



OCT 12 2005

Food and Drug Administration
College Park, MD 20740

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RE: Health Claim Petition – Calcium and (1) Essential Hypertension; (2) Gestational Hypertension; and (3) Pre-eclampsia (Docket No. 2004Q-0098).

Dear Mr. Emord:

This letter responds to the health claim petition dated October 9, 2003, submitted to the Food and Drug Administration (FDA or the agency), on behalf of Marine Bio USA, Inc. pursuant to Section 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(5)(D)). The petition requested that the agency authorize health claims characterizing the relationship between the consumption of calcium and a reduced risk of essential hypertension, gestational hypertension, and pre-eclampsia.

The petition proposed the following model health claims for calcium dietary supplements:

1. Calcium may reduce the risk of essential hypertension
2. Calcium may reduce the risk of gestational hypertension
3. Calcium may reduce the risk of pre-eclampsia

FDA informed you on October 24, 2003, that FDA was not able to acknowledge receipt of the petition and begin its preliminary review of the petition because the petition was not complete. In response, you supplied the needed information in a supplemental submission received by FDA on November 25, 2003 and December 8, 2003. FDA acknowledged the petition in a letter dated December 9, 2003, which initiated FDA's preliminary review of the petition. In that letter, FDA also informed you that the date by which FDA would either file or deny the petition was March 4, 2004.

Based on a preliminary review, FDA determined that the scientific evidence supporting the proposed health claims did not meet the "significant scientific agreement" standard in 21 CFR 101.14(c) which is applicable to dietary supplements. FDA notified you of this decision and you submitted a letter dated March 2, 2004, stating that your client, Marine

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Bio USA, Inc., chose to seek FDA review of the petition as a qualified health claim. Accordingly, FDA filed the petition on March 16, 2004 as a qualified health claim petition and posted the petition on the FDA website for a 60-day comment period, consistent with the agency's guidance for procedure on qualified health claims.¹ The agency did not receive any comments on this petition. In a letter dated June 16, 2004, you notified FDA that Marine Bio Co. Ltd. is now the petitioner of record for this petition, originally submitted by its wholly owned subsidiary, Marine Bio USA, Inc. The initial deadline for FDA's response on the petition was October 27, 2004. After mutual agreement, the deadline for the agency's response was last extended to October 12, 2005.

Throughout the text of this letter, the term, "hypertension" will be used instead of "essential hypertension" and the term, "pregnancy-induced hypertension," will be used instead of "gestational hypertension" to be consistent with the terminologies used in the scientific articles upon which FDA relied. Also, the amount of calcium discussed in this letter is expressed in weight of elemental calcium rather than weight of calcium compounds (e.g., calcium carbonate, calcium citrate).

This letter sets forth the basis of FDA's determination that the current evidence for the proposed qualified health claims is appropriate for consideration of qualified health claims for calcium and a reduce risk of hypertension, pregnancy-induced hypertension, and preeclampsia. This letter also sets forth the factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims for dietary supplements, with respect to consumption of calcium and a reduced risk of hypertension, pregnancy-induced hypertension, and preeclampsia.

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.² In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.³ FDA considers the data and information provided in the petition, in addition to other written data and information available to the

¹ "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003). [<http://www.cfsan.fda.gov/~dms/nuttf-e.html>]

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), *cert. denied*, 125 S.Ct. 310 (2004).

³ See guidance entitled "Interim Evidence-based Ranking System for Scientific Data," July 10, 2003. [<http://www.cfsan.fda.gov/~dms/hclmgi4.html>]

agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.⁴

The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.⁵

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,⁶ review articles,⁷ and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease or health-related condition, or both, but can not by themselves support a health claim 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 it. Therefore, FDA uses meta-analyses, review articles, and similar publications⁸ to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. 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. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine, National Academy of Sciences, 2005a). Animal and *in vitro* studies can be

⁴ For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of the section.

⁵ 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 are observed or their medical records are reviewed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See Guidance entitled "Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" (December 22, 1999). [<http://www.cfsan.fda.gov/~dms/ssaguide.html>]

⁶ A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

⁷ Review articles summarize the findings of individual studies.

⁸ Other examples include book chapters, abstracts, letters to the editor, and committee reports.

used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

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 et al., 1991, Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these 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.

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 cannot be used to support the health claim relationship, and these 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.⁹ 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 the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S.

⁹ See *supra*, note 3.

population or target subgroup, whether study results supporting the proposed claim have been replicated,¹⁰ and the overall consistency¹¹ of the total body of evidence.¹² Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified calcium as the substance for the proposed qualified health claims. Calcium, one of the essential nutrients for humans, is a component of milk and milk products (approximately 300 mg per serving) as well as other food sources (e.g., Chinese cabbage, kale, and broccoli) (IOM, 1997). Therefore, the agency concludes that the substance, calcium is a component of food and meets the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

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 dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified essential hypertension (i.e., hypertension), preeclampsia and gestational hypertension (i.e., pregnancy-induced hypertension) as the diseases or health-related conditions for the proposed health claims. Hypertension is a health-related condition that is diagnosed when systolic blood pressure is 140 mm Hg or higher and/or diastolic blood pressure is 90 mm Hg or higher.¹³ Hypertension Preeclampsia occurs after the 20th week of pregnancy and is characterized by the onset of hypertension, proteinuria, and

¹⁰ 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 also Ioannidis JPA. Contradicted and initially stronger effects in highly cited clinical research. *JAMA*, 294: 218-228, 2005).

¹¹ 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 Systems to rate the scientific evidence, Agency for Healthcare Research and Quality <http://www.ahrq.gov/clinic/epcsu/sums/strengthsum.htm#Contents> (defining "consistency" as "the extent to which similar findings are reported using similar and different study designs")).

¹² See *supra*, note 3.

