DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 91 N-0094]

RIN0905-AB67

Food Labeling: Health Claims; Calcium and Osteoporosis

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing its decision to authorize the use on the label and labeling of foods of health claims relating to an association between adequate calcium intake and osteoporosis. These rules are issued in response to provisions of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) that bear on health claims and are developed in accordance with the general requirements in the health claims rule published elsewhere in this issue of the **Federal Register**. The agency has concluded that, based on the totality of the scientific evidence, there is significant scientific evidence and agreement among qualified experts that maintaining a diet adequate in calcium has a significant impact on bone health particularly during the critical bone forming years and after menopause and may help to reduce the risk of osteoporosis. The agency has therefore concluded that claims on foods relating the calcium content to a reduced risk of osteoporosis in susceptible populations are justified.

EFFECTIVE DATE: May 8, 1993.

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 27, 1991 (56 FR 60689), the agency proposed to authorize the use on foods, including dietary supplements, of health claims relating to the association between calcium and risk of osteoporosis. The proposed rule was issued in response to provisions of the 1990 amendments (Pub. L. 101-535) that bear on health claims and in accordance with the proposed general requirements for health claims for food (56 FR 60537). With respect to health claims, the 1990 amendments amend the Federal Food, Drug, and Cosmetic Act (the act) by adding a new provision (section 403(r)(1)(B) (21 U.S.C. 343(r)(1)(B)) that provides that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition unless the claim is made in accordance with section 403(r)(3) or (r)(5)(D)of the act

Section 3(b)(1)(A) of the 1990 amendments specifically requires that the agency determine whether 10 nutrient/disease relationships meet the requirements of the section 403(r)(3) or (r)(5)(D) of the act. The relationship of calcium and osteoporosis was one of these areas. FDA published a notice in the **Federal Register** of March 28, 1991 (56 FR 12932), requesting scientific data and information on the 10 specific topic areas identified. Relevant scientific studies and data received in response to this request were considered as part of the agency's review of the scientific literature on calcium and osteoporosis and were included in the proposed rule (56 FR 60689). Because of time constraints, FDA addressed in that proposal only those comments submitted in response to the March 28,1991, notice that were in the form of scientific data. Comments of a more specific nature were not responded to at that time and are included among the comments responded to below.

Provisions of the proposed rule included qualifying and disqualifying criteria for the purpose of identifying foods eligible to bear a health claim. The proposal also specified mandatory content and label information for health claims statements and provided a model health claim and consumer summary statement. FDA also discussed potential safety issues relating to overfortification or oversupplementation with calcium. FDA requested written comments on the proposed rule, including comments on the issue of how to assess calcium bioavailability in products (conventional foods and supplements) to justify their eligibility to bear a health claim. Moreover, to ensure that calcium and osteoporosis claims will not mislead those individuals within the population for whom relatively higher calcium intake over a lifetime offers no apparent benefit to their bone health, FDA proposed that the subpopulations clearly at risk be identified on the label and solicited comments on how best to convey this information.

II. Summary of Comments and the Agency's Responses

In response to the proposed rule, the agency received more than 100 letters, each containing one or more comments, from consumers, consumer organizations, health care professionals, professional organizations, State and local governments, foreign governments, trade associations, and industry. In addition to these comments, the agency also considered statements made in a public hearing held on January 30 and 31, 1992 (57 FR 239, January 3, 1992) on a number of food labeling issues, including the proposed requirements for health claims. Some of the comments agreed with one or more provisions of the proposed rules without providing grounds for support other than those provided by FDA in the preamble to the proposal. Other comments disagreed with one or more provisions of the proposed rule without providing specific grounds for the disagreement. A few comments addressed issues outside of the scope of the regulations. Most of the comments provided specific support for their positions on the proposed regulations. The agency has summarized and addressed the relevant issues raised in all comments in the sections of this document that follow.

Before issuing the proposal, FDA contracted with the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology to evaluate independently the scientific literature on dietary calcium and osteoporosis. The preliminary draft of the LSRO report, "Calcium and Osteoporosis" (Ref. 13), was one of the authoritative documents reviewed by FDA in developing its proposal. After the proposal was issued, LSRO completed its evaluation of the scientific literature and submitted its final report in February 1992. The agency placed a copy of the final report in the administrative file (Ref. 138), and has considered the report as a comment on the proposal.

A. Validity Issues

1. No comments disputed FDA's tentative conclusion that a lifetime of adequate calcium intake is important to maintenance of bone health and may help reduce the risk of osteoporosis, particularly for individuals at greatest risk. Most comments supported the agency's position.

The LSRO report (Ref. 138) concluded that "the weight of the evidence supports the hypothesized relationship between calcium intake and bone health as expressed both in increased bone mass and in reduced fracture risk." According to LSRO, "the focus of calcium as a nutrient related to osteoporosis lies in its importance both for achieving genetically programmed bone mass during about the first 30 to 35 years of life and in maintaining that

bone during the remaining years of life." The report stressed that osteoporosis is a multifactorial disorder, and that inadequate calcium intake is only one of several interacting factors that determine whether low-trauma fracture will occur. The report also noted that "the data concerning level of [calcium] intake required for bone health can be safely generalized only to Caucasian females."

FDA acknowledges the significant agreement on this matter and reconfirms its position that adequate calcium intake is important for maintenance of bone health and may help reduce the risk of osteoporosis, particularly for individuals at greatest risk. FDA notes that the LSRO report is consistent with required health claim statements about the mechanism by which calcium works (proposed § 101.72(d)(3), finalized at § 101.72(c)(2)(i)(C)) and the population at greatest risk (§ 101.72(c)(2)(i)(B)). As discussed in the proposal (56 FR at 60698), FDA agrees that the general population is not at significant risk of developing osteoporosis. For example despite their generally lower calcium intake, data show that African Americans have higher bone mass at maturity and a very low incidence of osteoporosis-related bone fracture.

B. Advisability of Permitting Claims

2. One comment asserted that health claims pertaining to calcium and osteoporosis should not be permitted because (1) the target population for the claim is too small, and (2) older people with the condition may be misled into thinking the rate of bone loss will be slowed or reversed with increased calcium consumption.

FDA disagrees with this comment, which provided no support for its assertions. First, a large number of American women are at risk of developing osteoporosis (Ref. 18). Further, many of the elderly have low bone mass, and they continue to lose bone mass with further aging. These individuals will clearly benefit from information about how they may reduce their risk of the disease.

Secondly, as explained fully in the preamble of the proposal (56 FR at 60689), adequate calcium intake does help to slow the rate of bone loss in the elderly. Thus, while under § 101.72, claims may not imply that adequate calcium intake will reverse bone loss, under § 101.72 (c)(2)(i)(C), when reference is made to persons with a family history of the disease, menopausal women, and elderly men and women, the claim may state that adequate calcium intake is linked to reduced risk of osteoporosis through the mechanism of slowing the rate of bone loss. For these reasons, FDA disagrees that permitting claims to advise of the reduction in the rate of bone loss will mislead the elderly.

3. A few comments argued that a health claim should not be allowed because delay of the onset of osteoporotic fracture is not exclusively associated with adequate calcium intake. One of the comments justified this assertion by stating that many essential nutrients in addition to calcium, such as magnesium, copper, zinc, fluoride, and vitamins A, D, K, and C, are needed for normal bone growth and development.

