objected to the alternative offered in the soy protein reproposal that FDA would authorize the claim only for products that contain soy as the sole source of protein, if it could not proceed with a

regulation to provide access to records for compliance verification. These comments noted that such an action would give unfair advantage to certain products, unfairly penalize products that were equally beneficial, and dilute the potential benefit of the health claim to consumers. Because the agency has authorized the claim for any food that contains adequate amounts of soy protein, without regard to other sources of protein, these comments are moot.

(Comment 56). One comment noted that, in addition to providing FDA, upon request, information regarding substantiation of the claim, food processors may, on a voluntary basis, present information on the food label or in labeling that may support the eligibility of the product to bear the claim and facilitate an FDA compliance review. Such information might take the form of statements about the percentage composition of soy protein in a serving of food. The agency agrees that manufacturers may voluntarily provide such truthful and not misleading information and that the provision of such information may aid consumer understanding of the claim.

(Comment 57). Several of the comments strongly objected to the proposal for records inspection on the basis that FDA lacks the statutory authority to require access to records for foods. Another comment argued that, once the agency determined that a substance-disease relationship meets the standard of significant scientific agreement, the act requires the agency to authorize a claim, and the agency may not require that manufacturers maintain records or that FDA be able to request or inspect them. This comment also asserted that, were FDA to require recordkeeping, record production, or records inspection, it would violate the First Amendment by conditioning the exercise of speech rights on the recordkeeping, record production, or records inspection requirement.

FDA disagrees with these comments. Other comments have convinced the agency that, in this instance, it need not assert its rulemaking authority to provide for inspection of records. This issue is therefore moot. The agency maintains, however, that it has the legal authority, using section 701(a) of the act, to promulgate record inspection requirements for the efficient enforcement of the act. The requirements that records be maintained and submitted to the agency upon request pass the test in *National Confectioners Association v. Califano*, 569 F.2d 690, 693 & n.9 (D.C. Cir. 1979). First, these requirements are limited to those records that the manufacturer

reasonably determines substantiate the level of soy protein in its food, and only with respect to foods that contain a source of protein in addition to soy. Second, the requirements assist in the efficient enforcement of the act. They focus only on those foods for which an adequate analytical method is not available. They allow FDA to verify that the authorized soy health claim is truthful and not misleading when it is used on such foods. The requirements, therefore, assist in the effective and efficient enforcement of the act. Third, these requirements are not unduly burdensome. They require maintenance of records that manufacturers should already have to validate that their food product may lawfully bear the claim, and they permit them to identify the records that substantiate their claim. FDA requests copies of the records in writing without inspection. These burdens are not unreasonably onerous.

With respect to significant scientific agreement, the comment misreads the statute. Under section 403(r)(3)(B)(i) of the act, FDA authorizes a claim about a substance-disease relationship only if the standard of significant scientific agreement is met. Under that section, significant scientific agreement is a necessary condition, but not a sufficient one, for FDA to authorize a health claim. FDA may impose other requirements in accordance with section 403(r) of the act.

The agency also disagrees that the recordkeeping and record access provisions violate the First Amendment. Under section 201(g)(1) of the act, a food is not a drug solely because its labeling contains a health claim authorized and made in accordance with the requirements of section 403(r) of the act. Section 201(g)(1) provides no such provision for a food whose labeling contains a health claim that is not authorized and made in accordance with the requirements of section 403(r) of the act. Congress provided for the use on foods of health claims authorized under and made in accordance with the requirements of section 403(r) of the act to promote the public health by, in part, helping consumers maintain balanced and healthful diets (58 FR at 2514). FDA has required that foods whose labels contain an authorized health claim must contain a sufficiently high level of the substance that is the subject of the claim in question (see 21 CFR 101.14(d)(2)(vii)). This provision assures that a food bearing the claim in fact contributes to the claimed effect (56 FR at 60553) and so may help consumers to maintain a balanced and healthful diet. Absent the recordkeeping and access provisions, FDA could not assure that,

when the soy protein health claim appears on foods, they will, in fact, contain sufficiently high levels of soy protein. These provisions, therefore, directly advance Congress' substantial interest in permitting the use of health claims on foods and they are narrowly tailored to do so. In addition, when used on a food, the authorized soy protein health claim must identify the amount of soy protein in a serving of food. Accordingly, the provisions also permit FDA to assure that the claim as it appears on a food is not false and misleading.

3. Requirement that Food Meets the Criterion for Low Fat

In § 101.82(c)(2)(iii)(B), the agency proposed, consistent with other authorized heart disease health claims, that foods bearing the health claim meet the requirements for "low saturated fat," "low cholesterol," and "low fat." In the preamble to the final rule authorizing the fruits, vegetables, and grain products and heart disease claim (§ 101.77, 58 FR 2552 at 2572), the agency stated that populations with diets rich in these low saturated fat and low cholesterol foods experience many health advantages, including lower rates of heart disease. In the preamble to the saturated fat/cholesterol proposed rule (56 FR 60727 at 60739), the agency stated that while total fat is not directly linked to increased risk of CHD, it may have significant indirect effects. Foods that are low in total fat facilitate reductions in intakes of saturated fat and cholesterol to recommended levels. Therefore, the agency tentatively concluded that proposed § 101.82(c)(2)(iii)(B) set forth appropriate requirements for foods to be eligible to bear the soy protein and CHD claim.

(Comment 58). No comments objected to the requirements that a food meet the criteria for "low saturated fat" and "low cholesterol" in order to bear a health claim about the relationship of soy protein and CHD. However, many comments objected to the requirement that a food meet the criterion for "low fat," mainly on the basis that all foods made from whole soybeans would be disqualified by virtue of the inherent ratio of protein to fat (approximately 2 to 1) in soybeans. Several of these comments noted that makers of such foods would have to use soy protein isolates to develop qualifying products. The comments that provided additional rationale argued that saturated fat and cholesterol were properly restricted for a CHD claim, but that total fat need not be restricted to the same degree because it is not directly related to risk of CHD.

These comments noted that products derived from whole soybeans that contain 6.25 g of protein per RACC would just exceed the criterion for "low fat" of 3 g fat per RACC. However, these products would not lead to an increase in the intake of saturated fat or cholesterol and, thus, negate the health benefits of soy protein. In addition, they would serve as sources of the essential fatty acids, linoleic acid and linolenic acid.

As noted above, the FDA has required that foods bearing any of the previously authorized CHD health claims meet the requirements for "low saturated fat," "low cholesterol," and "low fat." In the saturated fat/cholesterol proposed rule, FDA proposed that in order for a food to bear the health claim, the food must also meet the requirements for a "low" claim relative to total fat content (56 FR 60727 at 60739). The agency noted that, while total fat is not directly related to increased risk for CHD, it may have significant indirect effects. Low fat diets facilitate reductions in the intake of saturated fat and cholesterol to recommended levels. Furthermore, the agency noted that obesity is a major risk factor for CHD, and dietary fats, which have more than twice as many calories per gram as proteins and carbohydrates, are major contributors to total calorie intakes. For many adults, maintenance of desirable body weight is more readily achieved with moderation of intake of total fat. The agency also concluded that this approach would be most consistent with the U.S. Dietary Guidelines and other dietary guidance that recommends diets low in saturated fat, total fat, and cholesterol. In the saturated fat/cholesterol final rule (58 FR 2739 at 2742), FDA reiterated the requirement for "low fat," but allowed for the exception that fish and game meats could meet the requirement for "extra lean," because these foods are appropriately included in a diet low in fat, saturated fat, and cholesterol. FDA also noted that the "low fat" requirement for foods to make the saturated fat/cholesterol and heart disease health claim would limit a manufacturer's ability to increase trans-fatty acid levels in foods, since any substitution of trans-fatty acids for saturated fatty acids would have to be accomplished within the 3 g per RACC or per 50 g limit for total fat. The agency considered this approach unlikely to result in significantly increased levels of trans-fatty acids in foods bearing the health claim (58 FR 2739 at 2744).

The latter consideration is not applicable to the case of foods made from whole soybeans. No substitution of one type of fatty acid for another is

contemplated for these products. The amount by which foods made from whole soybeans that are otherwise eligible to bear the soy protein health claim would exceed the "low fat" criterion due to the inherent fat content of soybeans is small and well below the disqualifying level for total fat that a food bearing any health claim must meet (§ 101.14 (a)(4)). FDA is persuaded that products derived from whole soybeans are useful sources of soy protein that they, like fish and game meats that are "extra lean," can be appropriately incorporated in a diet that is low in fat, saturated fat, and cholesterol. Thus, FDA is modifying § 101.82(c)(2)(iii)(B) to require that all products meet the criteria for "low saturated fat" and "low cholesterol" and adding § 101.82(c)(2)(iii)(C) to require that a food meet the criterion for "low fat" in order to bear the soy protein health claim, except for products consisting of or derived from whole soybeans without additional fat.