¹³ National Heart, Lung and Blood Institute (NHLBI), Heart and Blood Vessel Diseases (http://www.nhlbi.nih.gov/health/dci/Diseases/Hbp/HBP_WhatIs.html) and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and treatment of high blood pressure, 2003. (<http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf>)

hyperuricemia. There is no single test for diagnosing preeclampsia. Thus, a measurement of blood pressure alone is not sufficient for measuring the risk of preeclampsia. Pregnancy-induced hypertension is defined as a blood pressure elevation detected for the first time after mid-pregnancy and is distinguished from preeclampsia by the absence of proteinuria and hyperuricemia.¹⁴ Blood pressure is the primary diagnostic method for identifying pregnancy-induced hypertension. Because they are states of health leading to disease, the agency concludes that hypertension and pregnancy-induced hypertension are health-related conditions under 21 CFR 101.14(a)(5).¹⁵ Because preeclampsia is a state in which the body is not functioning properly, the agency concludes that it is a disease under 21 CFR 101.14(a)(5). Therefore, the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For dietary supplements, the applicable safety provisions require, among other things, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the Act (21 U.S.C. 342(f)(1)(A))). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (section 402(f)(1)(D) of the Act (21 U.S.C. 342(f)(1)(D))).

The petition stated that calcium is an essential mineral that has a multitude of vital biological roles and also asserted that there is an absolute lack of any reports of clinically significant adverse reactions attributed to dietary calcium. Further, the petition stated that the final rule authorizing the health claim about calcium and osteoporosis concluded that calcium complies with the requirements of 21 CFR 101.14(b)(3)(ii). The petition stated that FDA has determined that ten calcium compounds have been demonstrated to be safe and lawful for use in dietary supplements. 58 FR at 2670 citing 56 FR at 60691. The petition also stated that calcium has prior sanctioned status as safe and lawful under the Act. Further, the petition noted that the North American Menopause Society, in its 2001

¹⁴ National Heart, Lung and Blood Institute (NHLBI), Report of the Working Group on Research on Hypertension During Pregnancy, 2001. (http://www.nhlbi.nih.gov/resources/hyperten_preg/)

¹⁵ Note that this finding under 21 CFR 101.14(a)(5) does not alter the fact that hypertension may be a disease under 21 CFR 101.93(g), which defines "disease" to include states of health leading to disease.

Consensus Opinion, stated that the side effect profile from recommended levels of calcium intake is insignificant and that no serious side effects are associated with those levels, and that the Physicians' Desk Reference (PDR) reported that calcium supplements are generally well tolerated.

In the final rule for the authorized health claim about calcium and osteoporosis (21 CFR 101.72) (58 FR 2665 at 2670; January 6, 1993), FDA identified ten specific calcium compounds¹⁶ that are deemed to be safe and lawful for use in dietary supplements or as a nutrient supplement (i.e., added to food) that may bear the calcium/osteoporosis health claim. These calcium compounds were either approved as food additives (21 CFR 172), GRAS substances (21 CFR 182), or affirmed as GRAS substances (21 CFR 184). All ten were approved, recognized, or affirmed as safe for use in a dietary supplement or as a nutrient supplement. Although the petition asserted that calcium has prior-sanctioned status as safe and lawful under the Act, there are no food ingredients that have prior-sanctioned status for nutrient supplement purposes (21 CFR 181).

At the time FDA published the final rule authorizing the health claim about calcium and osteoporosis (January 6, 1993), ingredients used in dietary supplements were subject to the premarket safety evaluations required for new food ingredients and for new uses of food ingredients. That is, such ingredients were required to be approved as food additives, determined as GRAS substances, or affirmed as GRAS substances before they could be used in food, including dietary supplements. With passage of the Dietary Supplement Health and Education Act in 1994 (DSHEA) (Pub. L. 103-417), Congress amended the Act to provide that ingredients for dietary supplements are exempt from premarket safety evaluations for food additives or GRAS substances. Instead, Congress provided that dietary ingredients are subject to the adulteration provisions in section 402 of the Act (21 U.S.C. 342) (excluding the food additive adulteration provision), and, if applicable, the new dietary ingredient provisions in section 413 of the Act (21 U.S.C. 350b), which pertain to dietary ingredients that were not marketed in the United States before October 15, 1994.

Although calcium is known to be an essential nutrient, it can also cause adverse effects. The Institute of Medicine (IOM) of the National Academy of Sciences (IOM, 1997) noted that the adverse effects of excess calcium intake in humans concerns calcium intake from "nutrient supplements" and that the most widely studied and biologically important possible adverse effects of excessive calcium intake are kidney stone formation, the syndrome of hypercalcemia and renal insufficiency (milk alkali syndrome), and the interaction of calcium with the absorption of other essential minerals. Using milk alkali syndrome as the clinically defined critical endpoint, the IOM identified the lowest-observed-adverse-effect level (LOAEL) of calcium intake in the range of 4,000 to 5,000 mg/day. The IOM established 2,500 mg of calcium as the tolerable upper intake levels (UL) for individuals over 12 months old by dividing a LOAEL of 5,000 mg

¹⁶ Calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate.

by an uncertainty factor of two to account for the relatively high prevalence of renal stones in the U.S. population (12 percent) and potential increased risk of hypercalciuria and depletion of other minerals among susceptible individuals. The IOM defined the UL as the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population (IOM, 1997).

Calcium is often contained in multiple vitamin and mineral dietary supplement products. Most of these products contain about 100 to 200 mg of calcium per reference amount customarily consumed (RACC) and recommend consumption of the dietary supplement once per day. Alternatively, calcium is also often contained in calcium only or calcium and vitamin D dietary supplement products to the exclusion of other dietary ingredients. These types of dietary supplements contain larger amounts of calcium than the multiple vitamin and mineral supplements, about 500 to 800 mg of calcium per RACC. The RACC for dietary supplements is the maximum amount recommended, as appropriate, on the label for consumption per eating occasion, or in the absence of recommendations, one unit, e.g., one tablet, capsule, packet, teaspoonful, etc. (see Table 2 of 21 CFR 101.12(b)). The maximum daily intake level of calcium from calcium only or calcium and vitamin D dietary supplements suggested in these products generally varies between 1,000 and 1,600 mg/day. The most recent nationally representative data, 1999-2000 National Health and Nutrition Examination Survey found the median calcium intake from foods, excluding dietary supplements, to be 735 mg/day for all individuals, excluding nursing infants and children (Ervin, 2004). Therefore, FDA believes that the combined amount of calcium from diet and dietary supplements would likely be kept within 2,500 mg/day.