FDA recognizes that many nutrients are essential for normal bone growth and development. However, FDA disagrees that this fact should preclude the agency from permitting a health claim pertaining to calcium and osteoporosis. The requirement in § 101.72(c)(2)(i)(A) that claims advise consumers of the importance of healthful diets is intended to alert consumers to the need to consume essential nutrients in addition to calcium. As the agency explained fully in the proposal (56 FR at 60689), national food intake surveys (Refs. 35, 54, and 105) provide evidence identifying calcium from dietary sources as a problem nutrient in a subpopulation at risk for osteoporosis, namely women between 11 and 35 years of age. Furthermore, FDA has concluded that based on the totality of the scientific evidence, there is significant scientific agreement among qualified experts that the evidence overwhelmingly supports the significance of calcium in maintaining bone health. Thus, FDA believes that the population at greatest risk of osteoporotic fracture in later life should be advised through food labeling of the benefits of adequate calcium intake.

C. Clarity of Provisions

4. A number of comments on the proposed rule on general requirements for health claims (November 27,1991, 56 FR 60537) suggested that FDA revise provisions of all health claims rules to be more understandable.

FDA agrees that its regulations should be understandable. FDA has therefore made several nonsubstantive revisions in § 101.72 for the sake of clarity. For example, the provisions of the regulation have been grouped into general and specific requirements. The general requirements reference other regulations containing nutrition labeling requirements. The specific requirements are separated into requirements pertaining to the food and those pertaining to the claim. Finally, the model health claims, have been simplified.

D. Qualifying Levels

5. A few comments addressed the issue of an appropriate qualifying level for calcium in a food. All of the comments strongly supported the requirement that a food bearing a calcium-osteoporosis claim be "high" in calcium (i.e., contain a minimum of 20 percent of the reference daily intake (RDI)). A number of the comments, however, asserted that the RDI was being set too low. One comment stated that the proposed RDI for calcium (900 mg) was an inadequate intake guideline for those individuals at greatest risk of osteoporosis. Another comment argued that there is substantial evidence that the population-weighted means used to establish the RDI's may seriously understate the nutritional needs of an estimated 52 million Americans.

For reasons explained fully in the preamble of the final rule on Reference Daily Intake and Daily Reference Values, which Is published elsewhere in this issue of the **Federal Register**, FDA has adopted an RDI for calcium of 1,000 mg, the level in current § 101.9(c)(7)(iv). In view of the support for the proposal that only foods "high" in calcium qualify for calcium-osteoporosis claim, the agency has retained this requirement in the final rule in § 101.72(c)(2)(ii)(A) (proposed as § 101.72(c)(2)) with minor editorial revisions. Because the RDI for calcium is 1,000 mg, the reference amount customarily consumed for a food would need to contain at least 200 mg of calcium for it to qualify to bear the authorized calcium/ osteoporosis health claim.

E. Assimilability

All comments on this topic generally supported the concept of a requirement that the calcium content of the product be assimilable (proposed as § 101.72(c)(3) and finalized as § 101.72(c)(2)(ii)(B)). In response to an agency request in the proposal for comments about how to assess calcium assimilability (also referred to as "bioavailability"), a few comments suggested mechanisms to assess calcium bioavailability.

6. Several comments suggested that the agency establish a minimum standard that relates bioavailability to the amount of calcium actually absorbed from food. One comment cited the existence of a recognized data base describing the absorption of naturally occurring supplemental and fortified calcium in foods. However, the comment added that the cited data base

was actually a bibliography of various published articles describing calcium absorption from a variety of food sources. Another comment offered the following suggestion: "FDA should estimate the quantity of calcium in various foods that is rendered unavailable by oxalic acid, phytate, fiber, or other constituents and subtract this unavailable calcium from the amount of available calcium that the food would be expected to supply (which is usually only about half of the reported calcium content of food)." The comment suggested that FDA should not allow health claims on a given food if, after adjustment for oxalate and other constituents, the estimated quantity of "available" calcium is markedly lower than ordinarily expected, given the food reported calcium content. Similarly, another comment proposed the use of the indirect method of calciuric response to a calcium load as a convenient and reliable method of testing calcium absorbability and also proposed a test based on radiocalcium absorption.

FDA acknowledges these useful suggestions but notes that none of the proposed methods assesses calcium utilization. As discussed in the proposal, calcium bioavailability means both absorption and tissue utilization of calcium (56 FR at 60699). Appropriate tests for bioavailability need to include a measurement of the utilization of calcium by bone (calcium retention). A product that contains components that increase the urinary or fecal excretion of calcium or somehow impair the utilization of calcium by bone will not qualify for a calcium-osteoporosis claim. Monitoring only factors that alter absorption, such as the phytate content of a food, as suggested in the comment would not allow estimation of the effects of factors that promote obligatory calcium loss such as increased urinary loss due to a high sulfate content. Both increased excretion and impaired utilization cause the decreased deposition of calcium in bone.

7. Some comments requested that FDA clarify an acceptable level of "assimilability," such as an acceptable percent bioavailability. The comments asserted that it would be unrealistic to require bioavailability data on all foods bearing a calcium claim, but that such a requirement might be a logical prerequisite for new sources of calcium used to fortify foods. A number of comments suggested that food and supplement manufacturers should bear the burden of proof of the bioavailability of calcium-fortified products and supplements in order to avoid indiscriminate fortification and marketing of poorly bioavailable supplements.

FDA reiterates that a product bearing a calcium-osteoporosis health claim must contain calcium that can be assimilated by the body. As noted in the proposal, it would be misleading to put a health claim for a substance on a food if consumption of that food will not provide the substance (56 FR at 60699). Such a food would be misbranded under section 403 (a) of the act (21 U.S.C. 343(a)). Given that most currently marketed products that are likely to bear a calcium-osteoporosis claim contain bioavailable calcium. FDA does not consider it necessary at this time to set a minimum acceptable level of bioavailability. If a food bearing a calcium osteoporosis claim does not contain calcium in a bioavailable form, the Government can take enforcement under the act against the product or its manufacturer. Calcium sources whose bioavailability has not been demonstrated would be at risk for such enforcement action.

There are sufficient scientific data in published literature to support the bioavailability of many sources of calcium in current use. However, instances may develop in which the bioavailability of the calcium source has not been shown, including the use of new fortificants or food products in which the combination of the component nutrients raises concerns about the assimilability of calcium from the product (e.g., a new bread rich in a novel high phytate fiber source and fortified with calcium).

As discussed in the previous comment, there are various ways of testing for bioavailability. FDA considers human or growing animal models to provide the most accurate assessments. One approach would involve collection of human data from calcium balance studies using stable isotopes or radioisotopes as evidence of reasonable or adequate bioavailability (assimilability), as well as evidence from well-controlled calcium supplementation or dietary intervention studies that measure calcium absorption and bone mass or density change over time. An appropriate standard reference would be calcium carbonate or milk.

FDA recognizes that establishing calcium retention in humans is a difficult and costly procedure. Another approach would use a growing animal model (rat) to demonstrate calcium retention in bone. Use of the growing rat model offers ease of bone mass or mineral content assessment, and, unlike human subjects, rats show limited between-subject variation in calcium absorption. There are a number of suitable studies in the literature that could serve as models and the basis for a study design (e.g., Refs. 139 through 141). The common end-measures shared by these animal studies include measures of apparent calcium absorption and determination of calcium content of bone, either directly by bone ashing and mineral analyses (Refs. 139 and 140) or indirectly by densitometric or histomorphometric methods (Ref. 141).

8. A number of comments proposed that superiority claims regarding the bioavailability or absorbability of calcium in a food or supplement compared to a reference food or supplement be permitted. One comment proposed milk as an ideal reference food against which to make the proposed comparisons and suggested the use of human bioavailability tests to provide evidence in support of superiority claims. Several comments suggested that a statistically significant difference in calcium absorption between two products using the proposed techniques should provide the basis for a superior absorbability comparative claim.

