



*Producers of Quality
Nonprescription Medicines and
Dietary Supplements for Self-Care*

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CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

Formerly Nonprescription Drug Manufacturers Association

May 11, 2000

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition under § 701 and other applicable sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 371] and 21 CFR 10.30 to request the Commissioner of Food and Drugs to amend the Final Regulation on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body (Docket No. 98N-0044), to establish a regulation to define labeling requirements for certain dietary supplements, and to create a guidance on the scope and nature of safety-related evidence for support of structure/function claims for conditions associated with pregnancy and/or nursing a baby.

A. Action requested

The Consumer Healthcare Products Association (CHPA)¹ asks that FDA issue a regulation to require label statements on certain dietary supplements pertaining to their use in pregnancy and/or when nursing a baby. CHPA requests that the compliance date for a final regulation on this matter be one year from the publication of the final rule in the *Federal Register* based on date of manufacture.

CHPA asks that FDA's Center for Food Safety and Applied Nutrition develop and issue a guidance on the scientific basis for assessing the potential for possible effects of

¹ CHPA is the 119-year old trade organization representing dietary supplements and nonprescription drugs, including over 200 members across the manufacturing, distributing, supply, research testing, and advertising sectors of the self-care industry.

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CHPA asks that FDA's Center for Food Safety and Applied Nutrition develop and issue a guidance on the scientific basis for assessing the potential for possible effects of dietary supplements on reproduction/ development and the scope and nature of safety-related evidence that is needed to support a structure/function claim for conditions associated with pregnancy and nursing a baby.

CHPA asks that FDA amend its Final Regulation on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body (Docket No. 98N-0044)² to prohibit structure/function claims for foods concerning edema associated with pregnancy, by adding a new subsection (3) under Section 101.93 (g) stating that such claims are prohibited.

B. Statement of grounds

1. Background

On January 6, 2000, FDA issued a Final Regulation on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body. In this regulation, FDA distinguished between diseases and natural states, finding that the latter may be areas for structure/function claims for dietary supplements. Among the natural states included in the preamble to the Final Regulation was pregnancy. The structure/function claims in pregnancy cited by FDA were the associated conditions of morning sickness and edema. In this regard, FDA stated:

“FDA has reconsidered proposed Sec. 101.93(g)(2)(iii), and has concluded that it is not appropriate, under DSHEA, to treat certain common, nonserious conditions associated with natural states as diseases. There are a wide variety of conditions representing impaired function of an organ or system that are associated with particular stages of life or normal physiologic processes. These stages and processes include adolescence, the menstrual cycle, pregnancy, menopause, and aging. (FDA notes that, contrary to the comments, the proposed rule would not have classified these stages or processes themselves as diseases; it classified only certain abnormal conditions associated with these stages or processes as diseases.) The conditions associated with these stages or processes can vary from

² Food and Drug Administration: Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body; Final Rule [65 F.R 999-1000 (1/6/2000).

common, relatively mild abnormalities, for which medical attention is not required, to serious conditions that can cause significant or permanent harm if not effectively treated.

“For example, pregnancy is associated with common and mild abnormalities such as morning sickness and leg edema that cause no permanent harm if left untreated, as well as with such serious conditions as hyperemesis gravidarum, toxemia of pregnancy, and acute psychosis of pregnancy, which can be life-threatening if not effectively treated. The menstrual cycle is commonly associated with mild mood changes, edema, and cramping that do not cause significant or permanent harm if left untreated, but also, more rarely, with serious cyclical depression that can result in significant harm if not effectively treated. Aging is almost invariably associated with characteristic skin and scalp changes, such as wrinkles and hair loss, which do not need medical attention. It is also, however, associated with serious diseases that will result in significant, often irreversible damage, many of which can be effectively treated. These diseases include osteoporosis, glaucoma, and arteriosclerotic diseases of coronary, cerebral, and peripheral vessels. Adolescence is commonly associated with mild acne, which does not cause significant or permanent harm if not treated, and, rarely, with cystic acne, which can produce severe physical and psychological scars if not effectively treated.” (65 *Federal Register* at 1020)

On March 22, 2000, CHPA members adopted a voluntary pregnancy/nursing labeling program for dietary supplements (see Attachment A for full program). This program is based on the approach taken by FDA in 1982 for self-care products intended for use as drugs (i.e., OTC medicines), which is explained below in Section 4, and on the fact that the large majority of CHPA members already voluntarily comply with CHPA’s program. CHPA requests that FDA use the Association’s voluntary program as a basis for creating a regulatory framework for pregnancy/nursing label statements for dietary supplements.

- 2. Pregnancy/nursing are unique natural states when considering both fetal and maternal vulnerability to exogenous agents as well as a regulatory approach that is based on a relative lack of data.**

FDA’s proposed and final rule on structure/function claims identified aging, menopause, pregnancy, and the menstrual cycle as natural states, and CHPA agrees. These are conditions with bothersome symptoms, which do not fall within the definition

of disease used by FDA in the final rule on structure/function claims and for which consumers need, and should have, widely available self-care products including dietary supplements. CHPA has submitted detailed comments to the agency on August 4, 1999.³

FDA's final rule on structure/function claims states in the preamble: "Common conditions associated with natural states or processes that do not cause significant or permanent harm will not be treated as diseases under the final rule." Again, CHPA concurs, in general. However, in this regard, FDA cites certain symptoms associated with pregnancy, and it is here that CHPA takes exception.

