



JAN 4 2016

Sally Fallon, et al.
The Weston A. Price Foundation
BMP 106-380 4200 Wisconsin Avenue, NW
Washington, D.C. 20016

Re: Docket No. FDA-2008-P-0452-0001

Dear Ms. Fallon:

This letter responds to the Citizen Petition (FDA-2008-P-0452-0001) you submitted to the United States Food and Drug Administration ("FDA" or "the Agency") dated August 8, 2008, on behalf of the Weston A. Price Foundation ("petition"). The petition requests that FDA "revoke the Final Rule Re Food Labeling: Health Claims; Soy Protein and Heart Disease," which became effective October 26, 1999, 64 Federal Register 57700 (hereinafter, "1999 Final Rule"), and requests a hearing on the matter. Petition at 1.¹

I. DECISION SUMMARY

FDA has carefully considered the issues raised in your petition, the Complaint filed in *Weston A. Price Foundation v. FDA et al.*, No. 14-cv-2132 (D.D.C.), Dkt. No. 1 ("Complaint"), and the comments submitted to the petition docket, including your submission, "Weston A. Price Foundation Reply to the Soy Nutrition Institute's Comments," dated November 9, 2015 ("petition supplement"). For the reasons discussed below, FDA is denying your petition in accordance with 21 Code of Federal Regulations ("CFR") 10.30(e)(3), because the limited relevant evidence submitted in the petition and the petition supplement does not provide sufficient grounds for the Agency to revoke the soy protein and coronary heart disease ("CHD") health claim at this time. In order for the Agency to support an action to revoke the 1999 Final Rule, the Agency would first need to evaluate the totality of publicly available scientific evidence to determine whether there is no longer significant scientific agreement to support the soy protein and CHD health claim (*see* section 403(r)(3)(B)(i) [21 U.S.C. 343(r)(3)(B)(i)]). Contrary to your representations, you have not presented sufficient data to FDA to demonstrate that the significant scientific agreement standard has not been met for this health claim. E.g., Petition at 1.

FDA also denies your request for a hearing. Under 21 CFR 10.30(h), we may use a number of procedures in the review of a petition, including a meeting, a *Federal Register* notice requesting

¹ The petition's pages are unnumbered and are cited in this response as if they were numbered consecutively, starting with the cover page.

information and views, a proposal to issue, amend, or revoke a regulation, a hearing, or other specific public procedure. However, we do not consider any procedures, including a hearing, to be warranted at this time because we first must complete our review of the totality of the publicly available scientific evidence for the health claim before we consider what, if any, action may be needed with respect to the 1999 Final Rule.

II. BACKGROUND

A. Evidence-Based Review System for Evaluating Health Claims

The Nutrition Labeling and Education Act of 1990 (“NLEA”) (Pub. L. 101-535) was designed to give consumers more scientifically valid information about foods they eat. Among other provisions, NLEA directed FDA to issue regulations providing for the use of health claims in the labeling of foods after such health claims have been reviewed and authorized by FDA. A health claim characterizes the relationship between a substance and a disease or health-related condition.² 21 CFR 101.14(a)(1). A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunction. *Id.* at 101.14(a)(5). FDA has defined the term “substance” by regulation as a specific food or food component. *Id.* at 101.14(a)(2). Health claims are directed to the general population or designated subgroups (e.g., the elderly) and are intended to assist the consumer in maintaining healthful dietary practices.³

On January 6, 1993, FDA issued a final rule implementing the health claim provisions of the NLEA, with general requirements codified at 21 CFR 101.14. *See* 58 Federal Register 2478. Section 101.14 describes the requirements for the authorization and use of health claims. Additionally, 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 and sets out the types of information that any such petition must include.

In evaluating a health claim, FDA considers whether the evidence supporting the substance/disease relationship that is the subject of the claim meets the significant scientific agreement (“SSA”) standard. This standard derives from 21 U.S.C. 343(r)(3)(B)(i), which provides that FDA shall authorize a health claim to be used on conventional foods if the Agency “determines based on the totality of the publicly available evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.” *See also* 21 CFR 101.14(c).

² *See Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir. 2004) (upholding FDA’s interpretation of what constitutes a health claim).

³ *See* 21 CFR 101.14(b)(1). *See also* FDA, “Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final,” January 2009.

As described in FDA Guidance issued in 2009,⁴ FDA uses an evidence-based review system to evaluate the publicly available scientific evidence on the relationship between a substance and a disease or health-related condition in its review of a petition to authorize a health claim.⁵ An evidence-based review system is a systematic science-based evaluation of the strength of the evidence to support a statement. In the case of health claims, it evaluates the strength of the scientific evidence to support a proposed claim about a substance/disease relationship. The evaluation process involves a series of steps to assess scientific studies and other data; eliminate those from which no conclusions about the substance/disease relationship can be drawn; rate the remaining studies for methodological quality; and evaluate the strength of the totality of scientific evidence by considering study types, methodological quality, quantity of evidence for and against the claim (taking into account the numbers of various types of studies and study sample sizes), relevance to the U.S. population or target subgroup, replication of study results supporting the proposed claim, and overall consistency of the evidence. After assessing the totality of the scientific evidence, FDA determines whether there is SSA to support an authorized health claim.