FDA advises that it is not appropriate to permit requested superiority claims under the provisions of the 1990 amendments that govern health claims. To the extent that the 1990 amendments provide for comparative claims, it is only with respect to claims that characterize the level of a nutrient (section 403 (r)(1)(A) of the act). Regulations governing nutrient content claims, published elsewhere in this issue of the **Federal Register**, do not provide for superiority claims based on bioavailability. However, under § 10.30, an interested party can petition the agency to provide for superiority claims based on bioavailability. In considering such a petition, the agency would be concerned about ensuring that superiority claims are valid and nutritionally meaningful.

F. Disintegration and Dissolution of Calcium Supplements

9. The majority of comments concerned with the proposed requirement that calcium supplements meet the U.S. Pharmacopeia (U.S.P.) standards for disintegration and dissolution of calcium supplements (in proposed § 101.72(c)(4)) fully supported this aspect of the proposed regulation. The LSRO report strongly supported the proposed requirement noting that while the chemical form or solubility of the supplement makes little difference, the physical form of the salt and formulation of the tablet are critical. The comment stressed that "tablets so poorly formulated that they fail to disintegrate

under simulated gastric conditions appear to be widely distributed in the U.S. market." A public health advocacy group further suggested that since the U.S.P. is currently updating its standards for dietary supplements, the revised standards may include additional measures that FDA should adopt in the future. Two comments opposed this requirement. One argued that "the United States Pharmacopeia standards are not appropriately Complete enough to be an exclusive condition for a products health claim eligibility." The comment asserted that the U.S.P's are in vitro standards (meaning conducted in a test tube) and might not reflect human bioavailability of an individual calcium supplement, and they should therefore only establish a disqualifying presumption that would be rebuttable by the submission of human data supporting the product's bioavailability. Another comment emphasized the lack of justification for this testing, the inability to conduct all the tests since some of the calcium salts identified as safe for use as calcium supplements are not subject to U.S.P. dissolution requirements (calcium sulfate, and calcium oxide), the lack of fairness in that foods are not held to these criteria the inappropriate application of drug standards set forth in the U.S.P. monographs to supplements, the "questionable expertise" of the U.S.P. convention members to judge nutritional property of compounds, and finally the lack of basis to require these standards in order to qualify for a health claim.

FDA has carefully considered these comments and agrees with several points. FDA agrees that disintegration and dissolution testing methods used to screen calcium supplements for bioavailability are imperfect, because these in vitro tests do not adequately mimic the physiologic environment of the human stomach, and U.S.P. standards are not available for all calcium-containing compounds. However, the agency considers the U.S.P. standards to provide sufficient assurance of dissolution and disintegration for those products where U.S.P. standards exist. A supplement that does not dissolve and disintegrate clearly does not provide calcium in an assimilable form and thus, a claim for such a supplement would be misleading because the supplement would not provide the nutrient that is the subject of the claim. Calcium supplements not in conventional food form can be formulated in a manner that prevents rapid dissociation and disintegration in the stomach, preventing assimilation. This unique aspect justifies the requirement in § 101.72(c)(2)(ii)(C) for supplements.

However, when U.S.P. standards do not exist, the agency recognizes, as pointed out by one comment, the need for an alternative method of establishing the bioavailability of supplements under the conditions of use stated on the product label. Demonstration of acceptable bioavailability in human or animal studies when conducted under the conditions of use stated on the product label (i.e, fed as an intact tablet, not crushed) would fulfill the requirement. Section 101.72(c)(2)(ii)(C) has been revised to require that dietary supplements meet the U.S.P. standards for disintegration and dissolution, except that dietary supplements for which no applicable U.S.P. standards exist shall exhibit appropriate assimilability under conditions of use stated on the product label. In order for a dietary supplement to bear the authorized calcium osteoporosis health claim, it must comply with all provisions of this final regulation.

G. Phosphorus Content

For reasons explained fully in the preamble of the proposal (56 FR 60689 at 60699 to 60700), FDA proposed that high levels of phosphorus (naturally occurring or added) in conventional foods or supplements that result in calcium to phosphorus ratios lower than 1:1 will disqualify the product from bearing a calcium/ osteoporosis health claim. FDA's tentative decision to place a limit on the amount of phosphorus that a food could have to be eligible to bear a claim was based on the ubiquitous distribution of this mineral in the food supply, the low ratio of calcium to phosphorus that typifies current intake patterns, and current evidence demonstrating that high levels of dietary phosphorus coupled with low dietary calcium adversely influence hormonal factors that regulate calcium and bone metabolism (Refs. 17, 21, 29, 32, 46, 93, 114, and 116). Many of the comments addressing this issue strongly supported the proposed phosphorus provision because of the reasons given by FDA in the proposal.

10. One comment questioned the need for any requirement that the phosphorus content not exceed the calcium content, asserting that "any reasonable fortified or enriched product will meet this condition."

The agency believes that it is incorrect to assume that all enriched, fortified, or modified products will contain more calcium than phosphorus, or even that products traditionally known to be rich sources of calcium will have lower levels of phosphorus than calcium. For example, a recent article (Ref. 142) on the reduction of fat in a newly developed processed cheese showed how processing techniques used to lower fat resulted in a calcium to phosphorus ratio lower than one to one. Some products naturally rich in phosphorus cannot meet this condition even after calcium fortification, and some products that are traditionally recognized as calcium rich foods, such as puddings, are now available in convenient instant versions in which the added phosphorus content far exceeds the calcium content. Therefore, FDA concludes that this comment does not provide a basis not to adopt a level of phosphorus that, if found in a food, would render the calcium osteoporosis claim misleading.

11. Several comments were in strong opposition to the requirement that a product not contain more phosphorus than calcium on la per weight basis. One comment contended that FDA relied on erroneous information relative to the consumption levels of dietary phosphorus supplied by food additives. The comment included data indicating little change in the estimated daily consumption of phosphorus from food additives from 1980 to 1990, based on the International Food Additives Council's estimated disappearance of food grade phosphorus in the United States. According to these data, the average per capita phosphorus consumption from food additives increased from 9.5 to more than 11 percent of the acceptable daily intake of phosphorus from 1980 to 1990.

FDA's statement in the proposal that phosphorus intake may be understated by as much as 15 to 20 percent due to phosphorus supplied by numerous additives was apparently misinterpreted by these comments. The agency did not intend to imply that phosphorus-containing food additive consumption had increased 15 to 20 percent. Rather, the agency was relying on the finding of Oenning et al. (Ref. 106), who demonstrated that nutrient estimates calculated from food intake records using current nutrient composition data bases underestimated phosphorus intake when compared to direct chemical analysis of the food from the dietary record. The underestimation of phosphorus content demonstrated in this study apparently was due to errors in the nutrient data bases, which have not kept abreast of changes in manufacturing techniques and in the use of phosphorus-containing food additives. FDA made this point to emphasize that currently in the United States, total phosphorus intake greatly

exceeds that of calcium, and that the levels may be even higher than surveys suggest because of flaws in the nutrient composition data bases used in these surveys.

The agency disagrees with the comment and interprets data presented by the comment as evidence of an important increase in phosphate food additive use over the last decade. These data indicate that estimated per capita daily consumption of phosphorus from food additives reported by the International Food Additive Council for 1990 was 470 milligrams (mg) phosphorus per day per capita as compared to an estimated 400 mg of phosphorus per day per capita for 1980, or approximately a 17 percent increase in per capita use over the last decade. Thus, more than one line of evidence points to the fact that the consumption of phosphorus-containing additives is on the rise and contributes to the high phosphorus intake observed in the United States population.