FDA concludes at this time, under the preliminary requirements of 21 CFR 101.14(b)(3)(ii), that the use of calcium in dietary supplements at levels necessary to justify the qualified health claims described in section IV is safe and lawful under the applicable provisions of the Act.

II. The Agency's Consideration of a Qualified Health Claim

FDA has identified diastolic and systolic blood pressure as surrogate endpoints for predicting risk of hypertension. Systolic and diastolic blood pressure is recognized by the National Institutes of Health as valid surrogate endpoints for risk of hypertension.¹⁷ Therefore, blood pressure is used as a surrogate endpoint for predicting risk of hypertension during pregnancy (i.e., pregnancy-induced hypertension). Because either elevated systolic or diastolic blood pressure can be used to diagnose hypertension, the reduction of either can be considered beneficial in reducing the risk of hypertension.¹⁸ There is no valid surrogate endpoint was identified for preeclampsia. Therefore, the incidence of preeclampsia was used for evaluating the relationship with calcium intake. To evaluate the potential effects of calcium consumption on hypertension, pregnancy-

¹⁷ National Heart, Lung and Blood Institute (NHLBI), Diseases and Conditions Index (http://www.nhlbi.nih.gov/health/dci/Diseases/Hbp/HBP_WhoIsAtRisk.html)

¹⁸ See *supra*, note 13.

induced hypertension, and preeclampsia, FDA considered these endpoints as indicators or predictors of disease.

The petition cited 361 publications as evidence to substantiate the relationship for this claim (see docket number 2004Q-0098). These publications consisted of 51 reviews, 3 book chapters, 2 communications, 2 abstracts, 1 letter, 2 FDA documents, 1 article on calcium consumption, 31 animal studies, 16 articles on calcium bioavailability, 9 articles on calcium and fractures, 8 articles on calcium and kidneys, 1 article on pregnancy outcome, 1 article on antioxidants, 87 articles on the physiology/biochemistry of calcium, 4 articles on cardiovascular disease, 1 article on insulin resistance, 5 articles on the safety of calcium, 23 intervention studies on calcium intake and blood pressure in normotensive subjects, 32 intervention studies on calcium intake and blood pressure in hypertensive subjects, 60 observational studies on blood pressure or hypertension, 17 intervention studies on calcium intake and preeclampsia/pregnancy-induced hypertension, and 4 observational studies on calcium intake and preeclampsia/pregnancy-induced hypertension.

A. Assessment of Review Articles, Meta-Analyses and Abstracts

Although useful for background information, the review articles, meta-analysis, and abstracts do not contain sufficient information on the individual studies which they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. 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 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 it. As a result, the review articles, abstracts, and book chapters supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationships claimed by the petitioner.

B. 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, and they 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. FDA did not consider the animal studies submitted with the petition as providing any supportive information about the substance - disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of hypertension, pregnancy-induced hypertension, or preeclampsia nor can the studies mimic the human body's response to the consumption of calcium. Therefore, FDA cannot draw any scientific conclusions from the animal studies regarding

calcium and the reduction of risk of hypertension, pregnancy-induced hypertension, or preeclampsia.

C. Assessment of Intervention Studies

Calcium and Hypertension

FDA evaluated 55 human intervention studies for its evaluation of the relationship between supplemental calcium and hypertension. Because the mechanism by which calcium may reduce blood pressure in normotensive and hypertensive subjects is considered to be the same (Hatton and McCarron, 1994), hypertensive subjects were considered in this review.

Of the 55 intervention studies on calcium intake and blood pressure, 31 studies were not considered for further review for the various reasons discussed below.

Four studies lacked a control group (e.g., no placebo group) for comparing the relative effect of calcium (Pfeifer et al., 2001; Tabuchi et al., 1986; Grossman et al., 1997; Zemel et al., 1990). Without a control group, it cannot be determined whether changes in the endpoint of interest are due to calcium or due to unrelated and uncontrolled extraneous factors (Spilker, 1991). Hence, scientific conclusions could not be drawn from these studies.

Eleven studies did not conduct statistical analysis between the control and calcium group (Bierenbaum et al., 1988; Johnson et al., 1985; Van Beresteyn et al., 1986; Nowson and Morgan, 1988; Bostick et al., 2000; Davis et al., 1996; Meese et al., 1987; Jepersen et al., 1993; Bloomfield et al., 1986; Levey et al., 1995; Whelton et al., 1997). Statistical analysis of the relationship is a critical factor because it provides the comparison between subjects consuming calcium and those not consuming calcium, to determine whether there is a reduction in risk of hypertension. When statistics are not performed on the specific substance/disease relationship, it cannot be determine whether there is a difference between the two groups. As a result, these studies provided no information about how calcium may reduce the risk of hypertension; hence, no scientific conclusions could be drawn from them.

Two studies did not provide background information on the subjects, baseline information and/or information about randomization of the subjects (Luft et al., 1986; Dazai et al., 1996). Thus, it was not possible to determine whether the control and calcium supplemented groups were similar in various factors known to affect the risk of hypertension. For these reasons, scientific conclusions could not be drawn from these two studies.

Six intervention studies were conducted in countries where calcium intakes are very low (300 to 400 mg/day) (China, Japan and Central America) and therefore are not relevant to

the general U.S. population¹⁹ (Belizan et al., 1983a; Pan et al., 1993; Kawano et al., 1998; Takagi et al., 1991; Zhou et al., 1994; Saito et al., 1989).²⁰ Therefore, scientific conclusions could not be drawn from these studies on how calcium reduces the risk of hypertension in the general U.S. population.