Before the strength of the evidence for a substance/disease relationship can be assessed, FDA separates individual relevant articles on human studies from other types of data and information. FDA focuses its review primarily on articles reporting human intervention and observational studies because only such studies can provide evidence from which scientific conclusions can be drawn about the substance/disease relationship in humans.⁶

In addition to reports of individual human studies, the Agency also considers other types of data and information in its review, such as meta-analyses,⁷ review articles,⁸ and animal and *in vitro* studies. These other types of data and information may be useful to assist the Agency in

⁴ FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final," January 2009.

⁵ As discussed in Section II.A.1, authorized health claims require SSA based on the totality of publicly available scientific evidence. The Agency reviews qualified health claims to determine whether there is "credible evidence" to support the proposed claim and these claims may be supported by evidence that is not well enough established to meet the SSA standard. FDA, "Guidance for Industry: FDA's Implementation of 'Qualified Health Claims': Questions and Answers; Final Guidance," May 2006. The qualified health claim process provides a mechanism to request that FDA review scientific evidence regarding a substance-disease relationship and exercise enforcement discretion for the use of a qualified claim in food labeling. *Id.* We note that your petition requests only revocation of the authorized health claim at issue, and does not concern any questions related to the Agency's consideration of enforcement discretion for a qualified health claim about soy protein and risk of CHD.

⁶ In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (*i.e.*, disease). Intervention studies provide the strongest evidence for an effect. *See supra*, note 4.

⁷ A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991). *See supra*, note 4.

⁸ Review articles summarize the findings of individual studies. *See supra*, note 4.

understanding the scientific issues about the substance, disease, or both, but cannot by themselves support a substance/disease relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from the study. Therefore, FDA uses meta-analyses, review articles, and similar publications⁹ to identify reports of additional studies that may be useful to the health claim review and as background about the substance/disease relationship.¹⁰ If additional studies are identified, the Agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. However, animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease. This is because the physiology of animals is different than that of humans. With respect to *in vitro* studies, these are conducted in an artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, which affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine, 2005).

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study (Spilker, 1991; NRC, 2011). Studies from which FDA cannot draw any scientific conclusions are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the Agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance/disease relationship.

⁹ Other examples include book chapters, abstracts, letters to the editor, and committee reports. *See supra*, note 4.

¹⁰ Certain meta-analyses may be used as part of the health claim review process. *See supra*, note 4.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects – e.g., age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The Agency then rates the strength of the total body of publicly available evidence.¹¹ The Agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of studies of each type and study sample sizes), whether the body of scientific evidence supports a health claim relationship for the United States population or target subgroup, whether study results supporting the proposed claim have been replicated,¹² and the overall consistency¹³ of the total body of evidence.¹⁴ Based on the totality of the scientific evidence, FDA determines whether such evidence meets the SSA standard to support a health claim for the substance/disease relationship.

B. Soy Protein and Risk of Coronary Heart Disease Health Claim

On October 26, 1999, in response to a petition from Protein Technologies International, Inc., FDA authorized the use, on food labels and labeling, of health claims on the association between soy protein and reduced risk of CHD. Food Labeling: Health Claims; Soy Protein and Coronary Heart Disease, 64 Federal Register 57700 (Oct. 26, 1999).¹⁵ The Agency concluded that soy protein included as part of a diet low in saturated fat and cholesterol may reduce the risk of CHD

¹¹ See *supra*, note 4.

¹² Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990). See *supra*, note 4.

¹³ Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence. Hill A.B., The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300; see also Agency for Healthcare Research and Quality, "Systems to rate the scientific evidence" (March 2002) [<http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf>] (defining "consistency" as "the extent to which similar findings are reported using similar and different study designs"); see also *supra*, note 4.

¹⁴ See *supra*, note 4.

¹⁵ The 1999 Final Rule authorizing use of the soy protein and risk of CHD health claim preceded FDA's Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final, January 2009. The January 2009 guidance represents the Agency's current thinking on the process for evaluating the scientific

by lowering blood cholesterol levels. *Id.* at 57700. The substance that is the subject of the soy protein and CHD claim is soy protein from the legume seed *Glycine max.* 21 CFR 01.82(c)(2)(ii)(A), and CHD is the disease that is the subject of the health claim. 21 CFR 101.14(a)(5).