12. Another comment strongly opposed the proposed limit on phosphorus content for a number of reasons. The comment asserted that any health claim disqualifier must meet the same conditions as the claim itself, such as unanimous agreement among experts, and that no studies to date have demonstrated an adverse effect of excess phosphorus on bone in man or in monkeys or in calcium balance studies. This comment also asserted that there is a controversy over the effect of high phosphorus on calcium absorption and pointed to the fact that no single food contributes to the high phosphorus intake and to the remote possibility that reduction of phosphorus intake from one food will reduce total phosphorus intake,

The agency does not agree that any of these points warrants modification of the limit on phosphorus content in § 101.72(c)(2)(ii)(D). The limit on phosphorus is not a "disqualifying level" as that term is defined based on section 403(r)(3)(A)(ii) of the act. FDA is not limiting the phosphorus content because of its effect on the risk of a diet-related disease or health-related condition. FDA may have contributed to confusion in this regard by stating in the proposal that the level of phosphorus would disqualify a product from bearing a claim (56 FR at 60699). FDA is limiting the amount of phosphorus under the authority of section 403 (a) of the act. As explained above, high levels of phosphorus when calcium intakes is low, would impair the utilization of calcium by bone. Thus, the presence of a calcium/osteoporosis claim on a food that does not have an appropriate calcium-phosphorus ratio would be misleading, because it would not be possible to get the full benefits of calcium from such a food.

In response to the criticism that no studies have demonstrated direct adverse effects of excess phosphorus on bone in humans or primate models, the agency points out that evidence in humans demonstrates that high levels of dietary phosphorus coupled with low dietary calcium intake adversely influence hormonal factors that regulate calcium and bone metabolism (Refs. 17, 21, 29, 32, 46, 93, 114, and 116). These changes were consistent with those observed in a variety of animal models where the hormonal changes were shown to induce bone resorption and ultimately bone loss (Ref. 46). The agency is particularly concerned about teens and young adults who typically consume more phosphorus than calcium (Ref. 105) and for whom such diets have recently been shown to produce changes in serum calcium and bone-regulating hormones that may adversely affect attainment of peak bone mass (Ref. 32). The health claim is an effective means of alerting this vulnerable population to foods that have the desired ratio of these two nutrients. Therefore the agency does not agree with the comment's suggestion that the limit on phosphorus content be dropped.

The agency does not disagree with the other assertions made in this comment. These points are minor and, given that health claims are authorized in the context of the total daily diet, not particularly relevant. The agency did not assert that excess phosphorus impaired calcium absorption and has maintained that phosphorus is ubiquitously distributed in the food supply. Given the effects of phosphorus on hormonal factors that regulate calcium and bone metabolism, FDA concludes that the limit on phosphorus content for a food that bears a calcium/osteoporosis claim is appropriate.

H. No Quantification of Reduction in Risk

13. One comment urged FDA to avoid any possible misinterpretation and potential abuse of the calcium/osteoporosis regulation by specifying in the regulation that "the claim shall not convey the misconception that dietary calcium intake can cure osteoporosis." The comment included examples of labels of dietary supplements found in health food stores.

The agency agrees with the comments concern but remains confident that the claims being authorized will not mislead consumers into believing that calcium cures osteoporosis. This regulation authorize a health claim that relates calcium intake to a reduction in the risk of osteoporosis, A statement that calcium cures osteoporosis would constitute a drug claim under section 201(g)(1)(B) of the act (21 U.S.C. 321(g)(1)(B)), and a product bearing such a claim would be subject to regulation as a drug. In addition. § 101.72(c)(2)(i)(D) bars health claims on calcium and osteoporosis from attributing any degree of reduction in risk of osteoporosis to maintaining an adequate calcium intake throughout life.

I. Limitations of Benefit to Bone Health

14. Several comments opposed the upper-limit-of-benefit statement proposed in § 101.72(d)(5), saying that this statement was an effort to limit the potency of supplements. A number of comments supported the statement but required that it be qualified. One comment requested that the statement only be placed on products in which the calcium level is greater than 50 percent of the originally proposed RDI of 900 mg or 450 mg of calcium (presumably per serving or per recommended daily dose). This comment reasoned that for products with lower levels of calcium, an unreasonable number of servings of food would need to be consumed to exceed 200 percent of the RDI, and thus the statement was not necessary.

FDA does not agree with the assertion that it is seeking to limit the potency of supplements. This regulation relates only to the type of health claim that a product may bear. It ensures that a material fact about the consequences of consumption of more than a specified level of calcium is presented as part of the claim. FDA agrees in principle with the suggested change in proposed § 101.72(d)(5) and believes that this modification may help curb overfortiflcation. The agency has therefore added the following language to the proposed provision redesignated as § 101.72(c)(2)(i)(E)): "This requirement does not apply to foods that contain less than 40 percent of the recommended daily intake of 1,000 mg of calcium per day or 400 mg of calcium per reference amount customarily consumed or per total daily recommended supplement intake."

J. Safety

15. A public health advocacy association suggested that FDA require labels on high dose calcium supplements to disclose that high calcium intakes may increase the risk of kidney stones in susceptible people. The comment argued that levels greater than 1,000 to 2,500 mg calcium per day

many pose a risk to people with a history of kidney stones, and that, therefore, labels on supplements that contain 500 mg or more of calcium should inform consumers of this risk.

The agency does not agree that a warning is needed in addition to the statement on total dietary intakes greater than 200 percent of the RDI. Section § 101.72(c)(2)(i)(D) requires that the health claim identify the populations at greatest risk of osteoporosis, namely Caucasian and Asian women in their bone forming years. Kidney stones are more prevalent in men than women. (With respect to calcium exalate or mixed calcium stones, effected males outnumber effected females by three or four to one in the U.S. population (Ref. 143).) Thus, while men are at greater risk of the adverse effects of excess calcium intake due to their greater susceptibility to kidney stone formation, they are not at greater risk for osteoporosis and will not be targeted by the calcium-osteoporosis health claim. Consequently, there is no reason to expect that men will increase their consumption of calcium in response to the claim. Therefore, FDA concludes that the regulations offer sufficient protection without the proposed warning.

K. Consumer Summary

16. The comments specific to the proposed consumer summary were generally supportive, and some considered consumer summaries necessary to put any health claim into perspective as related to total diet. The use of the consumer summary on package inserts was suggested by several groups. Several comments suggested various ways to shorten the summary, while others suggested additional information to incorporate. One comment strongly opposed consumer summary, stating that in light of the detailed, balanced information provided in the model claims, summaries are redundant, costly, and inconvenient to the manufacturer.

As discussed in the final rule on general requirements for health claims, consumer summaries are not required, although their use remains an option. For this reason, FDA has not included the proposed consumer summary on calcium and osteoporosis in this final rule.

L. Regulatory History of Calcium-Containing Food Additive Use

The Agency advised that, in order for calcium-containing food ingredients in conventional foods or calcium supplement products to be considered eligible to bear the authorized calcium/ osteoporosis health claim, they must meet the requirements in § 101.14, which include that they have been shown to FDA's satisfaction to be safe and lawful under the applicable safety provisions of the act (56 FR at 60699). Safety and lawfulness can be demonstrated in a number of ways, including through a showing that a food is generally recognized as safe (GRAS), affirmed as GRAS by FDA, listed in the food additive regulations, or subject to a prior sanction. Of the 36 or more calcium-containing ingredients identified by the agency as currently in use (Ref. 33), FDA advised that only the following 10 compounds had been demonstrated to be safe and lawful for use in a dietary supplement or as a nutrient supplement: calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate (5G FR of 60691).