While pregnancy and nursing are natural states, or life stages, they are characterized by unique vulnerabilities not seen in other natural states. For both, pregnancy and the early postpartum period are times of high cell division and rapid tissue growth accompanied by unique energy demands. As a result, it is not surprising that both pregnant women and unborn children have been identified as especially vulnerable to nutrient inadequacies and the unborn child to developmental abnormalities induced by exogenous agents, including medicines and other potential toxins. The potential for irreparable harm to the fetus due to placental exposure to exogenous agents is unlike any other natural life stage, and the potential deleterious results can be, for a lifetime, literally life-altering, if not fatal.

CHPA's position that pregnancy and nursing a baby are unique among natural states was supported March 30, 2000, at the public meeting on the issue of structure/function claims for pregnancy (see transcript of meeting).

Pregnancy and nursing a baby are also unique as regulatory issues. First, it is important to recall in any potential safety or efficacy issue that FDA has a long-standing policy that label statements must be "scientifically documented, clinically significant, and important to the safe and effective use of the product by the consumer" [e.g., Final Rule Regarding Label Warning for Pregnant or Nursing Women; Delegations of Authority and Organization. 47 *Federal Register* 54750-58 (12/3/82)]. This policy has stood up very well as a

³ See CHPA's comments to Docket No. 98N-0044: Public Meeting on Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body.

framework for working through public health issues relating to the labeling of self-care products. It is a three part standard, with credible scientific documentation as the first hurdle. Without adequate scientific documentation there is no need to determine whether the effect under scrutiny has clinical significance, let alone importance to the consumer use situation. (See also: Soller, R.W.: "When to Warn." *Regulatory Affairs Focus*: Vol. 2, Issue 10, Oct. 1997.)

Second, unlike an ingredient-specific safety issue that is scientifically documented, the consideration of pregnancy/nursing claims is a unique situation relative to FDA's long-standing policy, since the potential safety issues associated with specific dietary supplement use in pregnancy are not uniformly scientifically documented. While a number of self-care products, such as prenatal dietary supplements, have good safety profiles for use in pregnancy, there are also a number of these self-care products for which the scientific documentation for use in pregnancy/nursing may not yet be fully developed. Hence, any approach to address this issue through labeling is based on the presence of safety information on some dietary supplements, but also – uniquely – on an absence of scientific documentation on many more dietary supplements, particularly botanical products.

In summary, pregnancy and nursing a baby are unique in relation to the issue at hand. Both FDA and industry typically make label decisions based on scientific data and their adequate documentation. Yet in this case, there is relatively little published documentation across the many dietary supplement products, and there is a particularly vulnerable population under consideration – the fetus. This situation should be viewed in accord with the December 3, 1982 Final Rule on pregnancy/nursing statements for OTC drug products, i.e., as unique, and out of an abundance of caution -- not because of a conclusive showing of adverse effects. CHPA would therefore expect that, in other situations involving possible labeling changes to dietary supplement ingredients, FDA's longstanding labeling policy would remain intact.

3. The pregnancy/nursing label statement for certain OTC drugs is a model for regulatory action.

The general pregnancy/nursing label statement adopted for OTC drugs intended for systemic absorption is:

“As with any drug, if you are pregnant or nursing, seek the advice of a healthcare professional before using this product.”

In the 1982 Proposed Rule regarding pregnancy/nursing label statements on OTC drug products, FDA set forth the position that the fetus is especially susceptible to harm from exogenous agents and that only a small number of drugs have been shown conclusively to have adverse effects on the developing fetus or newborn.

“FDA believes that it is in the interest of the public health to require OTC drugs to bear a warning against use by pregnant or nursing women in the absence of professional advice. Drugs taken by pregnant women pose the risk that they may affect the growth and development of the human fetus. Drugs taken by nursing women may be transferred by the mother's milk to the newborn child for whom they are not intended, and at this stage in a child's life its enzyme system is not fully mature and its kidney function not fully developed so that it is easy for toxic levels of drugs to accumulate in its body (Ref. 1). Although only a small number of drugs have been conclusively shown to have adverse effects on the developing human fetus or newborn, information of this type is inadequate to establish safety for most drugs (Refs. 2 through 7). There is evidence, however, that the developing human organism is most susceptible to the effects of teratogenic drugs or other agents from about 2 weeks to 8 weeks after fertilization when the major organ systems are developing (Refs. 3, 5, 7, and 8). Exposure of the fetus to toxic agents after the embryo stage (i.e., after the basic structures of the organ systems have developed), while not likely to cause major anatomical abnormalities, may result in reductions in cell size or number, or alterations in functional capacity (Refs. 3, 5, and 8). The central nervous system appears to be especially susceptible to changes in functional capacity during the last trimester of pregnancy when the rate of brain growth is normally rapid.”