On December 21, 2007, FDA announced, and requested public comment on, its intent to reevaluate the scientific evidence for soy protein and risk of CHD, among other authorized and qualified health claims (Health Claims and Qualified Health Claims; Dietary Lipids and Cancer, Soy Protein and Coronary Heart Disease, Antioxidant Vitamins and Certain Cancers, and Selenium and Certain Cancers; Reevaluation; Opportunity for Public Comment, 72 Federal Register 72738 (Dec. 21, 2007)). FDA uses the evidence-based review system described above when reevaluating a health claim in response to a petition or on its own initiative. To maximize the public health benefit of its health claims review, FDA endeavors to evaluate new information that becomes available to determine whether it necessitates a change to an existing SSA claim.

FDA decided to reevaluate the scientific basis for the soy protein and risk of CHD claim because new scientific evidence emerged regarding the relationship between soy protein and risk of CHD. 72 Federal Register at 72738. Since authorizing the health claim, numerous studies evaluating the relationship between soy protein and CHD have been published, and the findings of those studies were inconsistent. *Id.* at 72739. Specifically, FDA noted that the Agency for Healthcare Research and Quality (“AHRQ”) released a report in July 2005 outlining the effects of soy products on health outcomes including cardiovascular disease, and concluded that soy products appear to exert a small benefit on low-density lipoprotein (“LDL”)-cholesterol.¹⁶ *Id.* It was not clear whether soy protein (versus other types of soy products) was responsible for such a benefit. *Id.* Therefore, FDA sought public comment on soy protein and the risk of CHD to determine whether the totality of the scientific evidence continued to meet the SSA standard. *Id.*

III. DISCUSSION AND EVALUATION OF INFORMATION SUBMITTED

In your petition, you contend that soy protein is ineligible for a health claim because it is not safe. *See, e.g.*, Petition at 4. You further argue that your petition and the data referenced therein demonstrate that the SSA standard is not met for the soy protein and CHD health claim. *See, e.g., id.* at 12. In the petition supplement, you clarified that the sole issue before FDA in reviewing the petition is whether there is “significant scientific agreement supporting a soy/coronary disease relationship.” Petition Supp. at 3.¹⁷ As such, you have abandoned the contention that soy protein is ineligible for a health claim because it is not safe. *See also, e.g., id.*

evidence for a health claim but did not alter FDA’s previous understanding of what constitutes SSA in 21 U.S.C. 343(r)(3) and 21 CFR 101.14(c) as that standard was applied, for example, in the 1999 Final Rule.

¹⁶ The AHRQ report included studies that evaluated substances in addition to soy protein (e.g., isoflavones). In addition, the AHRQ report used risk biomarkers of cardiac function that are not validated surrogate endpoints recognized by the Agency for heart disease risk. 72 Federal Register at 72739.

¹⁷ The petition supplement’s pages are also unnumbered and are cited to in this response as if they were numbered consecutively, starting with the cover page.

at 2 (stating that a comment rebutting statements in the petition “on the harmful effects of soy” was “off point” and “irrelevant to . . . address the issue before . . . FDA in this case”).

In the 1999 Final Rule, FDA assessed whether the petitioner had demonstrated that soy protein is safe and lawful at the level necessary to justify the claim. 64 Federal Register 57700, 57701. FDA concluded that the health claim petitioner demonstrated, to FDA’s satisfaction, that soy protein is safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act at levels necessary to justify a claim, as required by 21 CFR 101.14(b)(3)(ii). *Id.* at 57703. FDA further noted that it lacked “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.” *Id.* Accordingly, the Agency concluded that the petitioner met the requirement in 21 CFR 101.14(b)(3)(ii). You do not appear to dispute that conclusion, nor do you maintain the position you took in the petition that soy protein is ineligible for a health claim because it is not safe. Accordingly, the Agency now considers whether the petition, Complaint, and petition supplement support your position that SSA has not been met.

A. Information Submitted Does Not Include the Totality of the Publicly Available Scientific Evidence to Support Your Conclusion that SSA Has Not Been Met

FDA considered the petition and the evidence cited in it, the Complaint, and the comments submitted to the docket for the petition, including the petition supplement, and other information before the Agency. We reviewed every publication you referenced in the petition, the Complaint, and the petition supplement and carefully considered your arguments.¹⁸ As discussed further below, the information you have submitted to FDA does not provide sufficient grounds for the Agency to revoke the 1999 Final Rule. The Agency would first need to evaluate the totality of publicly available scientific evidence to determine whether there is no longer SSA to support the soy protein and CHD health claim. Contrary to your representations, you have not presented sufficient data to FDA to demonstrate that the significant scientific agreement standard has not been met for this health claim. E.g., Petition at 1.

FDA has identified the following disease endpoints to use in identifying CHD risk reduction for purposes of a health claim evaluation: the incidence of coronary events (myocardial infarction, ischemia), cardiovascular death, coronary artery disease, and atherosclerosis. High blood pressure, blood (serum or plasma) total and LDL-cholesterol levels are considered surrogate endpoints for CHD.¹⁹ These disease and surrogate endpoints were used to evaluate the potential effects of consumption of soy protein on CHD risk.