D. Required Elements for the Claim

1. Context of the Total Daily Diet

In the soy protein proposed rule (63 FR 62977 at 62991), the agency tentatively found that, for the public to understand fully, in the context of the total daily diet, the significance of consumption of soy protein on the risk of CHD (see section 403(r)(3)(B)(iii) of the act), information about the total diet must be included as part of the claim. Therefore, in § 101.82(c)(2)(i)(D), the agency proposed to require that the claim include the fact that the effect of dietary consumption of soy protein on the risk of CHD is evident when it is consumed as part of a healthy diet and that, consistent with other authorized health claims related to CHD, the fat component of the diet be specified as "saturated fat" and "cholesterol."

(Comment 59). One comment objected to this requirement on several grounds: that FDA has been inconsistent in requiring specification of the need to consume diets low in saturated fat and cholesterol in previously authorized CHD health claims; that the effect of soy protein on blood cholesterol levels is independent of a low fat, low saturated fat, and low cholesterol diet; that the statutory requirement to place the claim in the context of the total daily diet need only relate the labeled product to the rest of the day's diet; and that consumers will conclude that soy protein will be of no benefit to them if they cannot reduce saturated fat and cholesterol in their diets. Other comments raised similar objections to the requirement. This comment and

others proposed that FDA allow a variety of shortened claims that would effectively render this requirement an optional element of the claim or that FDA permit the information in this requirement to be presented in a split claim.

FDA disagrees with some of the characterizations of FDA's requirements for currently authorized heart disease claims. The comment notes that the agency requires a statement of the role of low saturated fat and cholesterol diets in the reduction of risk of heart disease in three of the authorized claims' the dietary lipids claim (21 CFR 101.75), the claim for fruits, vegetables, and grain products that contain dietary fiber, particularly soluble fiber (21 CFR 101.77), and the claim for soluble fiber from psyllium seed husks (21 CFR 101.81)—because the effect of the subject food substances had been established only in the context of such a diet. However, the comment maintained that evidence for the hypocholesterolemic effect of soluble fiber from whole oats showed it to be independent of other dietary changes. Thus, in requiring that the claim for this substance be stated in the context of a diet low in saturated fat and cholesterol (21 CFR 101.81), the comment asserted that FDA had failed to provide a claim that accurately and truthfully reflected the underlying science.

FDA disagrees with this characterization. The petition for a health claim for oat products stated that there was significant scientific evidence to show that the effect of oats on lowering serum lipids is independent of a diet low in saturated fat and cholesterol. In light of this evidence, the petitioner argued that any health claim that is authorized need not refer to such a diet. In the proposed rule for a health claim for oat products, the agency acknowledged that there were a number of studies that showed that high intakes of oat bran and oatmeal lowered blood total and LDL-cholesterol in subjects that otherwise consumed a typical American diet (61 FR 296 at 305). However, the agency also recognized that CHD is a major public health concern in the United States, and that the totality of the scientific evidence provides strong and consistent support that diets high in saturated fat and cholesterol are associated with elevated levels of blood total and LDL-cholesterol, and thus CHD (56 FR 60727 at 60737). Dietary guidelines from both government and private scientific bodies conclude that the majority of the American population would benefit from decreased consumption of dietary saturated fat and cholesterol. Although

the results of several studies showed that daily consumption of oat bran or oatmeal lowered total cholesterol and LDL-cholesterol levels, the agency noted that the effects of dietary intake of oat bran or oatmeal were particularly evident when the diets were low in saturated fat and cholesterol (61 FR 296 at 306). Thus, the agency tentatively found it would be more helpful to Americans' efforts to maintain healthy dietary practices if the effect of oats on serum lipids were described in the context of a healthy diet (61 FR 296 at 306).

This tentative conclusion was supported by many of the comments received in response to the proposed rule and described in the final rule authorizing a health claim for soluble fiber from whole oats (62 FR 3584 at 3594). In the final rule, the agency noted that diets low in saturated fat and cholesterol are considered by expert groups to be the most effective dietary means of reducing heart disease risk, and that while soluble fiber from whole oats can contribute to this effect, its role is generally recognized as being of smaller magnitude (Ref. 5). Further, expert groups saw selection of foods with soluble fiber from whole oats as a useful adjunct to selection of diets low in saturated fat and cholesterol (Ref. 5). The agency concluded that it would not be in the best interest of public health or consistent with the scientific evidence to imply that selecting diets with soluble fiber from whole oats is a substitute for consuming diets low in saturated fat and cholesterol (62 FR 3584 at 3594). Therefore, FDA emphasized the importance of the dietary component of the health claim, *i.e.*, the necessity for soluble fiber from whole oats to be consumed as part of a low saturated fat, low cholesterol diet, for a complete understanding of the claim (62 FR 3584 at 3594).

The comment also characterized the claim for sodium/salt and hypertension (21 CFR 101.74) as a claim about risk of heart disease and indicated that FDA was not consistent because this claim is not required to be stated in the context of a diet low in saturated fat and cholesterol. FDA disagrees with this characterization of the claim and the conclusion that follows from it. This claim does not address the risk of heart disease, but rather is a claim specific for hypertension. The scientific evidence does not suggest that dietary saturated fat and cholesterol have a significant effect on blood pressure; thus, no mention of that dietary context is required. In addition, FDA has stated (58 FR 2739 at 2746) that it has not been presented with data that sodium intake

is a risk factor for heart disease and that a claim characterizing the relationship between sodium and heart disease would misbrand a food under section 403(r)(1)(B) of the act unless it were specifically authorized by the agency. The agency does agree with the comment that it has not found that all the risk factors for CHD must be stated in order to ensure that a heart disease health claim is truthful and not misleading. In fact, for CHD claims authorized more recently (21 CFR 101.81), FDA has not required that CHD be characterized in the claim as a disease caused by many factors, in contrast to the claims that FDA authorized earlier as part of the initial NLEA reviews (21 CFR 101.75 and 21 CFR 101.77).

In addition, FDA disagrees with the assertion that the cholesterol lowering effect of soy protein is independent of other dietary changes; the agency interprets the data differently. As noted in the discussion above, most of the scientific evidence for an effect of soy protein on blood lipid levels is provided by studies that used diets low in saturated fat and cholesterol. Although soy protein was found to lower blood lipid levels in some of the studies using "usual" diets, hypocholesterolemic effects of soy protein were more consistently observed with diets low in saturated fat and cholesterol. The agency concludes that the data supporting an independent effect for soy protein are more limited than those supporting an independent effect of soluble fiber from whole oats in reducing cholesterol levels. Moreover, because the hypocholesterolemic effects of soy protein are seen in addition to the effects of a low saturated fat, low cholesterol diet, combining the two practices will provide enhanced benefits.

Nor does FDA agree with the comment's assertion that the statutory requirement to place the claim in the context of the total daily diet need only relate the labeled product to the rest of the day's diet. In the 1993 health claims final rule (58 FR 2478 at 2513), the agency disagreed with comments that proposed that the requirement to enable the public to understand the significance of the claim in the context of the total daily diet would be fulfilled if a health claim merely characterized the level of a substance vis-a-vis a disease, provided that there was significant scientific agreement that that level of intake of the substance was beneficial in reducing the risk of disease. Rather, FDA found that section 403(r)(3)(B)(iii) of the act requires that a regulation that authorizes a health claim

provide that the claim be stated in a manner that enables the public to comprehend the information in the claim and to understand the relationship of the substance to the disease, the significance of the substance in affecting the disease, and the significance of the information in the context of the total daily diet. Thus, a claim may need to address a wide variety of factors to fulfill these requirements, and the agency is not limited to requiring only that information that is necessary to prevent a claim from being misleading.

Finally, the agency is not persuaded that requiring the soy protein claim to be stated in the context of a total daily diet low in saturated fat and cholesterol will deter consumers who are interested in dietary control of cholesterol levels, and who have made unsuccessful attempts to lower dietary intake of saturated fat and cholesterol, from incorporating soy protein into their diets. Consumers now have had experience with the claims for soluble fiber from whole oats and psyllium seed husks. These claims, like the soy protein claim, accurately draw the consumer's attention to the dietary pattern associated most strongly with reduction of risk from heart disease—a diet low in saturated fat and cholesterol—and offer choices of specific foods that can be incorporated into this dietary pattern to enhance its beneficial effects. Thus, FDA is not modifying the requirement that the health claim for soy protein be stated in the context of a diet low in saturated fat and cholesterol.