“...The requirement for a general warning is supported by the need to inform pregnant or nursing women of the advisability of minimizing exposure of the fetus or newborn child to drugs, since a drug taken during pregnancy or while nursing may pose some risk. Because this proposed general warning is based on a lack of data demonstrating that OTC drugs are safe for use by pregnant or nursing women, rather than on data demonstrating that the specific product is unsafe, the proposed warning

begins with the phrase "as with any drug." This phrase makes it clear that the general warning applies to all drugs and will help to enhance the effect of those specific warnings that represent demonstrated risks of particular drugs.

[Proposed Rule Regarding Label Warning for Pregnant or Nursing Women for Over-the-Counter Drugs Which Are Generally Recognized as Safe and Effective and Not Misbranded (47 *Federal Register*: 39470, 1982) (emphasis supplied)]

However, FDA's regulatory approach to dealing with the unique issue of a relative lack of data pertaining to OTC drug toxicity in pregnancy/nursing was not an across-the-board warning against use in pregnancy. Some OTC drugs can logically be used by pregnant women with a high degree of confidence since they pose no safety problem (e.g., topical OTC drugs), while for others there would not be the same general level of confidence (e.g., OTCs intended for systemic absorption). Further, as FDA noted in the proposed rule for OTC pregnancy/nursing label statements, "the advisory review panels gave particular consideration to evidence of teratogenicity in evaluating the safety of ingredients ...[and]...[F]or ingredients for which there were data to suggest a potential hazard, the panels recommended specific pregnancy warnings" (47 *Federal Register* at 39470). For example, a pregnancy warning for aspirin use in the last 3 months of pregnancy was recommended by the OTC Panel and eventually adopted by FDA [21CFR Sec. 201.63(e)]. Finally, FDA also exempted those drugs intended to benefit the consumer, stating:

"The regulation has also been revised to exempt from the warning requirement drugs intended to benefit the fetus or nursing infant during the period of pregnancy or nursing (Sec. 201.63(c)(1)). The agency finds this to be a reasonable exemption because such drugs would have been evaluated specifically for their effects on the fetus or infant and demonstrated to be beneficial. Drugs labeled exclusively for pediatric use are also exempted (Sec. 201.63(c)(2)) because pregnant or nursing women would not be taking such products." (47 *Federal Register* at 54752; emphasis supplied)

Thus, FDA adopted a general warning for OTC drug products intended for systemic absorption, creating exemption categories for those not intended for systemic absorption and for those intended to benefit the pregnant woman and fetus, while allowing the general warning to be superseded by a specific one where information on the extent of

the risk is available. In support of this regulatory structure, FDA stated that it “considers that the inclusion of a specific warning instead of a general warning will serve to identify those products for which there are data suggesting a particular risk in pregnant or nursing women” (47 *Federal Register* at 39471). Thus, FDA handled the unique situation for OTC medicines, where scientific documentation of a problem was, for the most part lacking, but not dispositive of safety.

In conclusion, OTC medicines and dietary supplements are self-care products used under conditions of widespread availability where pregnant and nursing women, nonetheless, have access to healthcare professionals for advice. As such, the framework for pregnancy/nursing label statements on OTC medicines serves as a model for addressing the similarly unique issue of dietary supplement use in pregnancy or when nursing. CHPA’s existing voluntary program and this petition build on this framework.

4. CHPA requests that FDA adopt a final rule for pregnancy/nursing label statements for dietary supplements.

CHPA asks FDA to issue a regulation that would require label statements on certain dietary supplements pertaining to their use in pregnancy and/or when nursing a baby.

This regulation would have the following three categorical elements:

- Label Statement for Dietary Supplements Contraindicated in Pregnancy: “Do not use if you are pregnant or nursing a baby.”
- Label Statement for Dietary Supplements Not Contraindicated in Pregnancy and Not Covered by the Permitted Exemptions: “If pregnant or nursing a baby, ask a healthcare professional.”
- Permitted Exemptions for Dietary Supplements that May Be Used in Pregnancy and Marketed Without the Label Statement.

As part of the creation of this categorical regulatory structure, CHPA also asks FDA to create a list of recognized compendia, including for example the Commission E monographs, the WHO monographs on dietary supplements, and possibly others, as a basis for facilitating the requested categorizations.

This categorical regulatory structure is consistent with the principles set forth in past FDA rulings for labeling self-care products (i.e., OTC drugs, see section 3 above), incorporates the CHPA voluntary labeling program for dietary supplements adopted on March 22, 2000, by the Association (see Attachment A), and addresses the need for pregnant/nursing women to have appropriate information through label statements, including when not to use a dietary supplement or when to consult a healthcare professional, as appropriate to the knowledge-base available on the particular dietary constituent. Specific commentary on each of these three elements follows.

**4.a. Label Statement for Dietary Supplements Contraindicated in Pregnancy:
“Do not use if you are pregnant or nursing a baby.”**

CHPA recommends that a category of dietary supplements be established which would bear the label, “Do not use if you are pregnant or nursing a baby.”