¹⁸ The Agency received and reviewed comments submitted to the docket; however, the comments did not provide any additional supporting data or other information not already considered by the Agency in response to your petition. For these reasons, we are not addressing them in our response.

¹⁹ See *supra* note 4.

You cite 145 publications in your petition as evidence to support your request to revoke the soy protein and CHD claim. These publications consisted of: 1 article written in a foreign language; 40 review articles; 3 meta-analyses; 14 *in vitro* studies; 28 animal studies; 1 publication from AHRQ; 12 books or book chapters; 9 websites; 2 letters; 19 intervention studies that did not evaluate the substance and disease relationship; 6 observational studies that did not evaluate the substance and disease relationship; and 10 intervention studies on soy protein consumption and CHD risk. The Complaint included 10 additional articles not included in the petition. The additional studies included 2 animal studies; 1 observational study that did not evaluate the substance and disease relationship; 1 observational study that evaluated the substance and disease relationship; 4 intervention studies that evaluated the substance and disease relationship; and 2 meta-analyses.

The petition supplement included 15 publications not included in the petition or the Complaint. These publications consisted of: 4 review articles; 2 meta-analyses; 1 *in vitro* study; 2 animal studies; 1 book chapter; 3 reports from the European Food Safety Authority; 1 observational study that did not evaluate the substance and disease relationship; 3 observational studies that evaluated the substance and disease relationship; and 3 intervention studies that evaluated the substance and disease relationship. As discussed below, the limited relevant information submitted in the petition, Complaint, and petition supplement fails to reflect the totality of scientific evidence that was publicly available at the time of the petition on the relationship between soy protein and risk of CHD and is insufficient to support the conclusion that the SSA standard has not been met.

1. Assessment of Review Articles, Meta-Analyses, Book Chapters, Letters, and Government Reports

Although useful for background information, the review articles, meta-analyses, book chapters, letters, and government reports you referenced do not contain sufficient information on the individual studies which they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. Specifically, FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement). Similarly, the lack of detailed information prevents FDA from determining whether the underlying studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the review articles, meta-analyses, book chapter, letters, and government reports you rely on do not provide information from which scientific conclusions can be drawn regarding the substance/disease relationship.

2. Assessment of Animal and *In Vitro* Studies

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. Animal and *in vitro* studies can also be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between the substance and the disease in humans.

The animal or *in vitro* studies you rely on do not provide any supportive information about soy protein and risk of CHD because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of CHD, nor can the studies mimic the human body's response to the consumption of soy protein. Therefore, FDA cannot draw any scientific conclusions from these studies.

3. Assessment of Intervention Studies

FDA evaluated in detail 22 individual studies that were designed to evaluate the relationship between soy protein and risk of CHD. Of the 22 studies reviewed, scientific conclusions could not be drawn from 17²⁰ studies for the reasons discussed below.

i. Studies you referenced from which scientific conclusions could not be drawn

Three studies²¹ did not conduct any statistical analysis between the control and the soy protein treatment groups. Statistical analysis of the substance/disease relationship is a critical factor in determining whether or not scientific conclusions can be drawn because it compares subjects consuming soy protein to those subjects not consuming soy protein to determine whether there is a reduction in CHD risk. Hence, because statistical analyses were not performed between the two groups, scientific conclusions cannot be drawn from these studies.

Four observational studies calculated soy protein intake from estimated dietary intake.²² In observational studies that calculate nutrient intake from conventional food, measures of soy protein intake are based on recorded dietary intake methods such as food frequency questionnaires, diet recalls, or diet records, in which the type and amount of foods consumed are estimated. A common weakness of observational studies is the limited ability to ascertain the actual food or nutrient intake for the population studied as a result of poor memory, over- or underestimation of portion sizes, and recall bias (Flegal, 1999). Furthermore, the nutrient content of foods can vary (e.g., due to soil composition, food processing and cooking procedures, or storage conditions such as duration or temperature). Thus, we cannot ascertain an accurate amount of soy protein consumed based on reports of dietary intake of foods.

Two studies did not measure a validated surrogate endpoint of CHD (i.e., blood total cholesterol, blood LDL cholesterol, blood pressure).²³ Because these studies did not measure a validated surrogate endpoint, scientific conclusions about the relationship between soy protein consumption and risk of CHD cannot be drawn.

²⁰ One study Anderson et al. 2007 contained data on blood LDL cholesterol and blood pressure. The data on blood LDL cholesterol was not used because the study did not control for other confounders that effects blood cholesterol levels. The data on blood pressure was used as part of this review.

²¹ Lovati et al., 1987; Sirtori et al., 1977; Potter et al., 1976.

²² Talaei et al., 2014; Pan et al., 2008; Yu et al., 2014; Yu et al., 2015.