There were duplicate publications of two studies (Zoccali et al., 1986; Siani et al., 1987). Thus, only one of each of the two publications was reviewed.

Seven studies provided diets or multi-nutrient supplements that contained nutrients other than calcium that alter calcium metabolism (vitamin D) (IOM, 1997) or affect blood pressure (potassium and sodium) (IOM, 2005b), that were not controlled; therefore, it was not possible to determine the specific effect of calcium on blood pressure (Van Beresteijn et al., 1990; Orwall and Oviatt, 1990; Rouse et al., 1986; Margetts et al., 1986; Kynast-Gales et al., 1992; Sacks et al., 1995; Zoccali et al., 1987). Therefore, scientific conclusions about the effect of calcium on hypertension could not be drawn from these studies.

Normotensive Subjects

Ten intervention studies evaluated the relationship between supplemental calcium and hypertension in normotensive subjects (Yamamoto et al., 1995; Cappuccio et al., 1986; Gillman et al., 1995; Weinberger et al., 1993; Lyle et al., 1987; Vinson et al., 1987; Lijnen and Petrov, 1995; McCarron and Morris, 1985; Thomsen et al., 1987; Trials of Hypertension prevention Collaborative Research Group, 1992). These 10 studies were considered to be of moderate to high methodological quality.

Yamamoto et al. (1995) was a 6 month study in which U.S. men and women ($n=235$ per group) were provided a placebo or 1 g/day of supplemental calcium. While there was no effect of supplemental calcium on systolic blood pressure, diastolic blood pressure was significantly lower in white women compared to the placebo. There was no significant effect of calcium supplementation on blood pressure in black men and women or white men.

Cappuccio et al. (1986) provided a low calcium diet with or without 1.8 g/day of supplemental calcium for 1 week in a cross-over design study to English men and women ($n = 8$ per group). There was no significant effect of calcium supplementation on systolic or diastolic blood pressure.

¹⁹ The activity of hormones that regulate calcium metabolism varies according to the level of calcium intake and calcium status (IOM, 1997). Therefore, the physiological response to calcium supplementation can vary depending on the level of calcium chronically consumed. Accordingly, the results of these studies in countries with low calcium intakes cannot be extrapolated to the general U.S. population where the calcium intakes are significantly higher.

²⁰ The median calcium intake in the United States is approximately 750 mg/day (IOM, 1997). A response to calcium supplementation in these studies may be due to the correction of suboptimal calcium status or a calcium deficiency for which health claims are not intended.

Gillman et al. (1995) was a 12 week randomized, double-blind placebo controlled study that provided 0.6 g/day of supplemental calcium to U.S. boys and girls ($n=50-51$ per group). Calcium supplementation had no significant effect on diastolic blood pressure, however, systolic blood pressure was significantly lower.

Weinberger et al. (1993) provided a placebo or 1.5 g/day of supplemental calcium to U.S. men and women ($n=29$ per group) for 8 weeks in a cross-over design study. There was no significant effect of calcium supplementation on systolic or diastolic blood pressure when compared to the placebo group.

Lyle et al. (1987) was a 12 week study in which U.S. men ($n=37$ per group) were provided either a placebo or 1.5 g/day of supplemental calcium. Systolic and diastolic blood pressure was significantly lower with calcium supplementation compared to the placebo.

Vinson et al. (1987) provided either no supplement or 0.5 g/day of supplemental calcium (calcium yeast or calcium gluconate) to young U.S. men ($n=4-5$ per group) for 7 weeks. There was no significant effect of supplemental calcium on systolic or diastolic blood pressure.

Lijnen and Petrov (1995) provided a placebo or 2 g/day of calcium to Belgian males ($n=16$ per group) for 16 weeks. Systolic blood pressure was significantly lower with calcium supplementation. There was no significant effect on diastolic blood pressure.

McCarron and Morris (1985) was an 8 week cross-over design study in which U.S. men and women ($n=32$ per group) were provided a placebo or 1 g/day of supplemental calcium for 8 weeks. There was no significant effect of calcium supplementation on systolic blood pressure. Diastolic blood pressure was significantly lower for the calcium group when compared to the placebo group.

Thomsen et al. (1987) provided Danish postmenopausal women ($n=14$ per group) either a placebo or 2 g/day of supplemental calcium for 1 year. There was no significant effect of calcium supplementation on systolic or diastolic blood pressure.

Trials of Hypertension Prevention Collaborative Research Group (1992) provided U.S. men and women ($n=235-237$ per group) either a placebo or 1 g/day of supplemental calcium for 6 months. There was no significant effect of calcium supplementation on systolic or diastolic blood pressure or incidence of hypertension.

Hypertensive Subjects

There were 13 studies that evaluated the relationship between supplemental calcium and hypertension in hypertensive subjects (Lyle et al., 1992; Strazzullo et al., 1986; Resnick et al., 1986; Grobbee and Hofman, 1986; Petersen et al., 1994; Zoccali et al., 1988; Siani

et al., 1988; Tanji et al., 1991; Cappuccino et al., 1987; Galloe et al., 1993; Wimalawansa et al., 1993; Rich et al., 1991; Zemel et al., 1988). These studies were considered to be of moderate to high methodological quality.

Strazzullo et al. (1986) provided a placebo or 1 g/day of supplemental calcium to Italian men and women ($n=35$ per group) for 15 weeks in a cross-over design study. There was no significant effect on diastolic blood pressure, whereas systolic blood pressure was significantly lower with calcium supplementation compared to the placebo.

Zoccali et al. (1986) was an 8 week cross-over design study in which Italian men and women ($n=21$ per group) were given a placebo or 1 g/day of supplemental calcium. There was no significant effect of calcium supplementation on systolic or diastolic blood pressure.