2. Daily Dietary Intake of Soy Protein and Contribution of One Serving

In the soy protein proposed rule (63 FR 62977 at 62991), the agency proposed that § 101.82(c)(2)(i)(G) require that the claim specify the daily dietary intake of soy protein needed to reduce the risk of CHD and the contribution one serving of the product makes to achieving the specified daily dietary intake. The agency noted this requirement was consistent with requirements set forth in § 101.81 for claims about soluble fiber from whole oats and psyllium seed husks, food substances that (like soy protein) do not have Daily Values that can serve as a guide to consumers for appropriate levels of intake. It is also required by § 101.14(d)(2)(vii).

(Comment 60). Almost all of the comments that addressed these requirements supported the need for the claim to contain this information. Some comments expressed concern that even with this information some consumers might be misled into believing that a

single serving of a soy protein-containing food would contribute the full daily amount needed for the claimed health benefit. FDA notes that these comments did not suggest what additional information might be helpful to consumers in understanding the claim.

(Comment 61). Several comments suggested that the daily dietary intake of soy protein needed to reduce the risk of CHD be required to be described as "at least 25 g/day of soy protein" or "a minimum of 25 g/day of soy protein."

FDA is not persuaded to require that such statements be used because it is concerned about the need to balance informing consumers about the effective level of soy protein intake needed to provide the claimed health benefit against encouraging excessive consumption of a single food substance. If consumers were to interpret the claim erroneously as supporting consumption of soy as the sole source of dietary protein or supplementing a diet already adequate in protein from various sources with additional soy protein, then the two most important tenets of a healthful diet—variety and moderation—would be violated.

(Comment 62). One comment noted that, in the second model claim, the characterization of the total dietary intake of soy protein appeared to have omitted indication that the amount is "per day." FDA agrees. This omission was inadvertent and the agency has corrected § 101.82 (e)(1).

Although comments generally viewed as desirable providing information on both the total daily dietary intake of soy protein and the contribution of a single serving of a food to the total intake, some comments urged that it need not be provided in one place on the label with all of the other required information. Many of these comments encouraged FDA to make provisions for the use of abbreviated claims that would include a referral statement directing the consumer elsewhere on the package for the full claim. Issues associated with abbreviated and split claims are addressed below.

3. Abbreviated/Split Claims

(Comment 63). Although there were not substantive objections regarding most of the required elements FDA specified, a large number of comments objected to the model claims proposed in § 101.82 (e), asserting that they are excessively long, complicated, and cumbersome, and requested that FDA devise shorter claim statements. Many of these comments expressed concerns that manufacturers would be reluctant to use and consumers unlikely to read

such long, complex messages. They frequently suggested that FDA provide for split claims in this rule. These would comprise a short or abbreviated claim (that need not contain all of the required elements identified in the rule) appearing on the principle display panel of the label together with a referral statement for the full claim elsewhere on the package. As support for these suggestions, many of the comments cited the Keystone Dialog's (Ref. 159) endorsement of shorter claims and FDA's own health claim consumer research (Ref. 160), which the comments characterized as showing that short claims were more effective than long claims and that splitting claims between the front and back panels made little difference.

FDA notes, however, that the results of its consumer research were more complicated than indicated by that brief summary. The short and long claims studied differed in the inclusion of information about non-dietary risk factors and special populations at risk for the subject disease. The soy protein health claim already lacks these requirements. The study also found that, for some products with an abbreviated claim and a referral statement on the principal display panel, subjects were less likely to look at the back of the package for the full claim.

Concerns about health claims being too wordy and too lengthy have been raised to the agency in various ways, including by a petition submitted by the National Food Processors Association (NFPA) (Docket No. 94P-0390). In response to the NFPA petition, the agency proposed several changes to the requirements for health claims in the **Federal Register** of December 21, 1995 (60 FR at 66206) (the 1995 proposal). At that time, FDA stated that it had no desire for its regulations to stand in the way unnecessarily of the use of health claims and the presentation of the important information contained in them. The agency stated that, while health claims are being used on the label and in labeling, they could be used more extensively. The agency, therefore, proposed to provide for shorter health claims by making optional some of the elements that are presently required. FDA also proposed to authorize the use of abbreviated claims.

FDA has reviewed the comments received in response to the 1995 proposal on changing the requirements for health claims, including permitting the use of abbreviated claims, but it has not completed work on the final rule. Given that this rule is pending, and given its relevance to the issue of abbreviated claims, FDA has decided to

defer a decision on allowing for abbreviated or split claims on soy protein and the risk of CHD. The agency intends to resolve this matter in the context of the rulemaking based on the NFPA petition. Thus, at this time, the agency is making provision only for a full claim.

E. Other Issues

1. Consideration of Health Claims for Benefits of Soy Protein in Addition to Effects on Cholesterol Levels and Risk of Coronary Heart Disease

(Comment 64). A few comments urged that FDA consider authorizing claims about other putative beneficial effects of soy protein or soy products on cardiovascular disease in addition to cholesterol lowering as well as putative beneficial effects on other diseases or health conditions such as cancer, osteoporosis, and menopausal symptoms. One comment suggested that statements derived from preliminary research on the putative beneficial effects of soy isoflavones be allowed on food labels and in labeling.

These suggestions are beyond the scope of the present rulemaking. The present rulemaking is based on FDA's review of information submitted in a petition about the relationship of soy protein and reduced risk of CHD based exclusively on studies of the cholesterol lowering effects of soy protein. The agency has neither received nor reviewed relevant data for any other possible effects of soy protein relevant to risk of heart disease or of other diseases or health-related conditions. Any interested person who has such data may submit a petition to the agency detailing the information for FDA's review and evaluation of whether such information meets the requirements for authorization of a health claim.

(Comment 65). At the same time, one comment expressed concern that the authorization of a health claim on the relationship of soy protein and risk of CHD might be read by some consumers as an implied claim for other putative benefits of soy foods.

FDA concludes, however, that the requirements it has set forth for the health claim already narrow the focus of the claim sufficiently to the relationship that FDA evaluated. Accordingly, consumers should not be so misled by the claim.

2. Drug Claims vs. Health Claims for Foods

(Comment 66). One comment objected to FDA's provision of a health claim for foods containing soy protein and reduced risk of CHD when FDA had not

approved estrogen as a drug to have an indication for prevention of cardiovascular disease despite a large body of supportive evidence. The comment asserted that FDA must evaluate all products with the same ground rules.

This assertion is incorrect. As the agency explained in the 1993 health claims final rule (58 FR at 2506), the scientific standard for authorization of a health claim is less stringent than the requirements for approval of a new drug under section 505 of the act (21 U.S.C. 355).

3. Claims for Other Vegetable Proteins

(Comment 67). One comment reviewed data on the possible mechanisms for soy protein's hypocholesterolemic effects and concluded that they may be due in part to its amino acid composition, specifically its high arginine and low methionine content. The comment noted that other vegetable proteins, such as pea proteins, have a similar amino acid profile and would likely have the same effect on risk of CHD as soy protein. The comment proposed that qualifying levels of both arginine and isoflavones be required for the health claim and that the claim not be limited to soy protein. FDA finds that this suggestion is outside the scope of the current rulemaking. FDA has not reviewed any data on the hypocholesterolemic effects of specific vegetable proteins other than soy.

(Comment 68). Another comment that also discussed the possible importance of the amino acid composition of soy protein to its cholesterol-lowering ability suggested that the title of the new claim should be "Protein from Certain Foods and Reduced Risk of CHD" in anticipation that data will be generated showing hypocholesterolemic effects of other vegetable proteins with amino acid compositions similar to soy protein. Having reviewed data only on soy protein and being aware of no similar body of evidence about any other vegetable protein, FDA finds this suggestion premature.

4. Regulatory Issues Regarding Soy Protein Claims in Other Countries

(Comment 69). One comment provided extensive information about a complaint brought against a company regarding a particular television advertising campaign for a non-dairy soy beverage product in New Zealand that was alleged to be deceptive. This information included an unpublished report of a study comparing the effects of the non-dairy soy beverage to milk that was inadequate for assessing a

hypocholesterolemic effect for soy protein or the soy product itself because dietary saturated fat and cholesterol varied substantially in the two dietary treatments. Another comment raised concerns about the importation of foods from the United States that may bear health claims in violation of Mexican law.

The FDA advises that violations of laws or regulations of other countries with respect to claims made on food labels or labeling or claims made in advertising are outside the scope of the present rulemaking. Companies doing business in other countries are responsible for complying with the relevant statutory and regulatory requirements of those countries.

5. Genetically Modified Soybeans

(Comment 70). Two comments noted that much of the current soybean crop in the United States consists of genetically modified varieties of soybeans. One comment requested that products bearing the health claim be required to indicate on the label whether genetically modified soybeans were used. The other comment noted that genetic modification may alter the content of isoflavones and other biologically active components of soy and suggested that research was needed to determine if such genetic modifications raise additional safety concerns. The comments provided no data or other information to justify labeling or substantiate any safety concerns.