17. One comment pointed out that the agency failed to include calcium ascorbate in this list of 10 compounds. The comment included also submitted an April 1969 letter from FDA stating the agency's lack of objection to the use of calcium ascorbate in dietary supplements. Another comment sought the addition of calcium hydroxide to the list of 10 calcium compounds discussed above, contending that "since calcium oxide is permitted and calcium hydroxide is simply the hydrate of the oxide formed on contact with water," calcium hydroxide should be included in the list.

As stated above, only 10 compounds have been demonstrated to FDA's satisfaction to be safe and lawful for use in a dietary supplement or as a nutrient supplement bearing a calcium/ osteoporosis health claim. In Ref. 33 of the proposal, the agency identified the calcium-containing ingredients currently in use, their functions, conditions of use, and limits on the levels at which they can be added to food. Only these ingredients with stated use as a nutrient supplement or in a dietary supplement are considered eligible for a health claim. Calcium ascorbate appears only under 21 CFR 182.9189 (Ref.33) for use as a chemical preservative. Thus, FDA's failure to list it was not inadvertent. Calcium ascorbate is not eligible at this time for consideration for a health claim; however, a petition may be filed requesting a safety review for a new use of calcium ascorbate. Based on the outcome of this petition and review, calcium ascorbate may be considered eligible for a calcium/ osteoporosis health claim.

The agency declines to add calcium hydroxide to the list of 10 calcium containing compounds that have been demonstrated to be safe and lawful for use in a dietary or nutrient supplement. In the list, FDA identified those ingredients with stated uses as a nutrient or dietary supplement, thus avoiding the use of potentially poorly suited or potentially harmful compounds FDA's failure to include calcium hydroxide on the list does not imply that the agency considers the use of this substance to be unsafe for use as a calcium supplement, but rather reflects that it has net been demonstrated safe and lawful for this use. Manufacturers who would like to be able to make a calcium/osteoporosis health claim based on the presence of calcium hydroxide in their product should submit an appropriate petition lo FDA.

M. Food Fortification

10. A public health and nutrition association expressed concern that manufacturers seeking a calcium/ osteoporosis health claim will fortify products of low nutritional value that do not naturally contain calcium. The comment recommended that FDA consider setting standards for the amount of fortification that is allowed and also suggested that FDA determine which products can be fortified.

Although the agency understands the concern expressed in the comment, the full implementation of these suggestions is beyond the scope of this rulemaking. The agency advises that fortification of feeds to qualify for a health claim must comply with the final rule on general requirements for health claims published elsewhere in this issue of the **Federal Register**.

N. Nutrition Claims

10. One comment argued that claims relating to a nutrient's effect on the structure or function of the body are not health claims but nutrition claims. The comment suggested amending the proposed regulations to clarify the distinction between nutrition and health claims. In the event that FDA's rejected this proposal, the comment asked that the agency acknowledge that the relationship between calcium and bone health is a nutrition claim that is substantiated in the proposed calcium/ osteoporosis health claim regulation.

FDA rejects these suggestions. The distinctions between nutritional guidance and health claims is discussed in the final rule on general requirements for health claims. The claim authorized

under this regulation relating calcium and osteoporosis is a health claim because it characterizes the relationship of a nutrient (calcium) to a disease or health-related condition (osteoporosis). A claim relating calcium to bone health would have to be evaluated on its own merits. Such a claim might be considered an implied health claim, rather than merely a statement about a food's effect on the structure or function of the body, and, if so, it would be subject to regulation under section 403(r)of the act.

O. Model Claim

20. Many comments discussed the length of the model health claim and its required components. Common to all comments was the complaint that the model message was too wordy. Comments were almost equally split between those supporting and those opposing the proposed model message. Supporting comments praised specific aspects of the model claim such as disclosure of other risk factors; the likely upper limit of beneficial calcium intakes, reflection of other factors that contribute to osteoporosis risk such as age, race, and sex; inclusion of the need for exercise; and disclosure of the mechanisms through which calcium may reduce the risk of osteoporosis. Opposing comments emphasized the burdensome length of the model claim. One comment stated that the length of the claim would not allow it to be translated into multiple languages on the label. Many comments requested that FDA remove the requirements that populations at special risk of osteoporosis and nondietary factors that can help prevent osteoporosis be identified. Several comments suggested that the length of the claim will limit its effectiveness and curtail manufacturers' incentives to make claims. An association of national advertisers asserted that no diet and disease relationship can be explained completely in one paragraph.

The agency agrees that the proposed model health claim was too long. However, as discussed in the proposal and elsewhere in this final rule, certain information is needed in the health claim in order for it to be truthful and not misleading to segments of the population that are not at high risk of developing osteoporosis or for whom no link between calcium and osteoporosis has been established. FDA notes that the proposed model claim contained optional as well as required information, and the example has been rewritten to demonstrate that all required information can be included in a model claim of less than 35 words: "Regular exercise and eating a healthful diet with enough calcium helps teen and young adult white and Asian women maintain good bone health and may reduce their high risk of osteoporosis later in life." Foods that contain less than 40 percent of the recommended daily intake of 1,000 mg of calcium per day (400 mg calcium) per reference amount customarily consumed or per total daily recommended supplement intake may bear this claim. Other foods that contain higher levels of calcium must also carry an additional statement (see §101.72(c)(2)(i)(E)).

Throughout FDA's responses to the comments in this preamble, the agency has presented various reasons that strongly support maintaining the requirements that make the claim lengthy. These points include the need not to mislead the public in thinking everyone is at risk for this disease, the need to identify those at greatest risk and thus to help individuals who are not at risk but who are susceptible to the adverse effects of oversupplementation with calcium avoid any problems, and the need to target the age group for which adequate calcium intake may have the greatest benefit for bone health and delayed risk of osteoporotic fracture.

P. Other Issues

21. One comment contended that FDA should permit health claims on OTC antacid products containing only calcium carbonate. Responding to a discussion on dual labeling in the proposal on general requirements for health claims (56 FR 60537), the comment asserted that FDA's objection to OTC drugs bearing health claims is not appropriate in the case of calcium-based antacids, because such products have been labeled for years with both food and drug labeling.

FDA has addressed the issues raised by this comment in the final rule on general requirements for health claims, published elsewhere in this issue of the **Federal Register**.

22. Another comment urged that the regulation require disclosure about the relationship between calcium and protein and suggested disqualifying high protein products based on the effect of dietary protein on the urinary loss of calcium, which affects bone health.

As mentioned in the preamble of the proposal (56 FR at 60699), the agency recognizes that high levels of dietary protein typically found in the American diet have been shown to increase the obligatory loss of calcium, i.e., the amount of calcium that the body must lose daily. The agency, however, did not propose to disqualify high-protein products from bearing a calcium/osteoporosis claim or to disclose the effect of high protein intake on calcium retention on the label. Like calcium, protein is not ubiquitously distributed in our food supply and is richest in specific food sources (Refs. 27 and 110). Relatively few foods are sources of calcium and protein, forcing consumers to be selective to meet the nutritional needs for both calcium and protein. Some protein rich foods, such as lowfat milk or lowfat milk products, contribute more than half the calcium and protein intake of some individuals, notably children. It would be misleading to the public not to allow an important food such as lowfat milk to have a calcium/osteoporosis claim due to its high levels of protein. To disqualify a product that is both rich in calcium and protein, and that would not be disqualified because of its fat, saturated fat, cholesterol, or sodium levels, because of its protein content, would effectively prevent several major food sources of calcium from bearing a claim.