Siani et al. (1988) was a 2-part study, each being of cross-over design and provided 1 g/day of supplemental calcium to Italian men and women for 3 to 4 weeks. Neither dose of calcium had a significant effect on the average systolic and diastolic blood pressure.

Tanji et al. (1991) provided U.S. men and women ($n=19$ per group) a placebo or 1.2 g/day of supplemental calcium for 3 months in a cross-over design study. There was no significant effect of calcium supplementation on systolic or diastolic blood pressure.

Cappuccio et al. (1987) was a 1 month cross-over design study in which 18 subjects were provided a placebo or 1.6 g/day of supplemental calcium. There was no significant effect of calcium supplementation on systolic or diastolic blood pressure.

Galloe et al. (1993) provided a placebo or 2 g/day of supplemental calcium to Danish men and women ($n=20$ per group) for 12 weeks in a cross-over design study. There was no significant effect of calcium supplementation on systolic or diastolic blood pressure.

Wimalawansa et al. (1993) was a 6 week study in which British men ($n=8$ per group) were provided either a placebo or 1.4 g/day of supplemental calcium. Systolic and diastolic blood pressure was significantly lower when provided calcium supplements compared to the placebo.

Resnick et al. (1986) provided a placebo or 2 g/day of supplemental calcium carbonate for 1 month to U.S. men and women ($n=4$ per group) who consumed either a low (< 1.15 g/day) or high (> 5.75 g/day) sodium diet in a crossover design study. While there was no significant effect of calcium on diastolic blood pressure with the low sodium diet,

diastolic blood pressure was significantly lower for the calcium group when consuming a high sodium diet compared to the placebo group consuming a high sodium diet.²¹

Grobbee and Hofman (1986) was a 12 week study in which Dutch men and women ($n=44-46$ per group) were provided a placebo or 1 g/day of supplemental calcium. While there was no effect on systolic blood pressure, diastolic blood pressure was significantly lower when compared to the placebo group.

Petersen et al. (1994) provided Danish men and women ($n=11-12$ per group) with end-stage renal disease a placebo or 2 g/day of supplemental calcium for 6 months. There was no effect of calcium supplementation on systolic blood pressure. Diastolic blood pressure was significantly lower with calcium supplementation compared to the placebo.

Lyle et al. (1992) was an 8 week study that provided a placebo or 1.5 g/day of supplemental calcium to U.S. men and women ($n=21$ per group). Diastolic and systolic blood pressure was significantly lower for the calcium group compared to the placebo group.

Rich et al. (1991) provided U.S. men and women ($n=9-12$ per group) either a low calcium (0.35-0.4 g/day) or high calcium (1 g/day) diet that was high in sodium for 7 days. The additional calcium in the high calcium diet was provided by calcium supplementation. Systolic and diastolic blood pressure was significantly lower when subjects consumed the high calcium diet compared to the low calcium diet.

Zemel et al. (1988) provided U.S. black men and women ($n=11$ per group) a low calcium (356 mg/day)/low sodium (1g/day), low calcium/high sodium (4g/day), high calcium (934 mg/day)/low sodium, or high calcium/high sodium diet for 14 days in a cross-over design study. The diets were controlled to remain isocaloric and with calcium and phosphorus being the only nutrients to be different between the low and high calcium diets. Systolic and diastolic blood pressure was significantly higher when consuming the low calcium/high sodium diet compared to the other 3 diets. The high calcium diet did not provide a beneficial effect on blood pressure when consuming a low sodium diet.

Calcium and Pregnancy-Induced Hypertension and Preeclampsia

FDA identified 17 intervention studies related to calcium intake and/or pregnancy-induced hypertension and preeclampsia (Levine et al., 1997; Lopez-Jaramillo et al., 1990; Lopez-Jaramillo et al., 1989; Zong et al., 1993; Purwar et al., 1996; Sanchez-Ramos et al., 1994; Belizan et al., 1991; Tomoda et al., 1995; Marya et al., 1987; Knight and Keith, 1992; Villar et al., 1987; Belizan et al., 1983b; Crowther et al., 1999; Villar and

²¹ The average dietary sodium consumption by adults in the United States is as high as 4.7 g/day (IOM, 2005) which does not include the amount of sodium that is added to food during cooking or while eating (IOM, 2005). Therefore, the high sodium intake level is applicable to the general U.S. population.

Repke, 1990; Niromanesh et al., 2001; Rogers et al., 1999; Herrera et al., 1998). Ten studies were not considered for further review for the various reasons discussed below.

Two studies did not conduct statistical analysis between the control and calcium group (Tomoda et al., 1995; Knight and Keith, 1992). Statistical analysis of the relationship is a critical factor because it provides the comparison between subjects consuming calcium and those not consuming calcium, to determine whether there is a reduction in risk of pregnancy-induced hypertension and/or preeclampsia. When statistics are not performed on the specific substance/disease relationship, it cannot be determined whether there is a difference between the two groups. As a result, these studies provided no information about how calcium may reduce the risk of pregnancy-induced hypertension and/or preeclampsia; hence, no scientific conclusions could be drawn from them.

For one study, the baseline blood pressure values were very different between the calcium and control group (Herrera et al., 1998). Therefore, it was not possible to compare the results between the two groups. Thus scientific conclusions about a relationship between calcium and pregnancy-induced hypertension could not be drawn from this study.

Six studies were conducted in countries where calcium intakes are very low (approximately 300 to 400 mg/day)²² or where malnutrition is prevalent and therefore not relevant to the general U.S. population^{23,24} (Lopez-Jaramillo et al., 1989; Lopez-Jamillo et al., 1990; Purwar et al., 1996; Zong et al., 1993; Niromanesh et al., 2001; Rogers et al., 1999). Therefore, scientific conclusions could not be drawn from these studies about the relationship between calcium and pregnancy-induced hypertension or preeclampsia in the general U.S. population.