²³ Persky et al., 2002; Greany et al., 2008.

Two studies²⁴ did not include a control group for comparing the relative effects of soy protein consumption. Therefore, we cannot determine whether changes in the endpoint of interest were due to soy protein consumption or due to unrelated and uncontrolled extraneous factors. Hence, scientific conclusions cannot be drawn from these studies.

Six studies substituted soy protein for animal protein or were feeding studies that had differences in dietary components or data not reported on dietary components that have an effect on blood cholesterol (e.g. fiber, saturated fat, dietary cholesterol).²⁵ Because of such large differences in nutrient intakes of fiber, saturated fat or dietary cholesterol, we cannot clearly delineate what may be causing a change in serum cholesterol levels; thus, the results of these studies cannot be interpreted. Hence, scientific conclusions cannot be drawn from these studies.

ii. Studies you referenced from which scientific conclusions could be drawn

Based on the above discussion, there were three intervention studies referenced in your petition (Bakhit et al., 1994; Anderson et al., 2007; Teede et al., 2001) and three studies in the Complaint and petition supplement (Mangano et al., 2013; Carmignani et al., 2014; Liu et al., 2012) from which scientific conclusions *could* be drawn about the relationship between soy protein and risk of CHD. Each of these studies is discussed in turn below.

Bakhit et al., 1994 was a four-week randomized, cross-over study of moderate quality in which 31 hypercholesterolemic men consumed a diet that substituted isolated soy protein plus cellulose or isolated soy protein plus soybean cotyledon fiber, or casein plus soybean cotyledon fiber, or casein plus cellulose. There was no significant difference between isolated soy protein groups and control groups for blood TC and LDL cholesterol.

Anderson et al., 2007 was a sixteen-week randomized, single blind, parallel trial of moderate quality in which 35 obese women were fed diets of approximately 22 g per day of casein (n=18) or approximately 21 g per day of soy protein (n=17). There was no significant difference in systolic blood pressure or diastolic blood pressure between the casein or soy protein diets.

Teede et al., 2001 was a three-month randomized, double blind, placebo controlled, parallel study of moderate quality in which 179 men and postmenopausal women who consumed a casein placebo (n=93) in addition to their usual diet or 40 g per day (n=86) soy protein isolate mixed with a beverage twice a day in addition to their usual diet. There was no significant difference in blood TC and LDL cholesterol between the casein control group and soy protein isolate group.

²⁴ Hanson et al., 2006; Sathyapalan et al., 2011.

²⁵ Kreijkamp-Kaspers et al., 2005 (Kreijkamp-Kaspers et al, 2004); Baum et al. 1998; Anderson et al., 2007; Nilausen and Meinertz, 1999 (same subjects as Nilausen and Meinertz, 1998 in 1999 Final Rule); Campbell et al., 2010; Thorp et al., 2008.

Mangano et al., 2013 was a moderate quality one-year randomized, double blind, controlled, parallel trial in which 97 postmenopausal women consumed 18 g per day soy protein plus 105 mg/d isoflavone tablets (n=25), 18 g/d soy protein plus placebo tablets (n=24), 18 g per day control protein (casein, whey, and egg protein) plus 105 mg/d isoflavone tablets (n=26), or control protein and placebo tablets (n=22). There was no significant difference in blood TC or LDL cholesterol between any of the soy protein groups and the control groups.

Carmignani et al., 2014 was a sixteen-week randomized, double-blind, controlled trial of moderate quality in which 40 postmenopausal women consumed 40 g per day placebo powder of maltodextrin (n=20) or 40 g per day protein powder containing 24 g per day soy protein and 90 mg isoflavone (n=20). There was no significant difference in blood TC and LDL cholesterol between the soy protein group and the control group.

Liu et al., 2012 was a moderate quality randomized, double-blind, parallel trial in which 120 postmenopausal Chinese women consumed 15 mg milk protein and 100 mg isoflavones (control) (n=60) or 15 mg soy protein and 100 mg isoflavones (n=60) for six months. There was no significant difference in the change in blood TC and LDL cholesterol between the milk protein and isoflavone group and the soy protein and isoflavone group.

iii. Other evidence available on soy protein and risk of CHD

You submitted the petition under 21 CFR 10.30, subsection (b)(3) of which requires that the statement of grounds include “all relevant information and views on which the petitioner relies, as well as representative information known to the petitioner which is unfavorable to the petitioner’s position.” You failed to include pertinent information on relevant studies in the literature that report a benefit of soy protein intake and reduced risk of CHD that were unfavorable to your position at the time the petition was submitted. For example, the Agency has identified at least 25 individual reports of human intervention studies that reported a reduced risk of CHD with soy protein intake. *See Proposed Rule, 63 Federal Register 62977; 1999 Final Rule; AHRQ, 2005.* However, you fail to address these studies in your petition or petition supplement.²⁶ The limited number of relevant studies you rely on to conclude that the soy protein and CHD health claim fails to meet the SSA standard did not reflect the significant body of literature relevant to this topic at the time the petition was submitted.