This category would be established using the following criteria:

- The dietary supplement, or constituents in the supplement product, have been identified as contraindicated in pregnancy and/or nursing by a recognized compendium that utilizes an advisory committee process for a thorough scientific review of the constituent’s safety in pregnancy and/or nursing. Such compendia include, for example, the German Commission E monographs, the WHO monographs, etc.
- The dietary supplement, or constituents in the dietary supplement product, has been identified as contraindicated in pregnancy and/or nursing by one or more well-designed, well-controlled, competent studies that have been evaluated by the Food and Drug Administration.

If either of these criteria are met, FDA would use a formal comment-and-review rulemaking process to potentially place the qualifying dietary supplement into a category of ingredients that would be required to be labeled with the statement: “Do not use if you are pregnant or nursing a baby.”

Dietary supplements intended for consumer use that fall within this category would include, for example, those identified in the Commission E Monograph. These appear below as a list of herbs contraindicated in pregnancy in the Commission E Monographs as translated and published by The American Botanical Council [Ed., M.

Blumenthal et al., *Integrative Medicine Communications*, page 441, Boston, MA, 1998 (ISBN 0-9655555-0-X)].

1. Aloe (Aloe barbadensis, Aloe capensis)
2. Autumn crocus (Colchicum autumnale)
3. Black Cohosh root (Cimicifugae racemosae rhizoma)⁴
4. Buckthorn bark (Frangulae cortex)
5. Buckthorn berry (Rhamni cathartici fructus)
6. Cascara Sagrada bark (Rhamni purshianae cortex)
7. Chaste Tree Fruit (Agni casti fructus)
8. Cinchona bark (Cinchonae cortex)
9. Cinnamon bark (Cinnamomi ceylanici cortex)
10. Coltsfoot leaf (Farfarae folium)
11. Comfrey herb and leaf (Symphyti herba/ -folium)
12. Comfrey root (Symphyti radix)
13. Echinacea Purpurea herb (injectable) (Echinacea purpureae herba)
14. F.C. of Angelica root, Gentian root and Fennel seed
15. F.C. of Anise oil, Fennel oil, and Caraway oil
16. F.C. of Anise oil, Fennel oil, Licorice root, and Thyme
17. F.C. of Anise seed, Fennel seed, and Caraway seed
18. F.C. of Anise seed, Ivy leaf, Fennel seed, and Licorice root
19. F.C. of Anise seed, Marshmallow root, Eucalyptus oil, and Licorice root (above 100 mg glycyrrhizin)
20. F.C. of Anise seed, Marshmallow root, Iceland Moos, and Licorice root (above 100 mg glycyrrhizin)
21. F.C. of Caraway oil and Fennel oil
22. F.C. of Caraway oil, Fennel oil, and Chamomile flower
23. F.C. of Caraway seed and Fennel seed
24. F.C. of Caraway seed, Fennel seed, and Chamomile flower
25. F.C. of Ivy leaf, Licorice root, and Thyme (above 100 mg glycyrrhizin)
26. F.C. of Licorice root, Peppermint leaf, and German Chamomile flower
27. F.C. of Licorice root, Primrose root, Marshmallow root, and Anise seed
28. F.C. of Marshmallow root, Fennel seed, Iceland Moss, and Thyme
29. F.C. of Marshmallow root, Primrose root, Licorice root, and Thyme oil (above 100 mg glycyrrhizin)
30. F.C. of Peppermint leaf and Fennel seed
31. F.C. of Peppermint leaf, Caraway seed, and Fennel seed
32. F.C. of Peppermint leaf, Caraway seed, Fennel seed, and Chamomile flower
33. F.C. of Peppermint leaf, Fennel seed, and Chamomile flower
34. F.C. of Peppermint oil and Fennel oil
35. F.C. of Peppermint oil, Caraway oil, and Fennel oil
36. F.C. of Peppermint oil, Caraway oil, Fennel oil, and Chamomile flower
37. F.C. of Peppermint oil, Fennel oil, and Chamomile flower
38. F.C. of Senna leaf, Peppermint oil, and Caraway oil
39. Fennel oil (Foeniculi aetheroleum)
40. Fennel seed (Foeniculi fructus)
41. Ginger root (Zingiberus rhizoma)
42. Indian snakeroot (Rauwolfiae radix)
43. Juniper berry (Juniperi fructus)
44. Kava kava (Piperis methystici rhizoma)
45. Licorice root (Liquiritiae radix)
46. Mayapple root and resin (Podophylli peltati rhizoma/ -resina)
47. Parsley herb and root (Petroselinii herba/ radix)⁵
48. Petasites root (Petasitidis rhizoma)⁶
49. Rhubarb root (Rhei radix)
50. Sage leaf (salviae folium)
51. Senna leaf (Sennae folium)
52. Uva Ursi leaf (Uvae ursi folium)

⁴ Not listed under contraindications in Commission E monograph, but identified as having estrogen-like action.

⁵ Daily dose of 6 g of the prepared constituent

⁶ Not listed in the contraindications list on page 441 of the translated Commission E monographs

4.b. Label statement for dietary supplements not contraindicated in pregnancy and not covered by the permitted exemptions: "If you are pregnant or nursing a baby, ask a healthcare professional."