For one study, it was not possible to determine the specific effect of calcium on pregnancy-induced hypertension or preeclampsia since vitamin D was included in the calcium supplement, and vitamin D is actively involved in the metabolism of calcium (Marya et al., 1987). Therefore, scientific conclusions could not be drawn from these studies about the relationship between calcium and pregnancy-induced hypertension or preeclampsia.

Seven intervention studies evaluated the effect of calcium intake on the risk of pregnancy-induced hypertension and/or preeclampsia. These 7 studies were parallel supplementation trials that included a control group that was given either a placebo or nothing (Levine et al., 1997; Belizan et al., 1991; Sanchez-Ramos et al., 1994; Villar et al., 1987; Crowther et al., 1999; Villar and Repke, 1990; Belizan et al. 1983b). All 7

²² See *supra*, note 20.

²³ See *supra*, note 20.

²⁴ Hormones associated with regulating blood pressure are altered during malnutrition (Torun, 2006). Therefore, the results of these studies in countries where malnutrition is prevalent cannot be extrapolated to the general U.S. population.

studies measured the incidence of pregnancy-induced hypertension or blood pressures during gestation. Five of the 7 studies measured the incidence of preeclampsia at the end of the supplementation trial. The study by Levine et al. (1997) was a large ($n=2,295$ per group) randomized, placebo-controlled trial conducted at the National Institutes of Health in which healthy pregnant women (13 to 21 weeks of gestation) were provided a placebo or 2 g/day of supplemental calcium. This high methodological quality study showed no significant effect of calcium supplementation on the incidence of preeclampsia or pregnancy-induced hypertension when compared to the control group.

The study by Belizan et al. (1991) was a high quality randomized, placebo-controlled study (approximately 580 women per group) that was conducted in Argentina. Healthy pregnant women (20 weeks gestation) were given either a placebo or 2 g/day of supplemental calcium. There was a significant reduction in the incidence of pregnancy-induced hypertension and preeclampsia when compared to the control group.

Sanchez-Ramos et al. (1994) conducted a double-blind, placebo-controlled study (approximately 32 women per group) in which high risk (angiotensin sensitive) pregnant women (24 to 28 weeks gestation) were provided a placebo or 2 g/day of supplemental calcium. This high methodological quality study showed that the incidence of preeclampsia was not significantly affected with calcium supplementation, whereas the incidence of pregnancy-induced hypertension was significantly reduced compared to the control group.

The double-blind controlled study by Villar et al. (1987) was conducted in the United States and Argentina. Healthy pregnant women (26 weeks gestation) ($n=25$ to 27 per group) were either given 1.5 g/day supplementation calcium or nothing. This high methodological quality study showed that there was no significant effect of the supplemental calcium on the incidence of pregnancy-induced hypertension compared to the control group.

The randomized, placebo-controlled study by Crowther et al. (1999) (approximately 228 persons per group) was conducted in Australia. Healthy pregnant women (less than 24 weeks gestation) were given either a placebo or 1.8 g/day of supplemental calcium. The relative risk for pregnancy-induced hypertension was not significantly different compared to the control group in this high methodological quality study, whereas the risk for preeclampsia was significantly reduced.

The study by Villar and Repke (1990) was a high methodological quality randomized, double-blind, placebo controlled study in which American, black girls (a high risk subpopulation) (23 weeks gestation) ($n=95$ per group) were given a placebo or 2 g/day of supplemental calcium. Neither the incidence of pregnancy-induced hypertension nor preeclampsia was significantly affected by calcium intake.

Belizan et al. (1983b) was a high methodological quality study that provided women ($n=11-14/\text{group}$) a placebo or 1 or 2 g/day of supplemental calcium beginning in the 15th week of gestation. Although this study was conducted in Guatemala where calcium intakes are usually much lower than in the United States, the calcium intake levels estimated in this study were similar. Blood pressure was measured at 20, 24, 28, 32, and 36 weeks of gestation. The group that received 2 g/day of calcium had significantly lower systolic and/or diastolic blood pressure levels compared to the placebo group.

D. Assessment of Observational Studies

Hypertension

Sixty observational studies on calcium intake and hypertension incidence or blood pressure were submitted in the petition. Fifty-nine of these 60 studies measured either urinary or serum calcium levels as a marker of intake or measured calcium intake from drinking water, the diet, or from both dietary and supplemental calcium.

The proposed claim is for a relationship between calcium dietary *supplements* and a reduced risk of hypertension. Urinary and serum calcium are not reliable estimates of calcium intake (Lee and Nieman, 1993). When calcium intake is low, the bone will provide calcium to the blood to maintain normal calcium levels. Urinary calcium is more responsive to changes in dietary calcium intake than serum levels. However, there are a number of factors that can affect urinary excretion and the level of calcium that is excreted in urine (dietary protein and phosphate, parathyroid and renal function). Because urinary and serum calcium levels are not reliable estimates of calcium intake, scientific conclusions could not be drawn from this study about the relationship between calcium intake and hypertension.

In observational studies that calculate nutrient intake from conventional food, measures of calcium 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. Furthermore, the nutrient content of foods can vary (e.g., due to demographics (soil composition), food processing/cooking procedures, or storage (duration, temperature)). Thus, it is difficult to ascertain an accurate amount of the nutrient consumed based on reports of dietary intake of foods.

In addition, conventional foods contain not only calcium, but also other nutrients that may be associated with the metabolism of calcium or the pathogenesis of hypertension. Because foods consist of many nutrients and substances, it is difficult to study the nutrient or food components in isolation (Sempos et al., 1999). For instance, vitamin D regulates calcium absorption and metabolism and sodium and protein increases the urinary excretion of calcium (IOM, 1997). (See Sempos et al. (1999), Willett (1990) and

Willett (1998) regarding the complexity of identifying the relationship between a specific nutrient within a food and a disease.) For studies based on recorded dietary intake of such foods, it is not possible to accurately determine whether any observed effects of calcium on hypertension risk were due to: 1) calcium alone; 2) interactions between calcium and other nutrients; 3) other nutrients acting alone or together; or, 4) decreased consumption of other nutrients or substances contained in foods displaced from the diet by the increased intake of calcium-rich foods.