As discussed above in section II.A, any determination by the Agency on whether or not the soy protein and CHD health claim still meets the SSA standard must be based on the totality of publicly available evidence (including evidence from well-designed studies conducted in a manner consistent with generally recognized scientific procedures and principles). FDA has identified over 700 publications available from the 1999 Final Rule, the AHRQ report, literature searches, and comments to the 2007 reevaluation notice that are relevant to determining whether

²⁶ The Complaint also did not include pertinent information unfavorable to your position on relevant studies in the literature that report a benefit from soy protein intake and reduced risk of CHD.

the soy protein and CHD health claim still meets the SSA standard in section 403(r)(3)(B). As noted below, the Agency is in the process of reviewing this entire body of literature.

A. Strength of the Evidence

When evaluating the strength of the evidence for an authorized health claim the Agency rates the strength of the total body of publicly available evidence. The Agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control,

cross-sectional), the methodological quality rating previously assigned, the number of studies and number of subjects per group, whether the body of scientific evidence supports a health claim relationship for the United States population or a target subgroup, whether study results supporting the proposed claim have been replicated,²⁷ and the overall consistency²⁸ of the total body of evidence.²⁹ Based on the totality of the scientific evidence, FDA then determines whether such evidence supports an authorized health claim for the substance/disease relationship.

As discussed, no scientific conclusions could be drawn from the vast majority of publications you cited in the petition, Complaint, and petition supplement. In fact, you reference only six studies of moderate quality that are relevant for evaluating soy protein and risk of CHD,³⁰ one of which (Bahkit et al., 1994) FDA previously evaluated in the 1999 Final Rule authorizing the soy protein and CHD health claim. The six relevant studies you cited did not show a benefit for intake of soy protein and risk reduction of CHD. Although FDA considers these studies to be relevant to its reevaluation of the soy protein and CHD health claim, they do not represent the totality of publicly available scientific evidence on soy protein and risk reduction of CHD. In order for the Agency to determine whether the soy protein and CHD health claim still meets the SSA standard, FDA needs to review all publicly available relevant studies that evaluate the substance and disease relationship—both those that are favorable and unfavorable to your petition.

As noted above, in 2007 FDA announced its intent to reevaluate the scientific evidence for the soy protein and CHD claim in light of inconsistent findings in studies conducted since issuance of the 1999 Final Rule. 72 Federal Register at 72738-72739. FDA sought public comment on the health claim to determine whether the totality of the scientific evidence continues to meet the SSA standard. FDA stated in the 2007 notice that the AHRQ report that outlined the effects of soy products on health outcomes including cardiovascular disease concluded that soy products appear to exert a small benefit on LDL-cholesterol, but it remained unclear whether soy protein (versus other types of soy products) was responsible for such a benefit. The AHRQ report, for example, included studies that evaluated substances in addition to soy protein (e.g., isoflavones)

²⁷ See *supra*, note 12.

²⁸ See *supra*, note 13.

²⁹ See *supra*, note 4.

³⁰ Bahkit et al., 1994; Anderson et al., 2007; Teede et al., 2001; Mangano et al., 2013; Carmignani et al., 2014; Liu et al., 2012.

that are not the substance that is subject of this health claim and risk biomarkers of cardiac function that are not validated surrogate endpoints recognized by the Agency for heart disease risk.

FDA is in the process of evaluating the strength of the totality of publicly available evidence to determine whether or not the soy protein and CHD health claim still meets the SSA standard. As noted above, this includes a review of over 700 publications identified through literature searches, comments to the Agency's 2007 reevaluation notice, the AHRQ report, and the 1999 Final Rule. Due to many other competing public health priorities and Agency resource

constraints (described more fully below in section IV), FDA has not yet completed the resource-intensive process of reevaluating the soy protein and CHD health claim but intends to complete this process as soon as practicable.

IV. COMPETING AGENCY PRIORITIES

United States consumers spend twenty-five cents of every consumer dollar on products regulated by FDA, and, of this amount, approximately 75 percent is spent on foods. FDA regulates \$417 billion worth of domestic food and \$49 billion worth of imported foods. FDA's responsibility in the food area covers nearly all domestic and imported food, including shell eggs, fruits and vegetables, seafood, grain products and pastas, cereal flours and related products, acidified and low acid foods, infant formula, dietary supplements, dairy products, food and color additives, bottled drinking water, juice, and other beverages. In addition, FDA regulates food ingredients, packaging, and labeling. There are hundreds of thousands of domestic and foreign registered food facilities and farms subject to FDA regulations. In addition to developing regulations, FDA's oversight of the food supply involves a wide range of activities, including inspecting food facilities, overseeing the safety of imported foods, responding to foodborne illness, developing guidance documents, and, where appropriate, seeking enforcement action.