Several other considerations reinforce the agency's position that protein content should not be a basis for disqualification from bearing a calcium/osteoporosis claim or for a disclosure statement. The scientific evidence demonstrating a persistent increase in the urinary loss of calcium when high protein intakes are sustained for months is weak and controversial, in addition, different protein sources have been shown to elicit varying degrees of calciuria (increased loss of calcium in urine), thus making it incorrect for the agency to consider all dietary protein sources equally potent in their calciuric effect. Moreover, no clear evidence exists demonstrating that high protein intake alters any of the hormones that control bone formation and resorption, or that high protein intake impairs bone mineralization.

FDA is making several minor changes in the regulation to improve its readability and to make it consistent with other regulations that FDA is adopting that authorize health claims. The most significant of these changes is the fact that FDA is adding to the paragraph on optional information a provision that will allow the declaration as part of the claim of the number of people who are affected by osteoporous (§ 101.72(d)(2)). This change makes § 101.72 consistent with the other regulations in Subpart E. Therefore, FDA is rejecting the comment's suggestion to require a statement about the relationship between calcium and protein or to establish a level of protein

that would disqualify a product from bearing a calcium/osteoporosis claim. The agency concludes that a product high in protein can still be an important source of calcium and that it cannot conclude that a claim would be misleading if it fails to reveal the relationship between calcium and protein.

III. Review of Scientific Evidence

FDA updated its review of the scientific literature by examining articles published since the proposed rule was issued. FDA's evaluation of recent human studies meeting the criteria outlined in the proposal (56 FR at 60693) is presented in Table 1 (Refs. 144 through 150). In addition, FDA also considered several review articles that were published since the proposal (Refs. 151 through 156). FDA sought to answer the same questions posed in the proposed rule.

First, do any of the recent studies present evidence documenting the role of calcium in achieving peak bone mass? A cross-sectional study examining spinal bone density in Caucasian girls 8 to 18 years of age demonstrated that calcium intake may be a major factor in achieving peak adult bone density (Ref. 148). Chan et al. (Ref. 145) also demonstrated higher bone mineral content in Caucasian boys and girls consuming greater than 1,000 mg of calcium per day. In this study 70 percent of the subjects younger than 11 years consumed at least their RDA of 800 mg of calcium per day, while 63 percent of the subjects older than 11 consumed less than their RDA of 1,200 mg per day. After adjustment for phosphorus and protein intake, multivariate analyses showed only calcium intake was related to bone mineral status of the children in this study. Thus, the most recent data, although not definitive, continue to strongly support the link between adequate calcium intake and optimal peak bone mass.

The second question asked in reviewing these studies is whether added calcium or high calcium intake reduces the risk of fracture or slows the rate of bone loss in younger or older subjects. Andon et al. (Ref. 144) showed, in a cross-sectional study, that Caucasian postmenopausal women consuming less than 600 mg calcium per day had significantly lower spinal bone mineral densities than women with higher calcium intakes. Because individuals who malabsorb lactose normally avoid dairy products, Wheadon et al. (Ref. 150) assessed lactose absorption and dietary calcium intake in elderly women with and without hip fractures and in young women. While 60 percent of the women with hip fractures were lactose malabsorbers, dietary calcium intakes did not differ significantly among the three groups. However, the authors cautioned against putting too much weight on the findings of the small study (n=31) since the aversion to milk and milk products ascribed to lactose intolerance may be shown to decrease calcium intake in a larger population.

As discussed in the earlier literature review, the responsiveness of postmenopausal women to calcium supplementation depends largely on their menopausal age. Calcium supplementation had no effect on spinal bone density early in menopause, but for women late in menopause, the rate of bone loss could be significantly reduced with calcium supplementation, if initial habitual calcium intakes were low (Refs. 47 and 151). Three recent prospective intervention studies (Refs. 146,147, and 149) shed further light on this observation. Elders et al. (Ref 146) reported a high rate of lumbar vertebral bone loss in late and early postmenopausal subjects, with the highest loss occurring in early postmenopause. However, no significant interaction was observed between menopausal status of the subjects and the effect of calcium supplementation. These authors reported a significant decrease in lumbar bone loss after 2 years for women treated daily with 1,000 mg and 2,000 mg of elemental calcium relative to controls. The effect of calcium supplementation was significant after the first year of supplementation but not after the second year. The authors speculate that calcium supplementation probably reduced bone turnover.

In a double-blind, placebo controlled trial in Caucasian, postmenopausal women, with low initial forearm bone density, Prince et al. (Ref. 147) showed significantly less bone loss in the distal forearm in those women treated with calcium and regular exercise, while a group treated with estrogen and regular exercise gained significant bone density at this site relative to the control group with normal initial bone density and the group treated with exercise alone. Thus, calcium supplementation and exercise slowed bone loss relative to exercise alone but less effectively than exercise combined with estrogen.

In the third prospective study, this one a 3-year study in 622 Caucasian women, Tilyard and co-workers measured rate of vertebral fractures in women treated twice a day with either 0.25 micrograms of calcitriol (a synthetic form of the active metabolite of vitamin D) or 1 gram of elemental calcium (Ref. 149). After 2 and 3 years, a significant reduction in the rate of vertebral fracture was observed in calcitriol-treated women relative to those treated with calcium alone. This study clearly demonstrates that supplementation of calcium intake alone is hot adequate to prevent vertebral fracture in postmenopausal women. In the absence of placebo-treated controls, the contribution of calcium supplementation to the reduction in vertebral fracture cannot be estimated. The results of these three prospective clinical trials support the hypothesis that adequate calcium intake helps to slow the rate of bone loss in postmenopausal women, but that calcium alone cannot effectively arrest this process, especially in early postmenopause.

The third question considered in evaluating the recent literature was whether any of the studies showed a threshold effect for the level of calcium intake associated with changes in bone mass. None of the findings from the recent studies were pertinent to this question.

To summarize, these new findings were consistent with and strengthened the conclusion that adequate calcium intake has a significant impact on bone health and risk of osteoporotic fracture.

IV. Decision to Authorize a Health Claim Relating Adequate Calcium Intake to Osteoporosis

The agency has reviewed recently published research articles and review articles relevant to calcium intake and osteoporosis (Refs. 144 through 156) and has concluded that the new studies are consistent with the tentative conclusions drawn in its proposed rule on calcium and osteoporosis (56 FR 60689). The agency also considered all comments received in response to the proposal. The overwhelming concurrence among the experts in this area and the totality of publicly available evidence supports an association between adequate calcium intake and risk of osteoporosis. Based on the totality of the publicly available scientific evidence, FDA has determined that there is significant scientific agreement among qualified experts that a health claim for calcium and osteoporosis is supported by the evidence. Under § 101.72, an authorized health claim will convey the message that an adequate intake of calcium throughout life may delay the development of osteoporosis and ultimately reduce the risk of bone fracture in some individuals later in life.

V. Environmental Impact

The agency has determined that under 21 CFR 25.24(a)(11) this action is of a type that does not individually or cumulatively have significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Economic Impact

In its food labeling proposals of November 27, 1991 (56 FR 60366 et seq.), FDA stated that the food labeling reform initiative, taken as a whole, would have associated costs in excess of the $100 million threshold that defines a major rule. Thus, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354), FDA developed one comprehensive regulatory impact analysis (RIA) that presented the costs and benefits of all of the food labeling provisions taken together. That RIA was published in the **Federal Register** of November 27, 1991 (56 FR 60856), and along with the food labeling proposals, the agency requested comments on the RIA.