In fact, evidence demonstrates that in a number of instances, epidemiological studies based on the recorded dietary intake of conventional foods may indicate a benefit for a particular nutrient with respect to a disease but it is subsequently demonstrated in an intervention study that the nutrient-containing dietary supplement does not confer a benefit or actually *increases* risk of the disease (Lichtenstein and Russell, 2005). For example, previous epidemiological studies reported an association between fruits and vegetables high in beta-carotene and a reduced risk of lung cancer (Peto et al., 1981). However, subsequent intervention studies, the Alpha-Tocopherol and Beta Carotene Prevention Study (ATBC) and the Carotene and Retinol Efficiency Trial (CARET), demonstrated that beta-carotene supplements increase the risk of lung cancer in smokers and asbestos-exposed workers, respectively (The Alpha-Tocopherol and Beta Carotene Cancer Prevention Study Group, 1994; Omenn et al., 1996). These studies illustrate that the effect of a nutrient provided as a dietary supplement exhibits different health effects compared to when it is consumed among many other food components. Furthermore, these studies demonstrate the potential public health risk of relying on results from epidemiological studies, in which the effect of a nutrient is based on recorded dietary intake of conventional foods as the sole source for concluding that a relationship exists between a specific nutrient and disease risk; the effect could actually be harmful.

For the above reasons, FDA concludes that scientific conclusions cannot be drawn from observational studies on foods for the proposed claim for supplemental calcium. Furthermore, because there were a sufficient number of intervention studies that evaluated the relationship between dietary supplement calcium and hypertension, it was not necessary to consider the observational studies as part of the body of evidence for evaluating the relationship.²⁵ In general, intervention studies provide the strongest evidence for an effect, regardless of existing observational studies on the same relationship.²⁶ Intervention studies are designed to avoid selection bias²⁷ and avoid

²⁵ See The Keystone National Policy Dialogue on Food, Nutrition, and Health: Final Report, Keystone Press, 1996, p. 37 (“When clinical trials are feasible, health claims need not arise from a multiplicity of accumulated observational data”)

²⁶ See *supra*, note 5.

²⁷ Subjects who are most likely to have a favorable outcome independent of any intervention are not preferentially selected to receive the intervention being studied (“Guidance for Industry Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements” (December 22, 1999). [<http://www.cfsan.fda.gov/~dms/ssaguide.html>]

findings that are due to chance or other confounders of disease. Therefore, intervention studies can be used to establish efficacy and identify strategies for disease prevention (Sempos et al., 1999). Although the evaluation of causal relationships often involves both interventional and observational studies, observational studies can not be used to rule out the findings from more reliable intervention studies (Sempos et al., 1999).

One observational study evaluated the relationship between supplemental calcium and hypertension (Freudenheim et al., 1991). This cross-sectional study, however, did not adjust for sodium or potassium intake, which is known to affect blood pressure (IOM, 2005). Therefore, scientific conclusions could not be drawn from this study about the relationship between supplemental calcium intake and hypertension.

Pregnancy-Induced Hypertension and Preeclampsia

Four observational studies were conducted on calcium intake and risk of hypertension, pregnancy-induced hypertension and/or preeclampsia during pregnancy. One study (Sibai et al., 1997) was a re-analysis of a calcium intervention study to identify risk factors associated with pregnancy-induced hypertension and preeclampsia (Levine et al., 1997). Thus, Sibai et al. (1997) did not provide additional data to that reported by Levine et al. (1997).

One case-control study compared the intake of calcium from the diet and/or supplements in pregnant women who were normotensive or hypertensive during the third trimester (Ortega et al., 1998). Only 2.6 percent of normotensive women took supplements containing calcium and none (0%) of the hypertensive women took calcium supplements. Thus, it was not possible to conduct statistical analysis between the two groups because the number for the hypertensive women was 0%. Thus, scientific conclusions could not be drawn about the relationship between supplemental calcium and pregnancy-induced hypertension. (Spilker, 1991).

Two observational studies evaluated the relationship between dietary calcium intake and risk of pregnancy-induced hypertension (Marcoux et al., 1991; Kesmodel et al., 1997). As explained above, scientific conclusions cannot be drawn from observational studies on foods for the proposed claim for supplemental calcium. Furthermore, there were a sufficient number of intervention studies that evaluated the relationship between supplemental calcium and pregnancy-induced hypertension and preeclampsia.

III. Strength of the Scientific Evidence

Below, 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 quantity of evidence (number of various types of studies and sample sizes), whether the body of evidence supports a health claim relationship for the

U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,²⁸ and the overall consistency²⁹ of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

Hypertension

As discussed in Section II, there were 10 intervention studies on normotensive subjects Yamamoto et al., 1995; Cappucio et al., 1986; Gillman et al., 1995; Weinberger et al., 1993; Lyle et al., 1987; Vinson et al., 1987; Linjen et al., 1995; MaCarron et al., 1985; Thomsen et al., 1987 ; Trial of Hypertension Prevention Collaborative Research Group, 1992) and 13 intervention studies on hypertensive subjects (Zemel et al., 1988; Lyle et al., 1992; Strazzullo et al., 1986; Resnick et al., 1986; Grobbee and Hofman, 1986; Petersen et al., 1994; Zoccali et al., 1988; Siani et al., 1987; Tanji et al., 1991; Cappuccino et al., 1987; Galloe et al., 1993; Wimalawansa et al., 1993; Rich et al., 1991) that evaluated the relationship between calcium intake and hypertension. Half (5 of 10) of the intervention studies on normotensive subjects showed a beneficial effect of supplemental calcium in reducing systolic and/or diastolic blood pressure. The majority of studies on hypertensive subjects (8 of 13 studies) showed a beneficial effect. Collectively, the studies were conducted on men and women, as well as boys and girls. These studies were conducted in the United States or in various European countries where calcium intake is similar to intakes in the United States.