FDA has been, and continues to be, engaged in an unprecedented number of novel and complex rulemakings to implement the FDA Food Safety Modernization Act of 2011 ("FSMA"). As part of FSMA implementation, FDA has been developing the following regulations and guidance documents, among others:

- Protection of Food Against Intentional Adulteration, Final Rule;
- Sanitary Transportation of Human and Animal Food, Final Rule;
- Amendments to Registration of Food Facility Registration, Final Rule;
- Third-Party User Fee, Final Rule;
- Laboratory Accreditation, Final Rule;
- Suspension of Registration, Proposed Rule; and

- Final Guidance on Third Party Model Accreditation Standards.

In addition to FSMA rulemakings, FDA currently is engaged in developing numerous other rulemakings and guidance documents, including, but not limited to:

- Food Labeling: Revision of the Nutrition and Supplement Facts Labels, Final Rule; Food Labeling: Serving Sizes of Foods That Can Reasonably Be Consumed in One Eating Occasion; Dual Column Labeling; and Modifying the Reference Amounts Customarily Consumed, Final Rule;
- Substances Generally Recognized as Safe, Final Rule; and
- Direct Food Substances Affirmed as Generally Recognized as Safe; Partially Hydrogenated Menhaden Oil and Rapeseed Oil, Proposed Rule.

Given the scope of FDA's responsibilities regarding the food supply, the Agency must make difficult choices regarding how to use its limited resources. For every initiative the Agency undertakes, there are many others it cannot. These other lower priorities are not undertaken for reasons that may include that they are not statutorily mandated or that they address less urgent public health and food safety concerns. In light of the Agency's many competing priorities, and based on our careful consideration of the information you submitted, FDA believes, as a matter of science and regulatory policy, that the most appropriate course of action at this time is to complete its ongoing review of the entire body of scientific evidence to allow the Agency to make a more well-informed reevaluation of this health claim. Once the Agency has evaluated all the information before it, FDA will reach a conclusion about next steps, including whether there may be grounds to initiate the rulemaking process for amending or revoking the health claim.

V. CONCLUSION

FDA appreciates your concerns about the soy protein and CHD health claim. For the reasons discussed above, we conclude that the limited relevant information in the petition and petition supplement does not provide sufficient grounds for the Agency to revoke the soy protein and CHD health claim at this time. Therefore, FDA is denying your petition in accordance with 21 CFR 10.30(e)(3).

Although FDA is not taking the action you request regarding the health claim at this time, the Agency is actively reviewing the entire body of scientific evidence to allow the Agency to make a more well-informed decision regarding next steps for this health claim. As part of its ongoing scientific reevaluation of this claim, FDA intends to consider the six relevant studies you submitted, as described in section III.A.3.ii *supra*, as part of its ongoing review. Once the

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Agency has evaluated all the information before it, FDA will reach a conclusion about next steps, including whether there may be grounds to initiate the rulemaking process for amending or revoking the health claim.

Sincerely,

A handwritten signature in black ink that reads "Susan T. Mayne". The signature is written in a cursive style with a long horizontal flourish at the end.

Susan T. Mayne, Ph.D., F.A.C.E.
Director
Center for Food Safety
and Applied Nutrition

APPENDIX

List of References

Agency for Healthcare Research and Quality, "Systems to rate the scientific evidence" (March 2002) [<http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf>].

Anderson JW, Fuller J, Patterson K, Blair R, Tabor A. Soy compared to casein meal replacement shakes with energy-restricted diets for obese women: randomized, controlled trial. *Metabolism* 2007;56:280-288.

Bakhit, RM, Klein BP, Essex-Sorlie D, Ham JO, Erdman, JW and Potter SM. Intake of 25 g of Soybean Protein With or Without Soybean Fiber Alters Plasma Lipids in Men With Elevated Cholesterol Concentrations. *J Nutr* 1994;124:213-222.

Balk E, Chung M, Chew P, Ip S, Raman G, Kupelnick B, Tatsioni A, Sun Y, Wolk B, DeVine D, Lau J. Effects of Soy on Health Outcomes. Summary, Evidence Report/Technology Assessment No. 126. (Prepared by the Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022.) AHRQ Publication No.05-E024-1. Rockville, MD: Agency for Healthcare Research and Quality. July 2005.

Baum JA, Teng H, Erdman JW, Weigel RM, Klein BP, Persky VW, Freels S, Surya P, Bakhit RM, Ramos E, Shay NF, Potter SM. Long-term intake of soy protein improves blood lipid profiles and increases mononuclear cell low-density-lipoprotein receptor messenger RNA in hypercholesterolemic, postmenopausal women. *Am J Clin Nutr* 1998;68:545-551.

Campbell SC. One-year soy protein supplementation does not improve lipid profile in postmenopausal women. *Menopause* 2010;17(3):587-593.