FDA has considered these comments and disagrees with both, for the following reasons. FDA has stated its expectation that companies consult with the agency early in the process of developing a bioengineered food and that they provide the agency with a summary of safety data and a nutritional assessment for its review (Ref. 161). To date, three companies have consulted with the agency about bioengineered soybeans. Two companies developed soybeans that are resistant to the herbicides glyphosate and glufosinate, respectively. A third company modified the oil composition of the soybean to increase its levels of oleic acid, and it must be labeled as high oleic acid soybean. One company stopped further development of a genetically modified soybean that involved the addition of a brazil nut protein when it discovered that the protein would cause allergic reactions.

The safety and nutritional assessments of the three bioengineered soybeans show that there are no unintended effects of the genetic modification (Refs. 162 through 167). In

particular, these soybeans possess the same nutritional profile as their parent or other commercially available soybeans, except that the high oleic acid soybean has a modified fat profile, as intended. In addition, levels of isoflavones, trypsin inhibitors, and endogenous allergens are unchanged. The agency therefore concludes that there is no basis to the comment's assertion that currently available bioengineered soybeans may raise additional safety concerns. Nor is there any basis to require that bioengineered soybeans be identified in food labeling as such.

III. Environmental Impact

The agency has previously considered the environmental effects of this rule as announced in the soy protein proposed rule (63 FR 62977 at 62993) and the soy protein reproposal (64 FR 45932 at 45935). The agency determined that this action is of a type that does not individually or cumulatively have a significant effect on the human environment, and that neither an environmental assessment nor an environmental impact statement is required, but provided incorrect citations for categorical exclusion in the proposed rules. The correct citation is 21 CFR 25.32(p). No new information or comments have been received that would affect the agency's previous determination.

IV. Analysis of Economic Impacts

A. Cost-Benefit Analysis

FDA has examined the impacts of this final rule under Executive Order 12866. Executive Order 12866 directs federal agencies to assess the costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects; distributive impacts; and equity). According to Executive Order 12866, a regulatory action is "economically significant" if it meets any one of a number of specified conditions, including having an annual effect on the economy of \$100 million or adversely affecting in a material way a sector of the economy, competition, or jobs. A regulation is considered "significant" under Executive Order 12866 if it raises novel legal or policy issues. FDA finds that this final rule is neither an economically significant nor a significant regulatory action as defined by Executive Order 12866.

In addition, FDA has determined that this rule does not constitute a significant rule under the Unfunded

Mandates Reform Act of 1995 requiring cost benefit and other analyses. A significant rule is defined in 2 U.S.C. 1532 (a) as "a Federal mandate that may result in the expenditure by State, local and tribal governments in the aggregate, or by the private sector, of \$100,000,000 (adjusted annually for inflation) in any 1 year."

Finally, in accordance with the Small Business Regulatory Enforcement Fairness Act, 5 U.S.C. 801(a)(1)(A)(ii), the Administrator of the Office of Information and Regulatory Affairs of the Office and Management and Budget has determined that this final rule is not a major rule for the purpose of Congressional review. A major rule for this purpose is defined in 5 U.S.C. 804 as one that the Administrator has determined has resulted or is likely to result in: (A) an annual effect on the economy of \$100,000,000 or more; or (B) a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or (C) significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

B. Regulatory Options

FDA did not discuss regulatory options in the analysis of the proposed rule, because no costs were identified in that analysis. Public comments on the proposed rule raised a number of potential costs and a number of issues that may affect the benefits of this rule. The comments also suggested a large number of regulatory options. The primary options suggested in the comments were as follows:

- (1) Take no new regulatory action.
- (2) Take no action, but generate or wait for additional information on which to base a future action.
- (3) Take proposed action.
- (4) Take proposed action, but specify a different minimum level of soy protein for products bearing the claim.
- (5) Take proposed action, but specify a minimum level of soy isoflavones in addition to a minimum level of soy protein for products bearing the claim.
- (6) Take proposed action, but revise the wording of the claim or require that warnings or other statements accompany the claim.
- (7) Take proposed action, but specify a different maximum total fat content or grant an exemption from the maximum total fat requirement for foods made with natural soy beans that have no added fat.

(8) Take proposed action, but use a different procedure for determining level of soy protein in particular products.

1. Option One: Take No New Regulatory Action

By convention, the option of taking no new regulatory action is the baseline in comparison with which the costs and benefits of the other options are determined. Therefore, neither costs nor benefits are associated with taking no new regulatory action.

2. Option Two: Take No Action, But Generate or Wait for Additional Information on Which To Base a Future Action

A number of comments suggested delaying action until further research is carried out on: (1) The mechanism by which soy protein reduces the risk of coronary heart disease (CHD), including the role of soy isoflavones; (2) the effect of particular methods of manufacturing soy protein isolates and products containing soy protein; (3) the effect of other characteristics of the diet such as fiber or mineral content; (4) potential health risks associated with increased intake of soy protein, soy isoflavones, other components of soybeans, and artifacts of particular methods of manufacturing soy protein isolates and products containing soy protein; (5) consumption patterns of foods containing soy protein and the percentage of such foods that meet the proposed requirements for the health claim; and (6) methods of measuring the level of soy protein in foods.

The cost of delay is the elimination of the benefits that would have been realized between the effective date of the non-delayed rule and the effective date of the delayed rule. The potential benefits of delay are: (1) The reduction of potential health risks, if any, associated with increased intake of soy protein and other relevant substances; (2) the reduced likelihood of the potential reduction in the perceived reliability of FDA-approved claims that might occur if future research were to require the soy protein health claim be revised; (3) the increase in the health benefits generated by a delayed health claim that, potentially, would be more accurate or complete.

As discussed below, the comments did not provide information establishing that the benefits of delaying the rule outweigh the costs.

3. Option Three: Take Proposed Action Costs

A number of comments suggested that this rule might lead to adverse health

effects. According to these comments, potential health risks are associated with an increased intake of: (1) Soy protein; (2) other components of soybeans including soybean trypsin inhibitors and isoflavones such as genistein; (3) artifacts of particular methods of manufacturing soy protein isolates or products containing soy protein, such as nitrates, nitrosamines, and lysinolanine; and (4) artifacts of genetically engineered soy protein. Among the potential health concerns related to these substances mentioned in the comments were the following: (1) Allergenicity; (2) reduced bioavailability of vitamins and minerals including zinc and iron; (3) hormonal alterations, including changes in fertility and functioning of sex glands; (4) toxicity in estrogen sensitive tissues and an increase in estrogen-related diseases; (5) vascular dementia; (6) adverse effects on the central nervous system and behavioral changes; (7) thyroid abnormalities, including goiter; (8) cancer; (9) diabetes; (10) liver disease; (11) adverse effects on the immune and endocrine systems; and (12) adverse effects on metabolism. Other comments argued that no health concerns would be associated with the intake levels of soy protein and the other substances that can be associated with soy protein, such as soy isoflavones or various by-products of manufacturing soy protein isolates, that are likely to result from the proposed health claim.

As discussed previously in the preamble to this rule, FDA finds that there is no evidence that any increase in the intake of soy protein or the other substances discussed in the comments presents a risk of adverse health effects.

The availability of the health claim may increase the number of products containing soy protein. Increased availability of products containing soy protein may increase the likelihood that those who are allergic to soy protein may consume such products. The net effect of this rule on the incidence of allergic reactions to soy protein is unclear. As discussed earlier in the preamble, the presence of the health claim will serve to notify consumers of the presence of soy protein in products that bear the claim. However, some consumers who are allergic to soy protein may not already know they are allergic to soy protein and some consumers who do know they are allergic may inadvertently consume such products despite the presence of the health claim. FDA has insufficient information to estimate the net effect on the incidence of allergic reactions to soy protein. In addition, the addition of soy protein to products that do not currently

contain soy protein may reduce, to some degree, the number of soy-free products that are available to those who are allergic to soy protein. This reduction in product choice may lead to utility losses for those consumers. However, a large number of products will continue to not contain soy protein, so this utility loss will probably be modest. This rule may also increase the incidence of the adverse health effects associated with zinc deficiency, which is typically related to largely plant-based diets, to some degree. However, FDA has insufficient information to estimate this effect.