Based on FDA's review of the strength of the total body of publicly available scientific evidence, FDA concludes that there is a low level of comfort for a claim about supplemental calcium and reduced risk of hypertension. Therefore, FDA concludes that although the evidence is inconsistent and inconclusive, there is some credible evidence that suggests a relationship between supplemental calcium and hypertension.

Pregnancy-Induced Hypertension and Preeclampsia

As discussed in Section II, there were 7 intervention studies on the effect of supplemental calcium on the incidence of pregnancy-induced hypertension (Levine et al., 1997; Sanchez-Ramos et al., 1994; Belizan et al., 1991; Villar et al., 1987; Crowther et al., 1999; Villar and Repke, 1990; Belizan et al. 1983b), of which 5 also measured the incidence of preeclampsia (Levine et al., 1997; Belizan et al., 1991; Sanchez-Ramos et al., 1994; Crowther et al., 1999; Villar and Repke, 1990).

²⁸ See *supra*, note 10.

²⁹ See *supra*, note 11.

Pregnancy- Induced Hypertension

As discussed in Section II, of the seven studies that measured the incidence of pregnancy-induced hypertension, three studies showed a beneficial effect of calcium supplementation in reducing the risk of pregnancy-induced hypertension. Therefore, FDA concludes that there is some credible evidence for a qualified health claim for pregnancy-induced hypertension. However, there were 4 studies that showed no benefit, and one of the four studies was a large clinical trial ($n=2,295$) conducted by the National Institutes of Health (Levine et al., 1997). Thus, there was little consistency in the findings among these 7 studies and consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.³⁰ Therefore, FDA concludes that it is highly unlikely that consuming calcium supplements during pregnancy will reduce the risk of pregnancy-induced hypertension.

Preeclampsia

As discussed in Section II, two of the 5 intervention studies that measured the incidence of preeclampsia showed a benefit (Sanchez-Ramos et al., 1994; Crowther et al., 1999), whereas 3 showed no benefit (Levine et al., 1997; Belizan et al., 1991; Villar and Repke, 1990). Therefore, FDA concludes that there is some credible evidence for a qualified health claim for preeclampsia. However, there were 3 studies that showed no benefit and one of the 3 studies included a large trial ($n=2,295$ per group) conducted by the National Institutes of Health (Levine et al., 1997). Thus, there was little consistency in the findings among these 5 studies and consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.³¹ Therefore, FDA concludes that it is highly unlikely that consuming calcium supplements during pregnancy will reduce the risk of preeclampsia.

IV. Other Enforcement Discretion Factors

Dietary supplements bearing the qualified health claim on calcium and reduced risk of hypertension, pregnancy-induced hypertension, and preeclampsia, for which FDA has indicated that it intends to consider the exercise of its enforcement discretion must still meet all applicable statutory and regulatory requirements under the Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. For example, such supplements must be labeled consistent with 21 CFR 101.36(b)(3). Dietary supplements also must not pose an unreasonable risk of illness or injury to the consumer or contain substances that may render the product injurious to health, or be otherwise adulterated or misbranded. In addition, FDA intends to consider the following factors in its exercise of enforcement discretion for the qualified health

³⁰ See *supra*, note 11.

³¹ See *supra*, note 11.

claim on calcium and reduced risk of hypertension, pregnancy-induced hypertension, and preeclampsia.

A. Qualifying Level of Calcium

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for "high" has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (see 21 CFR 101.14(d)(2)(vii)).

Since a "high" definition has been established for calcium, FDA intends to consider in exercising its enforcement discretion for dietary supplements bearing the qualified health claims described in section V when the supplements contain calcium at a level that meets or exceeds the requirement for a "high" level of calcium as defined in 21 CFR 101.54(b) (i.e., 200 mg or more per RACC under the current regulation).

B. Assimilability of Calcium, Disintegration and Dissolution of Dietary Supplements

FDA intends to consider, as a factor in the exercise of its enforcement discretion for dietary supplements bearing a qualified health claim about calcium and hypertension, pregnancy-induced hypertension, and preeclampsia, that the calcium content of dietary supplements is assimilable (i.e., bioavailable) (21 CFR 101.72(c)(ii)(B)). Also, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that the dietary supplements meet the United States Pharmacopeia (U.S.P.) standards for disintegration and dissolution applicable to their component calcium salts. For dietary supplements for which no U.S.P. standards exist, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that the dietary supplements exhibit appropriate assimilability under the conditions of use stated on the product label (21 CFR 101.72(c)(ii)(C)).

V. Conclusions

Based on FDA's consideration of the scientific evidence and other information submitted with the petition, and other pertinent scientific evidence and information, FDA concludes that there is some evidence for qualified health claims for calcium and hypertension, pregnancy-induced hypertension, and preeclampsia, provided that the qualified health claims are appropriately worded so as to not mislead consumers. Thus, FDA intends to consider exercising enforcement discretion for the following qualified health claims:

1. Some scientific evidence suggests that calcium supplements may reduce the risk of hypertension. However, FDA has determined that the evidence is inconsistent and not conclusive.

2. Four studies, including a large clinical trial, do not show that calcium supplements reduce the risk of pregnancy-induced hypertension during pregnancy. However, three other studies suggest that calcium supplements may reduce the risk. Based on these studies, FDA concludes that it is highly unlikely that calcium supplements reduce the risk of pregnancy-induced hypertension.
3. Three studies, including a large clinical trial, do not show that calcium supplements reduce the risk of preeclampsia during pregnancy. However, two other studies suggest that calcium supplements may reduce the risk. Based on these studies, FDA concludes that it is highly unlikely that calcium supplements reduce the risk of preeclampsia.

FDA intends to consider exercising enforcement discretion for the above qualified health claims for dietary supplements when all other factors for enforcement discretion identified in Section IV of this letter are met.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement, that will no longer support the use of the above qualified health claims, or that raises safety concerns about the substance that is the subject of the claims.

Sincerely,



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