FDA has evaluated more than 300 comments that it received in response to the November 1991 RIA. FDA's discussion of these comments is contained in the agency's final RIA published elsewhere in this issue of the **Federal Register**. In addition, FDA will prepare a final regulatory flexibility analysis (RFA) subsequent to the publication of the food labeling final rules. The final RFA will be placed on file with the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, and a notice will be published in the **Federal Register** announcing its availability.

In the final RIA, FDA has concluded, based on its review of available data and comments, that the overall food labeling reform initiative constitutes a. major rule as defined by Executive Order 12291. Further, the agency has concluded that although the costs of complying with the new food labeling requirements are substantial, such costs are outweighed by the public health benefits that will be realized through the use of improved nutrition information provided by food labeling.

VII. References

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List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements.

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

PART 101—FOOD LABELING

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

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348. 371).

2. Section 101.72 is added to subpart E to read as follows:

§101.72 Health claims: calcium and osteoporosis.

(a) Relationship between calcium and osteoporosis. An inadequate calcium intake contributes to low peak bone mass and has been identified as one of many risk factors in the development of osteoporosis. Peak bone mass is the total Quantity of bone present at maturity, and experts believe that it has the greatest bearing on whether a person will be at risk of developing osteoporosis and related bone fractures later in life. Another factor that influences total bone mass and susceptibility to osteoporosis is the rate of bone loss after skeletal maturity. An adequate intake of calcium is thought to exert a positive effect during adolescence and early adulthood in optimizing the amount of bone that is

laid down. However, the upper limit of peak bone mass is genetically determined. The mechanism through which an adequate calcium Intake and optimal peak bone mass reduce the risk of osteoporosis is thought to be as follows. All persons lose bone with age. Hence, those with higher bone mass at maturity take longer to reach the critically reduced mass at which bones can fracture easily. The rate of bone loss after skeletal maturity also influences the amount of bone present at old age and can influence an individual's risk of developing osteoporosis. Maintenance of an adequate intake of calcium later in life is thought to be important in reducing the rate of bone loss particularly in the elderly and in women during the first decade following menopause.

(b) *Significance of calcium*. Calcium intake is not the only recognized risk factor in the development of osteoporosis, a multifactorial bone disease. Other factors including a person's sex, race, hormonal status, family history, body stature, level of exercise, general diet, and specific life style choices such as smoking and excess alcohol consumption affect the risk of osteoporosis.

(1) Heredity and being female are two key factors identifying those individuals at risk for the development of osteoporosis. Hereditary risk factors include race: Notably, Caucasians and Asians are characterized by low peak bone mass at maturity. Caucasian women, particularly those of northern European ancestry, experience the highest incidence of osteoporosis-related bone fracture. American women of African heritage are characterized by the highest peak bone mass and lowest incidence of osteoporotic fracture, despite the fact that they have low calcium intake.

(2) Maintenance of an adequate intake of calcium throughout life is particularly important for a subpopulation of individuals at greatest risk of developing osteoporosis and for whom adequate dietary calcium intake may have the most important beneficial effects on bone health. This target subpopulation includes adolescent and young adult Caucasian and Asian American women.

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

(2) Specific requirements, (i) *Nature of the claim*. A health claim associating calcium with a reduced risk of osteoporosis may be made on the label or labeling of a food describe in paragraph (c)(2)(ii) of this section. provided that:

(A) The claim makes clear that adequate calcium intake throughout life is not the only recognized risk factor in this multifactorial bone disease by listing specific factors, including sex, race, and age that place persons at risk of developing osteoporosis and stating that an adequate level of exercise and a healthful diet are also needed;

(B) The claim does not state or imply that the risk of osteoporosis is equally applicable to the general United States population. The claim shall identify the populations at particular risk for the development of osteoporosis. These populations include white (or the term "Caucasian") women and Asian women in their bone forming years (approximately 11 to 35 years of age or the phrase "during teen or early adult years" may be used). The claim may also identify menopausal (or the term "middle-aged") women, persons with a family history of the disease, and elderly (or "older") men and women as being at risk;

(C) The claim states that adequate calcium intake throughout life is linked to reduced risk of osteoporosis through the mechanism of optimizing peak bone mass during adolescence and early adulthood. The phrase "build and maintain good bone health" may be used to convey the concept of optimizing peak bone mass. When reference is made to persons with a family history of the disease, menopausal women, and elderly men and women, the claim may also state that adequate calcium intake is linked to reduced risk of osteoporosis through the mechanism of slowing the rate of bone loss;

(D) The claim does not attribute any degree of reduction in risk of osteoporosis to maintaining an adequate calcium intake throughout life; and

(E) The claim states that a total dietary intake greater than 200 percent of the recommended daily intake (2,000 milligrams (mg) of calcium) has no further known benefit to bone health. This requirement does not apply to foods that contain less than 40 percent of the recommended daily intake of 1,000 mg of calcium per day or 400 mg of calcium per reference amount customarily consumed as defined in § 101.12 (b) or per total daily recommended supplement intake.

(ii) *Nature of the food*. (A) The food shall meet or exceed the requirements for a "high" level of calcium as defined in § 101.54(c);

(B) The calcium content of the product shall be assimilable;

(C) Dietary supplements meet the United States Pharmacopeia (U.S.P.) standards for disintegration and dissolution applicable to their component calcium salts, except that dietary supplements for which no U.S.P. standards exist shall exhibit appropriate assimilability under the conditions of use stated on the product label;

(D) A food or total daily recommended supplement intake shall not contain more phosphorus than calcium on a weight per weight basis.

(d) *Optional information*. (1) The claim may include information from paragraphs (a) and (b) of this section.

(2) The claim may include information on the number of people in the United States who have osteoporosis. The sources of this information must be identified, and it must be current information from the National Center for Health Statistics, the National Institutes of Health, or "Dietary Guidelines for Americans."

(e) *Model health claim*. The following model health claims may be used in food labeling to describe the relationship between calcium and osteoporosis:

Model Health Claim Appropriate for Most Conventional Foods:

Regular exercise and a healthy diet with enough calcium helps teen and young adult white and Asian women maintain good bone health and may reduce their high risk of osteoporosis later in life.

Model Health Claim Appropriate for Foods Exceptionally High m Calcium and Most Calcium Supplements:

Regular exercise and a healthy diet with enough calcium helps teen and young adult white and Asian women maintain good bone health and may reduce their high risk of osteoporosis later in life. Adequate calcium intake is important, but daily intakes above about 2,000 mg are not likely to provide any additional benefit.

Dated: December 17, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

Note: The following table will not appear In the annual Code of Federal Regulations.