Some comments suggested that this rule might indirectly increase the incidence of CHD. According to these comments, the proposed health claim could lead some consumers to overestimate the role of soy protein in preventing CHD and to neglect other actions that have an equal or greater effect on the risk of CHD. Other comments argued that this rule might lead to the adverse health effects caused by poor nutrition because the proposed health claim might lead some consumers to concentrate unduly on foods containing soy protein and to neglect the other components of a balanced diet. Another comment argued the proposed health claim could lead to miscellaneous adverse health effects because it might be interpreted by some consumers as an endorsement of the miscellaneous benefits that are sometimes claimed for soy products, such as the prevention of cancer or osteoporosis. This comment argued that this interpretation would lead some consumers to neglect the actions that reduce the risk of these other conditions.

Some consumers may misinterpret the proposed health claim (or any other health claim). However, the fact that the proposed health claim states that the risk of CHD may be reduced by an unspecified degree by consuming a specified level of soy protein per day, as part of a low saturated fat and low cholesterol diet, makes it unlikely that many consumers will neglect other activities that reduce the risk of CHD or neglect other types of foods. Similarly, the fact that the health claim specifies CHD makes it unlikely that many consumers will interpret the claim as an endorsement of other benefits that are sometimes claimed for soy products. The comments did not provide sufficient information to allow FDA to estimate the likelihood of these effects. Furthermore, these potential effects are no more likely to be associated with the proposed claim than with any other claim.

Some comments suggested that this rule might indirectly increase the incidence of miscellaneous adverse health effects by decreasing the perceived reliability of FDA-approved health claims in general. Some comments noted the presence of a certain degree of uncertainty concerning the mechanism by which soy protein reduces the risk of CHD. One comment argued that if further research on this mechanism were to find that isoflavones or other components of soybeans are involved, and the health claim were subsequently revised to reflect those findings, then FDA's scientific reputation and the perceived value of FDA-approved health claims could be adversely affected. Other comments implied that uncertainty over the mechanism means that future research might show that soy protein does not affect the risk of CHD. Other comments argued that the proposed claim would reduce FDA's scientific credibility because it would mean that FDA is treating soy protein in a manner that is inconsistent with how FDA treats certain other substances that may reduce the risk of CHD, including estrogens and linseed oil.

Future research could lead to results that would lead FDA to revise the soy health claim. However, the comments did not provide sufficient information to allow FDA to estimate the likelihood of revisions or to assess the impact of these revisions on the perceived reliability of FDA-approved health claims in general. The latter relationship is highly speculative, because it depends on consumers not knowing that scientific knowledge is in a constant state of development. In addition, although some revisions may be necessary, it is unlikely that future research will indicate that soy protein has no effect on CHD. As stated earlier in the preamble, FDA has concluded that the scientific evidence establishes that increased intake of soy protein reduces the risk of CHD and that this effect is not simply an artifact of the substitution of lower fat and cholesterol products for higher fat and cholesterol products. The comment that suggested otherwise ignores the many studies in which fat, saturated fat, and cholesterol were the same in treatment and control groups and soy protein still exerted an effect on the risk of CHD. Also, FDA disagrees that the only mechanism discussed in the petition was the soy isoflavone mechanism. Finally, the comments did not provide sufficient information to estimate the effect of the purported inconsistencies on the perceived value of FDA-approved health claims.

However, in general, it is unclear that the failure to authorize a health claim for one substance would reduce the effectiveness of a health claim for another substance.

A number of comments addressed the method FDA proposed to use to determine the level of soy protein. Many of the comments recommended revising the proposed rule. These comments are discussed under Option 8 below.

C. Benefits

The analysis of the proposed rule discussed the benefit of this rule in terms of the value to consumers of the information communicated in the proposed health claim. The comments did not provide information directly relevant to estimating this value. However, a number of comments addressed the health and other benefits that might be generated by changes in consumer behavior that might follow from this rule. As discussed in the analysis of the proposed rule, the value of these other benefits may be considered a lower bound on the value to consumers of the information communicated in the health claim. This value is a lower bound because some consumers might want that information, but nevertheless choose not to modify their behavior. In addition, the value of these other benefits may be considered an appropriate independent metric for valuing the benefits of this rule because consumers may value the information in the claim based on the usefulness of that information for reducing the risk of CHD but may underestimate or overestimate the usefulness of that information.

Many comments argued that this rule would lead to a reduction in the incidence of CHD and provided information relevant to estimating that reduction. A few comments argued that this rule would not lead to a reduction in the incidence of CHD because soy protein does not affect the risk of CHD. One comment argued that this rule would generate benefits by obviating, in some cases, the need for riskier and more expensive pharmacological treatments for reducing the risk of CHD. Thus, according to this comment, this rule might generate benefits even if no reduction in the incidence of CHD were to take place.

Quantifying the effect of the proposed health claim on the incidence of CHD would involve a number of uncertainties and any ensuing estimate would be imprecise. In addition, there would be little value to generating such an estimate because, as discussed above, the comments did not provide sufficient information to estimate the purported costs of this rule. Therefore, although

FDA believes this final rule will generate benefits, this analysis will not attempt to quantify the effect of this rule on the incidence of CHD.

Some comments argued that increasing soy intake would generate benefits other than a reduction in the risk of CHD, including reduction in the incidence of cancer, osteoporosis, and menopausal symptoms. These types of effects would be relevant to the estimation of the benefits of this rule. However, FDA has reviewed no scientific evidence to assess whether such benefits exist or to estimate the size of such benefits.

4. Option Four: Take Proposed Action, but Specify a Different Minimum Level of Soy Protein for Products Bearing the Claim

Many comments suggested revising the minimum level of soy protein that is required for a product to be able to bear the proposed health claim. Some comments addressed the significance of the 25 g per day of soy protein on which the proposed 6.25 g per RACC requirement was based. One comment noted that studies have found that soy protein affects the risk of CHD at intake levels of between 17 g and 31 g per day. Another comment argued that between 30 g to 50 g of soy protein per day is necessary to produce clinically significant results on the incidence of CHD.

Specifying the particular daily intake of soy protein that will have a significant effect on the risk of CHD involves some uncertainty. However, FDA does not have sufficient information to estimate the effect of specifying different levels and the comments did not provide sufficient information to allow FDA to do so. As discussed earlier in the preamble, FDA believes the 25 g soy protein per day level is supported by the scientific literature and disagrees that intake levels of 30 g to 50 g per day is necessary to produce clinically significant results on the incidence of CHD.

Other comments did not address the 25 g soy protein per day target level but did address the 6.25 g per RACC requirement derived from the daily target level. Some comments argued that the per RACC requirement was overly restrictive and that few products would qualify for the health claim under this requirement. One comment analyzed the list of products that was presented in the petition as qualifying for the health claim and found that only 61 products would qualify if multiple flavors of the same product were omitted, and that 88 products would

qualify if multiple flavors were not omitted. This comment also noted that many of the products on the list that would qualify are products that are meant to be added to other products rather than consumed on their own, that it was unclear whether the final products would themselves meet the requirements for the proposed claim. Another comment noted that many of the qualifying products listed in the petition were varieties of non-dairy soy beverages or tofu, which this comment argued have not been well accepted by American consumers. Other comments noted that most of the soy products that are available on the market that would meet the proposed per RACC requirement are entree-type products that consumers would probably not consume four times per day. Some comments suggested that only vegetarian or soy burgers, shakes, tofu, and non-dairy soy beverages would meet the proposed per RACC requirement. One comment noted that many of the products that meet the RACC requirements are specialty items that are only available at health food stores.

In contrast, other comments argued that many existing soy products meet the proposed per RACC requirement or could easily be reformulated to meet that requirement. One comment suggested that the vast majority of products containing soy protein that are currently available on the market meet the proposed RACC level. These comments argued that the assumption of four eating occasions per day that was used to derive the 6.25 g per RACC requirement from the 25 g per day level was reasonable. Among the products listed in these comments were the following: tofu, soy-based beverages, soy burgers and other meat alternatives, frozen deserts, protein bars, cheese and yogurt alternatives, soybeans, soy nut butter, soynuts, tempeh, miso, and soy flour or soy protein powder. Another comment implied that any product in which protein is normally consumed could easily be modified to meet the per RACC requirements, including snack foods, breakfast cereals, burger patties, and more formal entrees.

Some comments argued that the 6.25 g per RACC restrictions would effectively prevent baked products from bearing the claim. One comment noted that achieving a level of 6.25 g per RACC in these products would require incorporating soy flour at 15 percent inclusion or greater and that would yield a product that would be unacceptable to consumers and would also be too costly to compete effectively with other products. Many comments

argued that the benefits of this rule would be greater if commonly consumed products such as baked products were able to bear the proposed health claim. One comment argued that a per RACC requirement that allowed baked goods containing soy protein to bear the health claim might lead to additional benefits in terms of encouraging the consumption of products from grain group of the USDA/DHHS Food Guide Pyramid, which this comment claims are currently underconsumed.