CHPA recommends that a category of dietary supplements be established which would bear the label, "If you are pregnant or nursing a baby, ask a healthcare professional." This category would be established using the following criterion:

- If there are insufficient data or information to support the safe use of the dietary supplement in pregnancy or when nursing a baby without professional supervision, then the dietary supplement would bear the label statement: "If you are pregnant or nursing a baby, ask a healthcare professional."

Under certain circumstances, a healthcare professional may recommend certain dietary supplements, for example, at low infrequent doses for conditions that are experienced during pregnancy or when nursing a baby and that may or may not be related to pregnancy or nursing per se.

In general for oral medications, conventional medical wisdom is that "a pregnant woman shouldn't take any medication, even an over-the-counter one, unless she checks with her doctor first...If possible, she should avoid taking drugs in the first trimester or taking more than one medication at a time...She can also ask for the lowest dose possible to treat her condition."⁷ Such conservative recommendations are appropriate for many dietary supplements as well, although for vitamin/mineral supplements with recommended daily intakes (RDI's), for example, there is general recognition that such supplementation is helpful and conservative recommendations against use are not appropriate.⁷

In relation to women nursing a baby, FDA's current public statement about the use of drugs during nursing is relevant, considering the fact that, although most dietary supplements like most medications have not been tested in nursing women, there have been very few reports of problems with either class of self-care products.

⁷ A daily vitamin supplement, while not an adequate substitute for a healthy diet, helps fill in the gaps on days when a woman's diet is less than perfect." Williams, R. *Healthy Pregnancy*. Health Baby. *FDA Consumer*, March-April, 1999.

Under a healthcare professional's supervision, the advice for moderation and only when necessary, given the history of safe use of these products, is appropriate.⁸

Dietary supplements identified in certain compendia as contraindicated in pregnancy/nursing except under the supervision of a healthcare professional would be included in this category, as well as other dietary supplements that meet the recommended criterion for this category. Dietary supplements that are included in section 4.a. (i.e., where there is an absolute contraindication against use in pregnancy or when nursing a baby) or are included in section 4.c. (permitted exemptions) would not be included in this category.

4.c. Permitted Exemptions for Dietary Supplements that May Be Marketed Without the Label Statement

CHPA recommends that FDA establish the following categories of dietary supplements as exempt from the labeling requirements in 4.a. and 4.b.:

Exemptions:

- (1.) Dietary supplements with recognized nutrient value that have adult recommended daily intake values (RDIs) and are labeled at or below the RDI, subject to 3. below;
- (2.) Dietary supplements with recognized nutrient values which are intended for prenatal use and/or for use during nursing and which contain only vitamins and minerals with RDIs at levels safe for these intended uses;
- (3.) Dietary supplements that may be used during pregnancy and/or by nursing mothers based on recognized compendia and/or based on determinations or pending recommendations of other authoritative bodies such as the National Academy of Sciences and United States Pharmacopeia or others and/or based on company-generated research, or information, etc.;
- (4.) Dietary supplements that are labeled exclusively for pediatric use.
- (5.) Dietary supplements that are labeled exclusively for postmenopausal women;
- (6.) Dietary supplements that are labeled exclusively for use by men.

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"Medicines and Nursing Mothers: "Most medications have not been tested in nursing women, so no one knows exactly how a given drug will affect a breast-fed child. Since very few problems have been reported, however, most over-the-counter and prescription drugs, taken in moderation and only when necessary, are considered safe." Food and Drug Administration: Breast-feeding Best for Babies. *FDA Consumer* October 1995.

These exemptions are part of the existing CHPA voluntary pregnancy/nursing labeling program (Attachment A). In developing these exemptions, CHPA considered:

- The division of the dietary supplement category into vitamin/mineral products and botanical and other products;
- The accepted safety of many vitamins and minerals based in part on their known nutritive value and use/presence in the general daily diet;
- The intended uses of some dietary supplements for target consumer populations not likely to become pregnant or breast feed.

Specifically on the matter of exemptions under 4.c.(1) and 4.c.(2.) which reference supplements with RDIs, the recommended daily allowances of the vitamins and minerals established by the Food and Nutrition Board of the National Academy of Sciences and adopted by FDA as recommended daily intakes (RDI's) are based on considerations of safety and health maintenance. Where the values may be higher for pregnant and nursing women (e.g., as in the case of folate), the benefits in the context of optimizing a healthy pregnancy have been considered in developing the recommended values. Dietary supplement products containing vitamins and minerals labeled at or below the RDI's for the general population or for the sub-population of women who are pregnant or nursing would therefore not be expected to pose any potential harm to the fetus or mother. Indeed, the consumption of an adequate diet, that would be ensured by dietary supplements with RDI's, is to be encouraged. Having a label statement that advises a woman to consult a healthcare professional for the use of these products could deter such use and be contrary to the advocacy of public health messages encouraging such use⁹. Indeed, FDA recommends supplementation for certain vitamins/minerals such as folate, calcium and iron (see