BILLING CODE 4160-01-F

TABLE

Calcium and Osteoporosis: Effects of Calcium on Bone Status

Reference (author date)	Study Design	Number and Description of subjects	Duration of study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Andon, N., et al. (1992) (Ref. 200)	Cross-sectional measured: vertebral bone density (??-??) by dual photon absorption.	101 women, caucasian aged ?? to ?? years. Mean age: 61.7 years mean year past menopause: 10.1 years.	N/A	Habitual diet	Dietary calcium intake ??????? from food frequency questionnaire		Controlled for other factors including body weight, ??????? and alcohol use	Multiple regression analysis used to estimate effect of calcium intake on spinal bone density. Subjects grouped according [to] calcium intake c? < or > 606(?) mg ca/ day	Significant correlation of body weight and ????? Calcium with vertebral bone mineral density. Women consuming < 606(?) mg ca per day had significantly lower bone mineral density than those consuming > 606(?) mg/day	Study weakened(?) by use of food frequency questionnaire. Not a reliable method of accurately estimating calcium intake.
Chan, O., (1991) (Ref. 145)	Cross-sectional measured: bone mineral density of the distal third radius of nondominant ???? using single photon absorption and calcium intake ????? parameters also measured	164 healthy caucasian children 90(?) boys 74(?) girls	N/A	Habitual diet		Habitual nutrient intake was estimated from two 2-day dietary histories		Correlation of age weight and height was significant to bone mineral content in all 164 children	70% of subjects < 11 years consumed at least (1)000(?) mg/day ??% of subjects >11 consumed less than their recommended Dietary Allowance of 1000 mg ca/day mean intake= 750 mg/ girl While 53% of boys >11 years consumed at least 1,200(?) mg/ day Multiveriate analysis showed only calcium intake related to children ?? bone mineral status (partial corrolation coefficient= 0?10 p<0??)	Employed a weak method of determining calcium intake Children consuming > 1,000 mg of ca/day had higher bone mineral content

TABLE—CONTINUED

Reference (author date)	Study Design	Number and Description of subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Eldoro(?) p,(?) et al. (1991) (Ref 14(0))	Prospective Randomized Clinical Trial Measured, Bone mineral density of the lumber spine (L2 Ld) by dual photon absorption and combined metacarpal cortical thickness in second, third and fourth metacarpals of both hands.	295 women, mostly caucasian 46 to 55 years of age Menopausal statues was assessed by menstrual history and classified into four menopausal groups	2 years	Supplemental calcium source was effervescent tablet with 5?23 g of calcium lactogluconate and 0 (?) 9 g calcium carbonate	3 treatments no calcium supplements - 1,000 mg calcium at night - 2,000 mg calcium in two doses at night and in morning	Habitual Intake	47/(?) 295 of the original subjects dropped out 44 of the calcium treated group switched forms of calcium to calcium citrate due to ?? upset.		A significant decrease in lumber bone loss observed after 2 years for the 1,000 and 2,000 mg supplemented groups relative to control (1.3%, 0.7% and 3.5% mean loss after 2 years) The effect of calcium on lumber bone loss was significant after the first year, but not after the second. Calcium did not significantly effect metacarpal cortical bone loss	Authors concluded that calcium supplementation retards lumber bone loss in the first year of supplementation, probably through reduced bone turnover Rate of lumber bone loss was significantly more pronounced in late peri and early postmenopause and was highest in early menopause
Prince, R., et al., (1991) (Ref 147)	Double blind Placebo Controlled Randomized Clinical trial Measured: Bone density at 3 forearm sites using single photon absorption every 3 months . Urine and blood measurements every 6 months	120 women caucasian mean age, 56± 4 years All had low forearm bone density 42 women mean age 55 5±3 years All had normal forearm bone density	2 years	Exercise alone: n= 41 Exercise + 1 g Ca (calcium lactategluconate n=39 Exercise + progesterone and estrogen	2.5(?) mg/ day medroxyprogesterone acetate and 0.625(?) mg/day estropipate for 1 month then 1.25(?) mg/ day for 23 months	Habitual diet No significant difference observed between treatment groups Mean calcium intakes for all treatment groups > 650 mg	All exercise regimens consisted of one weekly class and two brisk 30 minute walks per week Every 6 months, physical activity recorded over 4 days and scored Four day dietary records were recorded at beginning and end	All women in treatment groups had initial forearm bone density not lower than one standard deviation below mean for normal control Among 3 treatments no differences in baseline physical activity score calcium intake or forearm density observed	At the distal site both the normal control and the exercise alone group lost significant forearm bone (> 2.6%/y) and the exercise + estrogen group gained significant bone density (+2.7%/y)	A combined therapy of estrogen and exercise was the most effective in increasing forearm bone mass but with more undesirable side effects Calcium and exercise slowed bone loss relative to exercise alone but less effective then exercise + estrogen Exercise alone was not effective

TABLE—CONTINUED

Reference (author date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Contipal(?), J., et al., (1991) (Ref 140)	Cross-sectional Measured, Vertebral bone density by dual x(?)-ray absorption (L1 Ld) and current calcium intake	40(?) adolescent girls 0 to 10 years caucasians	N/A	Habitual diet	Current calcium intake estimated from 3(?)-day diet records		3-day activity records used to determine average daily energy expenditure 10% of 11 to 10 year olds not their Recommended Dietary Allowance of 1000 mg for calcium, while 67(?)% of the 0to 10 year olds not their Recommended Dietary Allowance of 000(?) mg calcium	Relative contributions to difference is vertebral body density contributed by calcium intake, age weight height, total energy expenditure, SMR, were estimated by total linear regression SMR= Tanner Sexual Maturity Rating	?1% of the variance in vertebral bone density was contributed by SMR, age, and calcium intake	Data suggest that calcium intake may influence peak bone mass and may be a major limiting factor in achieving adult bone density
Tilyard, M., et al., (1992) (Ref 1??)	Prospective ???????? single-blind randomized intervention study measured, ???? of vertebral fracture, as defined as a decrease of 15(?)% or more during any 1 year in the anterior or posterior height of the vertebral body from L? through Ld estimated from early roentgenograms	??? women caucasian aged 50 to 79 years All had one or more nontraumatic vertebral compression fracture None on estrogens 515 completed 1 year, 47? completed 3 years, 4?? completed ? years	3 years	Calcitriol group n=314 Calcium group n=300	? 25 mg calcitriol twice/day 1 gram calcium ?? 5.2 g calcium gluconate twice/day	Baseline dietary calcium intake measured in both groups	Monitored serum(?) chemistry changes relative to baseline over the 3 years of treatment	Measured incidence of nephrocalcinosi ? since both treatments are associated with it Measured calcium absorption status at 30 months	At year 1, fracture rate was 0.0 in calcitriol and 10.3 in calcium groups At year 2, Fracture rates of spine were significantly reduced in calcitriol and even more pronounced difference between treatments shown after 3 years Calcium goup has a higher rate of vertebral fracture compared to calcitriol treated subjects at all times	Study lacked a compliance assessment High patient attrition, 31% of women did not complete the study Study clearly shows that calcium supplementation alone is not adequate to prevent vertebral fractures in menopausal women Calcium absorption status did not affect rate of fracture in groups

TABLE—CONTINUED

Reference (author date)	Study Design	Number and Description of Subjects	Duration of study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Wheadon, M., et al., (1991) (Ref. 150)	Assessed lactose absorption and dietary calcium intake in elderly women with and without hip fractures Measured, Lactose tolerance and dietary calcium	Women with hip fractures: n= 15 type II osteoporosis mean age = 66±10 years Control: Normal n= 16 mean age = 65±9 years			Dietary calcium intake was estimated from a food frequency questionnaire			Since bone density was not measured, there is a strong possibility that the elderly controls also had type II osteoporosis, but had not sustained a fracture	60% of elderly hip fracture group were lactose malabsorber 19/31 total elderly subjects were lactose malabsorber Dietary calcium intake did not differ significantly among the 3 groups	Authors were not able to show a decreased dietary calcium intake associated with lactose malabsorption, but the aversion to milk and milk products ascribed to lactose malabsorption may be shown to decrease calcium intake in a larger population In elderly, decreased calcium intake may exacerbate calcium bone from loss

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