Other comments argued that the proposed per RACC requirement would effectively prevent other types of products from bearing the health claim. One comment argued that it is difficult to incorporate 6.25 g soy protein into a single RACC of most such foods in a way that it would be palatable to most American consumers, given current and reasonably anticipated technology.

Some of the comments that argued that few products would be able to meet the 6.25 g per RACC requirement recommended lowering the minimum per RACC level to allow a wider variety of foods to qualify for the health claim and to make it easier for consumers to achieve an intake of 25 g soy protein per day. Some comments argued that a level of 4 g per RACC would allow baked goods, allow soy pasta, low-fat extended meat products, and vegetarian burgers made with soy flour and textured soy protein to bear the claim. These comments noted that assuming intake levels of 5 to 6 servings per day of these types of products would be reasonable and that 4 g per RACC would, therefore, be consistent with a daily intake of 25 g per day. Another comment suggested that FDA has legal precedent for setting the per RACC requirement as low as 2.5 g per RACC.

In contrast, some of the comments that argued that few products would meet the 6.25 g per RACC requirement recommended raising the per RACC level to reduce the number of servings that would be necessary to obtain 25 g soy protein per day. Some comments argued that if the primary source of soy protein were from meals in which high protein meat dishes are currently eaten, then the per RACC requirement should be based on two or three servings per day, rather than the proposed assumption of four servings per day. Thus, these comments suggested that FDA revise the per RACC requirement from 6.25 g to either 8.3 g or 12.5 g.

FDA has insufficient information on the characteristics of the soy products that are currently on the market to determine the proportion of such products that would qualify for the

health claim, the ease with which existing products can be reformulated to meet the requirements for making the health claims, or the ease with which new products can be developed that would meet the requirements for making the health claim. In addition, FDA has insufficient information on the consumption patterns of the relevant products to determine whether lowering the per RACC level would lead more or fewer consumers to consume 25 g soy protein per day.

Some comments noted that the proposed health claim contains information on (1) the daily intake level of soy protein that is associated with reduced risk of CHD and (2) the level of soy protein in a serving of the product bearing the claim. According to these comments, the provision of this information obviates the need to restrict the claim to products having 6.25 g or more soy protein per RACC, because consumers can easily determine the relative significance of particular products as a source of soy protein. These comments implied that specifying a much lower minimum level of soy protein would increase benefits because a wider variety of products would then be able to bear the claim and consumers would more easily be able to achieve an intake of 25 g soy protein per day.

Allowing the claim to appear on products containing very low levels of soy protein might increase the usefulness of the claim for consumers and might lead to a greater reduction in CHD than would be produced by taking the proposed action. The agency is unable to determine the likelihood of this effect.

Other comments suggested revising the per RACC requirement for other reasons. One comment argued that the per RACC requirement should be changed to a requirement based on serving size. This comment argued, for example, that a single veggie burger that contains 6.25 g of soy protein should qualify for the health claim, even if the product does not meet the per RACC requirement because the burger patty is larger than the applicable RACC.

Changing the per RACC requirement to a per serving requirement would probably increase the number of products that would be able to bear the proposed health claim and might, therefore, increase the health benefits generated by the claims. However, the comments did not provide sufficient information to estimate this effect. In addition, this revision would require revision of the regulations at 21 CFR 101.12(g), and is, therefore, beyond the scope of this rulemaking.

One comment noted that the correct declaration of 6.25 g soy protein is 6 g because current law mandates that the amount of protein be rounded to the nearest whole number. According to this comment, this rounding might confuse consumers. If consumers were confused about the level of soy protein in the RACC of a particular product and the significance of that product for meeting the specified daily intake level, then the benefits of the health claim might be lower than they would be otherwise. This comment suggested that the per RACC requirement be revised from 6.25 g to either 6 g or 7 g. As discussed previously, the rounding requirement applies only to the Nutrition Facts Panel and soy protein content is not allowed to appear on the Nutrition Facts Panel.

5. Option Five: Take Proposed action, but Specify a Minimum Level of Soy Isoflavones in Addition to the Proposed Minimum Level of Soy Protein for Products Bearing the Claim

Some comments argued that the effect of soy protein on the risk of CHD may depend on the presence of soy isoflavones. These comments recommended that the health claim be restricted to products that contain a minimum level of total soy isoflavones, of particular isoflavones, of both total isoflavones and particular isoflavones, or of amino acids such as arginine and methionine. Some of the comments that argued that the beneficial effects of soy protein may depend on the presence of soy isoflavones also noted that particular manufacturing or processing methods can affect the level of soy isoflavones. These comments recommended that the health claim be restricted to products that have been manufactured or processed in particular ways. For example, many comments noted that alcohol washing reduces isoflavone content and suggested that products containing alcohol washed or extracted soy protein isolate should not be authorized to bear the health claim. Some comments added that there is no evidence that adding purified soy isoflavone extract back into such products is effective and argued that any isoflavone requirement should be based on naturally occurring isoflavones.

As discussed earlier in this preamble, FDA finds that the scientific evidence does not indicate that the effect of soy protein on the risk of CHD varies with the presence of soy isoflavones or amino acids. Therefore, no additional benefit would result from restricting the claim to products having particular levels of isoflavones, or produced using particular methods of manufacture.

6. Option Six: Take Proposed Action, but Revise Wording of the Claim or Require That Warnings or Other Statements Accompany the Claim

Some comments suggested that FDA require additional information be put on the labels of product bearing the proposed claim that explains the conditions under which soy protein reduces the risk of CHD. For example, some comments suggested that product labels should make it clear that no benefits should be expected for daily soy protein intake levels of less than 25 g. Some comments argued that the beneficial effects of soy protein accrue only to consumers who have high cholesterol levels and suggested that the proposed health claim be revised to communicate this fact.

Although requiring a label statement clarifying that benefits should not be expected for daily soy protein intake levels of less than 25 g might generate benefits, the marginal benefits of such a statement are unclear given that the proposed health claim relates health effects to an intake of 25 g per day and not to the intake of any particular product. The comment did not provide sufficient information to estimate the marginal benefit of an additional statement concerning the significance of the 25 g per day intake level. Finally, as discussed previously in this preamble, FDA has determined that the effect of soy protein on the risk of CHD may depend, in part, on initial cholesterol levels, but does not accrue only to those with high initial cholesterol levels. Therefore, restricting the health claim to apply to only those with high initial cholesterol levels would not generate marginal benefits.

Some of the comments that argued that the increased consumption of products containing soy protein could lead to health risks suggested that FDA require warning labels on those products to alert consumers of the risks. Other comments suggested that various types of information relevant to the purported health risks be reported on product labels. For example, one comment that argued that increased intake of soy protein could lead to zinc deficiency suggested that the labels of products bearing the health claim indicate the phytate and zinc content per serving for those products. One comment suggested that labels indicate a recommended maximum daily intake of soy protein to prevent the health risks associated with overconsumption of products containing soy protein. This comment argued that daily consumption of between 25 g and 100 g of isolated soy protein could result in nitrosamine

exposures that exceeds established No Significant Risk Levels. One comment argued that manufacturers should voluntarily provide information on product labels on various issues such as manufacturing methods and the use of pesticides, because consumers have a right to such information.

FDA has determined that there is no evidence that health risks are associated with increased intake of soy protein or the other substances discussed in the comments. Label statements warning of possible allergic reactions to soy protein would provide some potentially valuable information to consumers who do not realize they are allergic to soy protein or that such allergies are possible. However, such labeling would not provide useful information to those consumers who are already aware of the fact that allergies to common foods are possible, and might discourage the consumption of soy protein by those who are not allergic to soy protein. FDA has insufficient information to estimate the costs or benefits of such a warning statement or to determine if such a warning statement would provide a net benefit to consumers. Associating warning statements with the proposed health claim would generate no marginal benefits for consumers who know they are allergic to soy protein because the health claim would already indicate the presence of soy protein.

Label statements addressed to the potential effect of increased consumption of products containing soy protein on zinc deficiency, such as a warning statement, indications of the zinc and phytate content of products containing soy protein, or recommended maximum daily intakes, might reduce the likelihood that increased consumption of these products will lead to zinc deficiency. Earlier in the preamble to this rule, FDA determined that consumers would not find information relating to the zinc and phytate content of products containing soy protein useful. The other suggested labeling approaches for addressing the effect of increased consumption of these products on zinc deficiency may be useful for some consumers. However, again, the benefit of such labeling must be compared to the possible costs in terms of discouraging the use of such products among those who are not at risk of zinc deficiency. FDA has insufficient information to estimate the costs or benefits of the other suggested labeling approaches or determining whether such approaches would generate net benefits.