⁹ FDA: Healthy Pregnancy, Healthy Baby. *FDA Consumer* March-April 1999
Health and Human Services: Folic Acid to Fortify U.S. Food Products to prevent Birth Defects. HHS News Release, February 29, 1996.
FDA: How Folate Can Prevent Birth Defects. *FDA Consumer* Revised February 1999.
FDA: All About Eating for Two. *FDA Consumer* April 1990.
FDA: Perplexities of Pregnancy. *FDA Consumer* November 1990.

footnote 2).¹⁰ Examples of dietary supplements that might fall into these categories are: fat soluble vitamins A, D, E, K; water soluble vitamins C, thiamine, riboflavin, niacin, B6, folate, and B12; and the minerals -- calcium, phosphorus, magnesium, iron, zinc, iodine, selenium; among others. Finally, as a matter of prior regulatory action on pregnancy/nursing label statements for OTC medicines, FDA specifically exempted OTC drugs intended to benefit the fetus or nursing infant (47 *Federal Register*: 54752, 1982).

In relation to the exemption under 4.c.(3.), CHPA recommends that FDA create an exemption for those products with evidence pertaining to the safe use of the product for pregnant and nursing women. Recognized compendial evaluations or statements from an authoritative body (e.g., the National Academy of Sciences Food and Nutrition Board, United States Pharmacopeia, etc.), as well as company-compiled research and information on the safe use of such products in pregnancy, should be permitted as a basis for the use of dietary supplements in this category. Such products would be permitted to make structure/function and/or health claims as appropriate for conditions associated with pregnancy. These products would also be able to make claims unrelated to pregnancy/nursing without a pregnancy/nursing label statement if a safety-evidence base exists per 4.c.3. In addition, CHPA asks FDA to issue a guidance on this matter (see Section 5. below).

With respect to the exemptions listed under 4.c.(4.), 4.c.(5.), and 4.c.(6.), there are certain dietary supplements that are not intended for use by pregnant or nursing women, such as dietary supplements labeled specifically for use by young children (e.g., pediatric liquid vitamins), or for postmenopausal women (e.g., calcium supplements), or for men (e.g., products for helping to ensure a healthy prostate gland). A pregnancy/nursing label statement is not needed for such products, which should be exempted from a final regulation.

As a final note, FDA created exemptions under the OTC rulemaking for pregnancy/nursing statements for nonprescription medicines. The broadest of these

¹⁰ See footnote 2 at FDA: Healthy Pregnancy, Healthy Baby. *FDA Consumer* March-April, 1999.

exemptions pertains to drugs that are not intended for systemic absorption. A second exemption was specific to a target population – OTC medicines intended for use in pediatric populations (*47 Federal Register: 54752, 1982*). Hence, the framework requested under this petition, which includes categories of exemptions, is consistent with regulatory policy previously established for another self-care product category, OTC medicines.

5. Evidence Needed to Support Dietary Supplement Use in Pregnancy and When Nursing a Baby

FDA has rightly defined natural states as suitable for structure/function claims for dietary supplements (see also above, Section B.2.).¹¹ CHPA maintains in this petition that pregnancy and nursing a baby are unique among natural states in the context of the special vulnerability that exists for mother and fetus and in the context of the relative lack of scientific information supporting use of self-care products (i.e., dietary supplements as well as OTC medicines) in pregnancy and nursing. However, this is not a reason to prohibit companies from developing evidence in support of the safe and beneficial use of dietary supplements for minor conditions associated with either pregnancy or nursing a baby. Indeed, CHPA urges FDA to support a framework through a guidance that would permit structure/function claims for dietary supplements intended for use by pregnant and nursing women.

Requested Action: CHPA asks that FDA issue a guidance on the scientific basis for assessing the potential for possible effects of dietary supplements on reproduction/development and the scope and nature of safety-related evidence that is needed to support a structure/function claim for conditions associated with pregnancy and nursing, principally where developed by company-generated research or information. Government determinations or reports of authoritative bodies such as the NAS or FASEB would have independent status and should not be re-reviewed by the FDA.

¹¹ See also: Food and Drug Administration: Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body; Final Rule [65 F.R 999-1000 (1/6/2000)].

CHPA recognizes that there has been considerable activity under the International Conference on Harmonization (ICH) in developing international guidance on the use of reproductive/developmental toxicity studies as a basis for assessing the safety of drug products for use in pregnancy and/or when nursing a baby. CHPA recommends that FDA draw on these guidelines to establish through public comment a specific guidance in this area for the dietary supplement industry. The guidance should address the scientific basis for assessing the potential for possible effects on reproduction/ development. It should also address the scope and nature of evidence that would be required to establish the safe use without professional supervision of: (a.) new dietary supplements marketed after the passage of the Dietary Supplement Health Education Act (DSHEA) in 1994; and (b.) dietary supplements marketed pre-DSHEA which fall within section 4.b. of this petition (i.e., contraindicated unless a healthcare professional has been consulted) and for which companies or other interested parties may seek to petition to remove the label statement, "If you are pregnant or nursing, ask a healthcare professional."