Carmignani LO, Pedro AO, Costa-Paiva L, Pinto-Neto A. The effect of soy dietary supplement and low dose of hormone therapy on main cardiovascular health biomarkers: a randomized controlled trial. *Rev Bras Ginecol Obstet* 2014;36(6):251-258.

Flegal KM. Evaluating epidemiological evidence of the effects of food and nutrient exposures. *Am J Clin Nutr* 1999;69:1339S-1344S.

Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. *Eur J Clin Nutr* 2008;62:1419-1425.

Hanson LN, Engelman HM, Alekel DL, Schalinske KL, Kohut ML, Reddy MB. Effects of soy isoflavones and phytate on homocysteine, C-reactive protein, and iron status postmenopausal women. *Am J Clin Nutr* 2006;84(4):774-780.

Hill AB. The environment and disease: Association or causation? *Proc R Soc Med* 1965;58: 295-300.

IOM (Institute of Medicine, National Academy of Sciences). 2005. *Dietary Supplements: A Framework for Evaluating Safety*. Chapter 7, Categories of Scientific Evidence – In Vitro Data. The National Academies Press, Washington, D.C.

Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, Lampe JW, van der Schouw YT. Randomized controlled trial of the effects of soy protein containing isoflavones on vascular function in postmenopausal women. *Am J Clin Nutr* 2005;81:189-195.

Kreijkamp-Kaspers S, Kok, Grobbee DE, de Haan EHF, Aleman A, Lampe JW, van der Schouw. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women. *J Am Med Assoc* 2004;292:65-74.

Liu ZM et al. The effects of isoflavones combined with soy protein on lipid profiles, C-reactive protein and cardiovascular risk among postmenopausal Chinese women. *Nutr Metab Cardiovasc Dis* 2012;22(9):712-9

Lovati MR, Manzoni C, Canavesi A, Sirtori M, Vaccarino V, Marchi M, Gaddi G, Sirtori CR. Soybean protein diet increases low density lipoprotein receptor activity in mononuclear cells from hypercholesterolemic patients. *J Clin Invest* 1987; 80:1498-1502.

Mangano KM et al. Soy proteins and isoflavones reduce interleukin-6 but not serum lipids in older women: a randomized controlled trial. *Nutr Res* 2013 ;33(12):1026-33.

National Research Council. 2011. *Reference Manual on Scientific Evidence: Third Edition*. The National Academies Press, Washington, DC, page 220.

Nilausen K, Meinertz H. Lipoprotein (a) and dietary proteins: casein lowers lipoprotein (a) concentrations as compared with soy protein. *Am J Clin Nutr* 1999;69:419-425.

Nilausen K, Meinertz H. Variable lipemic response to dietary soy protein in healthy, normolipemic men. *Am J Clin Nutr* 1998;68:1380S-1384S.

Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr* 2008;138: 2413-2421.

Persky VW, Turyk ME, Wang L, Freels S, Chatterton R Jr, Barnes S, Erdman J Jr, Sepkovic DW, Bradlow HL, Potter S. Effect of soy protein on endogenous hormones in postmenopausal women. *Am J Clin Nutr* 2002;75(1):145-153.

Potter JM, Nestel PJ. Greater bile acid excretion with soy bean than with cow milk in infants. *Am J Clin Nutr* 1976;9:546-551.

Sathyapalan T. The effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized, double-blind, crossover study. *J Clin Endocrinol Metab* 2011;96(5):1442-1449.

Sirtori CR, Agradi E, Conti F, Mantero O, Gatti E. Soybean-protein diet in the treatment of type-II hyperlipoproteinaemia. *Lancet* 1977;275-277.

Spilker B. 1991. *Guide to Clinical Studies*. Raven Press, New York, New York, pp. 59-64, 793-800.

Talaei M, Koh W, van Dam R, Yuan J, Pan A. Dietary soy intake is not associated with risk of cardiovascular disease mortality in Singapore Chinese adults. *J Nutr* 2014;144(6):921-8.

Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab* 2001;86:3053-3060.

Thorp AA et al. Soy food consumption does not lower LDL cholesterol in either equal or nonequal producers. *Am J Clin Nutr* 2008; 88(2): 298-304.

Wilson EB. 1990. *An Introduction to Scientific Research*. Dover Publications, New York. pp. 46-48.

Yu D, Shu X, Li H, Yang G, Cai Q, Xiang YB, Ji B, Franke AA, Gao Y, Zheng W, Zhang X. Dietary isoflavones, urinary isoflavonoids, and risk of ischemic stroke in women. *Am J Clin Nutr* 2015;102:680-686.

Yu D, Zhang X, Xiang YB, Yang G, Li H, Fazio S, Linton M, Zheng W, Gao Y, Shu X. Association of soy food intake with risk and biomarkers of coronary heart disease in Chinese men. *Int J Cardiol* 2014; 72(2): e285--e287.