One comment suggested eliminating the language relating the effect of soy protein to diets low in saturated fat and

cholesterol because the effect of soy protein on the risk of CHD is independent of these other factors. The benefit of eliminating this language is that consumers who are not currently eating a diet low in saturated fat and cholesterol may be more likely to react to the health claim if the effect of soy protein is not presented as applying only to those eating diets low in saturated fat and cholesterol. An increase in the number of consumers likely to react to the health claim may increase the benefits of the health claim. However, the size of this marginal benefit is unclear because, as discussed earlier, the available data on the effects of soy protein show that soy protein has a more consistent effect on CHD for those consuming a low fat and cholesterol diet than for others. The cost of eliminating this language is that some consumers might believe that achieving a certain intake of soy protein can substitute for eating a diet low in saturated fat and cholesterol and might, therefore, indirectly increase the intake of saturated fat and cholesterol. FDA has insufficient information to determine if eliminating the language relating the effect of soy protein to diets low in saturated fat and cholesterol would generate net benefits or costs.

Some comments suggested that the proposed health claim was either too long or too complicated to be effective. Many comments argued that the health claim would be more effective if it were shortened or replaced by a "split claim." Many comments suggested wording for a shorter health claim. Increasing the effectiveness of the health claim would increase the benefits associated with the health claim and would not affect costs. However, FDA has insufficient information to analyze the effect of different labeling formats or wording. Although FDA has studied the effectiveness of split claims for other types of claims, the relevance of that information for a health claim on soy protein is unclear.

7. Option Seven: Take Proposed Action, but Specify a Different Maximum Total Fat Content or Grant an Exemption from the Maximum Total Fat Requirement for Foods Made With Natural Soybeans That Have No Added Fat

Many comments noted that the low fat requirement for products bearing the proposed health claim would prevent soybeans and traditional soybean products from bearing the health claim. This rule has been revised so that foods made from whole soybeans with no added fat are exempted from the low fat requirement. The benefit of this revision is that more products will be able to

bear the proposed health claim and the benefits generated by the health claim may be increased. The cost of this revision is that the total fat content of some products bearing the claim may be slightly higher than under the proposed rule. As explained earlier in the preamble, a reduction of total fat facilitates maintenance of normal body weight and, therefore, reduces the risk of obesity. The reduction of this effect would cause an increase in the risk of obesity and, therefore, produce a countervailing increase in the risk of CHD. In this case, the benefit of increasing the number of products probably outweighs the slight increase in the total fat content of qualifying products.

8. Option Eight: Take Proposed Action, but Use a Different Procedure for Determining Level of Soy Protein in Particular Products.

Many comments on the proposal addressed the analytical method that FDA proposed to use to confirm the level of soy protein in products bearing the proposed health claim. These comments were discussed in the reproposal. The reproposal specified various types of records that might allow FDA to calculate the level of soy protein in particular products. FDA received a number of comments on the reproposal. Most of these comments addressed the issue of which records FDA will use to determine the soy protein content of foods. Many comments argued that the reproposal appeared to allow FDA wide discretion in determining which records to inspect and duplicate. These comments also expressed the concern that FDA might inspect and duplicate records of each of the various types that were specified as potentially relevant in the reproposal, and might also inspect and duplicate as yet unspecified records that FDA later determines are relevant. According to these comments, some of the resulting record inspection and duplication might be unwarranted. Many comments suggested that the rule be revised to require manufacturers to provide FDA with records that provide a reasonable basis for concluding that a particular product has sufficient soy protein content to bear the health claim. According to these comments, this revision would eliminate the possibility that FDA will use the records inspections clause to inspect and duplicate records in situations in which such actions are not strictly necessary. One comment argued that the records inspection provision would give an unfair market advantage to firms that manufacture products whose sole

source of protein is soy and which, therefore, need not provide FDA access to records to establish the level of soy protein in their products.

If FDA were to require the inspection and duplication of records that firms attempting to use the soy protein health claim considered unnecessary to establish compliance with the requirements for making that claim, then those firms would have less incentive to use the claim and the benefits associated with allowing that claim would be reduced. However, FDA has modified its proposal to inspect records to provide, instead, that manufacturers must identify and supply to FDA, on written request, records that substantiate the amount of soy protein in a food that bears the soy protein health claim if soy is not the sole source of protein in the food. Therefore, this rule will not require record inspection or unnecessary duplication of records. This rule may generate some distributive effects because it may put firms that are required to provide such records at a competitive disadvantage relative to firms that produce products in which soy is the only source of protein. However, these effects will probably be small because manufacturers probably already maintain the necessary records.

D. Small Entity Analysis

FDA has examined the impacts of this proposed rule under the Regulatory Flexibility Act. The Regulatory Flexibility Act (5 U.S.C. 601-612) requires federal agencies to consider alternatives that would minimize the economic impact of their regulations on small businesses and other small entities. No compliance costs are generated by this rule because this rule does not require any labels to be changed, or any product to be reformulated. Therefore, small businesses will only relabel or reformulate products if the benefits to those small businesses outweigh the costs. FDA did not receive any comments that challenged this conclusion. Accordingly, pursuant to the Regulatory Flexibility Act, 5 U.S.C. 605(b), FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

V. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). The title, description, and respondent description

are shown below with an estimate of the annual recordkeeping and reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Record Retention Requirements for the Soy Protein/CHD Health Claim

Description: The regulation set forth in this rule authorizes the use in food labeling of a health claim about the relationship between soy protein and CHD. Section 403(r) of the act requires that food bearing a health claim authorized by regulation on a petition to the agency be labeled in compliance with the regulation issued by FDA. In response to comments received on the soy protein proposed rule (63 FR 62977), the agency proposed an alternative procedure for assessing compliance with the requirement that a food contain a qualifying amount of soy protein in the soy protein reproposal (64 FR 45932). This procedure would have required that a manufacturer of a product bearing the proposed soy protein health claim whose product contains a source or sources of protein in addition to soy retain the records that permit the calculation of the ratio of soy protein to other sources of protein in the food. The manufacturer of such a food product would have been required to make those records available for review and copying by appropriate regulatory officials upon request and during site

visits. Comments received on the soy protein reproposal have been addressed by the agency in section II.C.2 of this document, and this rule reflects modifications made in response to those comments. This final rule requires a manufacturer of a product bearing the soy protein health claim whose product contains a source or sources of protein in addition to soy to identify and retain records that reasonably substantiate the ratio of soy protein to total protein. The rule also requires the manufacturer of such a food product to provide those records upon written request to appropriate regulatory officials.

FDA had submitted the information collection requirements to OMB for review under the PRA at the time the August 1999 soy protein reproposal was published. In response, OMB requested that FDA respond to the need for the collection and the burden hours that will be imposed as a result of this collection.

To bear the soy protein and CHD health claim, foods must contain 6.25 g soy protein per RACC. For foods that contain soy as the sole source of protein, analytical methods for total protein can be used to quantify the amount of soy protein. At the present time, there is no validated analytical methodology available to quantify the amount of soy protein in foods that contain other proteins. For these latter foods, FDA must rely on information known only to the manufacturer to assess compliance with the qualifying amount of soy

protein. Thus, FDA is requiring manufacturers to have and keep records to substantiate the amount of soy protein in a food that bears the health claim and contains sources of protein other than soy, and to make such records available to appropriate regulatory officials upon written request.

Although no comments on the soy protein reproposal specifically addressed the estimated burden of the information collection requirements, several indicated that recordkeeping and record inspection would be burdensome. These comments expressed concern about FDA's record inspection authority. In response to this concern, FDA has determined that, in this case, it need not assert record inspection authority in order to obtain the information needed for compliance assessment. The comments also expressed concern about the potentially broad array of records that FDA might demand. In response to this concern, FDA clarified that it did not intend to specify the records to be supplied. Rather, the final rule indicates that records will be requested in writing and that manufacturers will be responsible for identifying the records that they have used to substantiate the proportion of soy protein in their products.

FDA estimates the burden of this collection of information as follows:

Description of Respondents: Businesses or others for-profit.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN ¹

21 CFR	No. of respondents	Annual frequency per response	Total annual responses	Hours per response	Total Hours
101.82(c)(2)(ii)(B)	25	1	25	1	25

¹ There are no capital costs or operating and maintenance costs associated with this collection.

TABLE 3.—ESTIMATED ANNUAL REPORTING BURDEN ¹

21 CFR Section	No. of respondents	No. of responses per respondent	Total annual responses	Hours per response	Total hours
101.82(c)(2)(ii)(B)	5	1	5	1	5

¹ There are no capital costs or operating and maintenance costs associated with this collection.