As stated earlier in this petition, CHPA believes that the issue of the unborn child is so unique from both toxicological and regulatory standpoints that CHPA's request for a guidance that would suggest the type of safety-related evidence needed to support a structure/function claim in pregnancy/nursing should not be construed, considered or otherwise acted upon through regulation as a basis to challenge or change the basic framework for evidence for other structure/function claims, as permitted under DSHEA.

6. Amendment of the final rule to prohibit structure/function claims related to edema associated with pregnancy.

Requested Action: CHPA asks that FDA amend its final regulation to prohibit structure/function claims for foods concerning edema associated with pregnancy, by adding a new subsection (3) under Section 101.93 (g) of the final rule stating that such claims are prohibited.

It is generally recognized that preeclampsia (toxemia of pregnancy) is a serious condition warranting medical supervision. Preeclampsia can result in premature delivery and can develop into eclampsia, which itself is even a more significant complication of

pregnancy that carries high maternal mortality and morbidity rates¹². The symptoms of preeclampsia include excessive swelling of the hands or feet (e.g., see American Academy of Family Physicians¹³), although swelling alone does not necessarily mean a woman has preeclampsia. Some swelling is normal during pregnancy. For example, rings or shoes might become too tight. However, a review of the conditions/symptoms associated with of preeclampsia (i.e., toxemia of pregnancy, which FDA identifies as a disease in the Final Rule on structure/function claims) points to the seriousness with which edema associated with pregnancy should be considered in the context of potential dietary supplement structure/function claims, as well as to the uniqueness of pregnancy as a natural state (described above in Section 2 of this petition). As stated by Mayo Health:

“Preeclampsia is a disease characterized by high blood pressure, swelling of the face and hands, and protein in the urine after the 20th week of pregnancy. It is a potentially serious condition that, if left untreated, can lead to complications or death in the mother or the baby. ... Because its cause is not known, there is no specific treatment for preeclampsia, nor is it known how to prevent it. The only sure way to end the preeclampsia is to deliver the baby, sometimes despite the fact that the baby may be premature.

“Premature delivery may be necessary because of the serious risks posed by preeclampsia to the mother and the baby. Possible problems for the mother include liver damage, kidney damage, bleeding problems, or seizures. Problems for the baby include not getting enough oxygen or nutrients from the placenta. This problem can lead to growth retardation or fetal distress.

“Preeclampsia is a relatively common disorder, affecting 6 to 8 percent of all pregnancies. Eighty-five percent of all cases occur in the first pregnancy.

“In some women, the first sign of preeclampsia may be a sudden weight gain — more than 2 pounds (about 1 kilogram) in a week or 6 pounds (about 2 3/4 kilograms) in a month. This weight gain is due to the abnormal retention of fluids, rather than the accumulation of fat. Swelling of the face and hands, headaches, vision problems, and pain in the upper abdomen may also occur.”

¹² E.g: Mattar, F., and B. Sibai : Eclampsia; Risk factors for maternal mortality. *Am. J. Obstet. Gynecol.* Feb;182(2):307-12, 2000; Obed S.A. et al.: Eclampsia: 134 consecutive cases. *Int. J. Gynaecol.* 45(2): 97-103, 1994.

¹³ See: <http://obgyn.about.com/health/obgyn/msub11.htm>.

["Your Pregnancy: Third Trimester: Complications: Mayo Health O@sis,
2000. Linked to About.com: Obstetrics/Gynecology.]

Hence, CHPA believes that, in the interest of maternal and fetal health, edema associated with pregnancy, which may be experienced in part as swelling, should not be a condition for which structure/function claims should be permitted, unless a manufacturer can specifically show FDA that its products are safe and beneficial for use for that purpose.

C. Environmental impact

CHPA does not believe under 21 CFR 25.30 that the requested actions individually or cumulatively have a significant effect on the human environment. Therefore, CHPA believes that neither an environmental assessment nor an environmental impact statement is required.

D. Lack of Economic Impact and Compliance Date

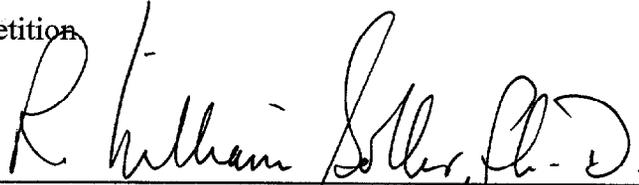
Although FDA specifies that specific economic information is to be submitted only when requested by the Commissioner following review of the petition, CHPA points out that the majority of CHPA members already comply with the CHPA voluntary pregnancy/nursing labeling program.

In addition, the CHPA voluntary program has a compliance date of April 2, 2001, for its dietary supplement member companies. The compliance date is approximately one year after the formal adoption of the voluntary program, which was on March 22, 2000. The approximate one-year compliance date is consistent with the one-year compliance date stipulated in the final rule pertaining to the OTC pregnancy/nursing label statement (47 *Federal Register*: 54750-58, 1982).

Action requested: CHPA requests that the compliance date for a final regulation on the pregnancy/nursing labeling program be one year from the publication of the final rule in the *Federal Register* based on date of manufacture.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



R. William Soller, Ph.D.

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TEL: 202-429-9260
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Attachment A CHPA Voluntary Pregnancy/Nursing labeling Program
Adopted March 22, 2000.



*Producers of Quality
Nonprescription Medicines and
Dietary Supplements for Self-Care*

A

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

Voluntary Labeling Program for Dietary Supplements *Formerly Nonprescription Drug Manufacturers Association* Proposed Pregnancy/Nursing Label Statement

Members of the Consumer Healthcare Products Association (CHPA)¹ which market dietary supplements formally initiated a voluntary labeling program on March 22, 2000 which relates to the use of the following label statement on dietary supplement products:

If you are pregnant or nursing a baby, ask a health professional.

This statement (or its reasonably substantial equivalent; see 2.b.), when included in the labeling of dietary supplement products defined by the voluntary program, will be prominent and conspicuous and may appear in one of a number of alternative forms which convey essentially the same information intended by the label statement cited above (see below re: Alternative Statements). Certain dietary supplements logically do not need such a label statement because, for example, their intended uses are not for women of child-bearing age, or because they have recognized uses for women of child-bearing age (e.g., prenatal vitamins and minerals) or have data to support the use of the product by women who are pregnant and/or nursing a baby. Types of products that fall in these categories are listed below under "Exemptions."

The implementation time for this program is at the next label printing, but no later than April 2, 2001.

1. **Voluntary Pregnancy/Nursing Statement:** If you are pregnant or nursing a baby, ask a health professional.
2. **Provisions:** The following provisions apply to the voluntary use of this label information statement by CHPA members marketing dietary supplements:
 - a. **Scope:** This label information statement is intended for use on dietary supplements defined by the Dietary Supplement Health and Education Act (DSHEA), with certain exemptions:
 - (1.) **DSHEA Definition of Dietary Supplements:** "a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients."
 - (2.) **Exemptions:**
 - (a.) Dietary supplements with recognized nutrient value that have adult recommended daily intake values (RDIs) and are labeled at or below the RDI, subject to 2.c. below;

¹ CHPA, founded in 1881, represents manufacturers and distributors of dietary supplements. CHPA has over 200 members across the manufacturing, distributing, supply, research testing and advertising sectors of the self-care industry.

- (b.) Dietary supplements with recognized nutrient values which are intended for prenatal use and/or for use during nursing and which solely contain vitamins and minerals with RDIs at levels safe for these intended uses;
- (c.) Dietary supplements that may be used during pregnancy and/or by nursing mothers based on recognized compendia and/or based on determinations or pending recommendations of other authoritative bodies such as the National Academy of Sciences and United States Pharmacopeia or others and/or based on company-generated research, or information, etc.;
- (d.) Dietary supplements that are labeled exclusively for pediatric use;
- (e.) Dietary supplements that are labeled exclusively for postmenopausal women;
- (f.) Dietary supplements that are labeled exclusively for use by men.

(3.) **Stay of Use of Structure/Function Claims for Certain Conditions Associated with Pregnancy:** Under this voluntary program, member companies would not make claims relating to edema associated with pregnancy.

b. **Alternate Statements:** As with other CHPA voluntary label statements, this proposed pregnancy/nursing statement may be used in reasonably substantially equivalent wording, such as:

- consult (or, *ask*; or *contact*)² a (or, *your*) doctor (or, *health professional*; or, *health practitioner*) if you are pregnant or nursing (or, *breast feeding*) a baby;
- before using (or, *before using this product*) consult (or, *ask*; or *contact*) a (or, *your*) doctor (or, *health professional*; or, *health care practitioner*) if you are pregnant or nursing a baby (or, *lactating*; or, *breast feeding*);
- ask (or, *consult*; or *contact*) a (or, *your*) doctor (or, *health professional*; or, *health care practitioner*; or, *doctor or other health professional*) before using (or, *before using this product*) if you are pregnant or nursing a baby;
- if you are pregnant or nursing a baby, ask (or, *consult*; or, *contact*) a (or, *your*) doctor (or, *health professional*; or *doctor or other health professional*; or, *health care practitioner*);
- not for use during pregnancy and lactation, unless directed by a health care practitioner (or, *doctor*; or, *doctor or other health professional*);
- Or other substantially equivalent statements.

c. **Combination of the Voluntary Pregnancy/Nursing Label Statement with Other Similar Voluntary Label Statements:** The voluntary pregnancy/nursing label statement may be combined with other voluntary labeling statements provided the combined language creates a logical construct (e.g., If you are taking a prescription medicine, or, if you are pregnant or nursing a baby, ask a doctor).

d. **Implementation Date:** At the next label printing, but not later than April 2, 2001.

² Words in italics represent examples of reasonably equivalent wording, and are not to be considered inclusive of all possible reasonably equivalent statements.



*Producers of Quality
Nonprescription Medicines and
Dietary Supplements for Self-Care*

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

Formerly Nonprescription Drug Manufacturers Association

May 11, 2000

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 98N-0044

To Whom It May Concern:

Enclosed please find an original and two copies of CHPA Citizen Petition to Docket 98N-0044.

Jkq/s

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4b Express Freight Service

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* Call for Confirmation.

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