Manufacturers must determine that their products are qualified to bear any claim used on foods labels or in labeling, including meeting the requirement for a qualifying amount of soy protein to bear the health claim authorized for use by this regulation. In the absence of a validated analytical methodology for soy protein in foods that contain other proteins,

manufacturers will need to use records, e.g., the food's formulation or recipe, to determine if such a food contains 6.25 g per RACC. In this rule, FDA is requiring that firms maintain the records they use to determine that a food is qualified to bear the claim, and that those records be submitted to FDA upon written request. Based upon its experience with the use of health

claims, FDA estimated that 25 firms would market products bearing a soy protein and CHD health claim and that one of each firm's products would contain a source or sources of protein in addition to soy. FDA received no comments that challenged this estimate. FDA estimates that, annually, it would request records to assess compliance from 20 percent of firms subject to the

recordkeeping requirement. The records that would be required to be retained by § 101.82(c)(ii)(B)(2) are records that, as described above, FDA believes a prudent and responsible manufacturer uses and retains as a normal part of doing business. Thus, the burden to the food manufacturer would be that involved in assembling and providing the records to appropriate regulatory officials upon written request. The requirements contained in this rule would require only a minimal burden, no more than one hour per response, from respondents.

The information collection provisions of this final rule have been submitted to OMB for review. FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VI. References

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List of Subjects in 21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 101 is amended as follows:

PART 101—FOOD LABELING

The authority citation for 21 CFR part 101 continues to read as follows:

1. **Authority:** 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 342, 343, 348, 371.

2. Add § 101.82 to subpart E to read as follows:

§ 101.82 Health claims: Soy protein and risk of coronary heart disease (CHD).

(a) *Relationship between diets that are low in saturated fat and cholesterol and that include soy protein and the risk of CHD.* (1) Cardiovascular disease means diseases of the heart and circulatory system. CHD is one of the most common and serious forms of cardiovascular disease and refers to diseases of the heart muscle and supporting blood vessels. High blood total cholesterol and low density lipoprotein (LDL)-cholesterol levels are associated with increased risk of developing CHD. High CHD rates occur among people with high total cholesterol levels of 240 milligrams per deciliter (mg/dL) (6.21 millimole per liter (mmol/L)) or above and LDL-cholesterol levels of 160 mg/dL (4.13 mmol/L) or above. Borderline high risk total cholesterol levels range from 200 to 239 mg/dL (5.17 to 6.18 mmol/L) and 130 to 159 mg/dL (3.36 to 4.11 mmol/L) of LDL-cholesterol. The scientific evidence establishes that diets high in saturated fat and cholesterol are associated with increased levels of blood total and LDL-cholesterol and, thus, with increased risk of CHD.

(2) Populations with a low incidence of CHD tend to have relatively low blood total cholesterol and LDL-cholesterol levels. These populations also tend to have dietary patterns that are not only low in total fat, especially saturated fat and cholesterol, but are also relatively high in plant foods that contain dietary fiber and other components.

(3) Scientific evidence demonstrates that diets low in saturated fat and cholesterol may reduce the risk of CHD. Other evidence demonstrates that the addition of soy protein to a diet that is low in saturated fat and cholesterol may also help to reduce the risk of CHD.

(b) *Significance of the relationship between diets that are low in saturated fat and cholesterol and that include soy protein and the risk of CHD.* (1) CHD is a major public health concern in the United States. It accounts for more deaths than any other disease or group of diseases. Early management of risk factors for CHD is a major public health goal that can assist in reducing risk of CHD. High blood total and LDL-cholesterol are major modifiable risk factors in the development of CHD.

(2) Intakes of saturated fat exceed recommended levels in the diets of many people in the United States. One of the major public health recommendations relative to CHD risk is to consume less than 10 percent of calories from saturated fat and an average of 30 percent or less of total calories from all fat. Recommended daily cholesterol intakes are 300 mg or less per day. Scientific evidence demonstrates that diets low in saturated fat and cholesterol are associated with lower blood total and LDL-cholesterol levels. Soy protein, when included in a low saturated fat and cholesterol diet, also helps to lower blood total and LDL-cholesterol levels.

(c) *Requirements.* (1) All requirements set forth in § 101.14 shall be met.

(2) *Specific requirements—(i) Nature of the claim.* A health claim associating diets that are low in saturated fat and cholesterol and that include soy protein with reduced risk of heart disease may be made on the label or labeling of a food described in paragraph (c)(2)(iii) of this section, provided that:

(A) The claim states that diets that are low in saturated fat and cholesterol and that include soy protein "may" or "might" reduce the risk of heart disease;

(B) In specifying the disease, the claim uses the following terms: "heart disease" or "coronary heart disease";

(C) In specifying the substance, the claim uses the term "soy protein";

(D) In specifying the fat component, the claim uses the terms "saturated fat" and "cholesterol";

(E) The claim does not attribute any degree of risk reduction for CHD to diets that are low in saturated fat and cholesterol and that include soy protein;

(F) The claim does not imply that consumption of diets that are low in saturated fat and cholesterol and that include soy protein is the only recognized means of achieving a reduced risk of CHD; and

(G) The claim specifies the daily dietary intake of soy protein that is necessary to reduce the risk of coronary heart disease and the contribution one serving of the product makes to the specified daily dietary intake level. The daily dietary intake level of soy protein that has been associated with reduced risk of coronary heart disease is 25 grams (g) or more per day of soy protein.

(ii) *Nature of the substance.* (A) Soy protein from the legume seed *Glycine max*.

(B) FDA will assess qualifying levels of soy protein in the following fashion: FDA will measure total protein content by the appropriate method of analysis given in the "Official Methods of Analysis of the AOAC International," as

described at § 101.9(c)(7). For products that contain no sources of protein other than soy, FDA will consider the amount of soy protein as equivalent to the total protein content. For products that contain a source or sources of protein in addition to soy, FDA will, using the measurement of total protein content, calculate the soy protein content based on the ratio of soy protein ingredients to total protein ingredients in the product. FDA will base its calculation on information identified and supplied by manufacturers, such as nutrient data bases or analyses, recipes or formulations, purchase orders for ingredients, or any other information that reasonably substantiates the ratio of soy protein to total protein. Manufacturers must maintain records sufficient to substantiate the claim for as long as the products are marketed and provide these records, on written request, to appropriate regulatory officials.

(iii) *Nature of the food eligible to bear the claim.* (A) The food product shall contain at least 6.25 g of soy protein per reference amount customarily consumed of the food product;

(B) The food shall meet the nutrient content requirements in § 101.62 for a "low saturated fat" and "low cholesterol" food; and

(C) The food shall meet the nutrient content requirement in § 101.62 for a "low fat" food, unless it consists of or is derived from whole soybeans and contains no fat in addition to the fat inherently present in the whole soybeans it contains or from which it is derived.

(d) *Optional information.* (1) The claim may state that the development of heart disease depends on many factors and may identify one or more of the following risk factors for heart disease about which there is general scientific agreement: A family history of CHD; elevated blood total and LDL-cholesterol; excess body weight; high blood pressure; cigarette smoking; diabetes; and physical inactivity. The claim may also provide additional information about the benefits of exercise and management of body weight to help lower the risk of heart disease;

(2) The claim may state that the relationship between intake of diets that are low in saturated fat and cholesterol and that include soy protein and reduced risk of heart disease is through the intermediate link of "blood cholesterol" or "blood total and LDL-cholesterol";

(3) The claim may include information from paragraphs (a) and (b) of this section, which summarize the relationship between diets that are low in saturated fat and cholesterol and that include soy protein and CHD and the significance of the relationship;

(4) The claim may state that a diet low in saturated fat and cholesterol that includes soy protein is consistent with "Nutrition and Your Health: Dietary Guidelines for Americans," U.S. Department of Agriculture (USDA) and Department of Health and Human Services (DHHS), Government Printing Office (GPO);

(5) The claim may state that individuals with elevated blood total and LDL-cholesterol should consult

their physicians for medical advice and treatment. If the claim defines high or normal blood total and LDL-cholesterol levels, then the claim shall state that individuals with high blood cholesterol should consult their physicians for medical advice and treatment;

(6) The claim may include information on the number of people in the United States who have heart disease. The sources of this information shall be identified, and it shall be current information from the National Center for Health Statistics, the National Institutes of Health, or "Nutrition and Your Health: Dietary Guidelines for Americans," USDA and DHHS, GPO;

(e) *Model health claim.* The following model health claims may be used in food labeling to describe the relationship between diets that are low in saturated fat and cholesterol and that include soy protein and reduced risk of heart disease:

(1) 25 grams of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of food] supplies ____ grams of soy protein.

(2) Diets low in saturated fat and cholesterol that include 25 grams of soy protein a day may reduce the risk of heart disease. One serving of [name of food] provides ____ grams of soy protein.

Dated: October 19, 1999.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.
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