

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 101**

[Docket No. 91N-100H]

RIN 0910-AA19

**Food Labeling: Health Claims and Label Statements; Folate and Neural Tube Defects**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is authorizing the use on the labels and in the labeling of food, including dietary supplements, of health claims on the association between adequate intake of folate and the risk of neural tube birth defects. This rule is issued in response to provisions of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) that bear on health claims. The agency has concluded that, based on the totality of the publicly available scientific evidence, there is significant scientific agreement among qualified experts that, among women of childbearing age in the general U.S. population, maintaining adequate folate intakes, particularly during the periconceptional interval, may reduce the risk of a neural tube birth defect-affected pregnancy.

**EFFECTIVE DATE:** April 19, 1996.

**FOR FURTHER INFORMATION CONTACT:** Jeanne I. Rader, Office of Food Labeling (HFS-175), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-205-5375.

**SUPPLEMENTARY INFORMATION:**

I. Background

A. *Procedural History*

1. The 1990 Amendments

The 1990 amendments to the Federal Food, Drug, and Cosmetic Act (the act) provided for extensive changes in the way foods are labeled. Under these amendments, FDA can authorize the use, in the labeling of foods, of health claims that characterize the relationship of a nutrient to a disease or a health-related condition. Section 403(r)(1)(B) of the act (21 U.S.C. 343(r)(1)(B)) provides that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or a health-related condition unless the claim is made in accordance with procedures and standards established under section 403(r)(3) and (r)(5)(D) of

the act. The 1990 amendments required that FDA evaluate 10 nutrient/disease relationships with respect to their appropriateness as the subjects of health claims. The topic of folic acid and neural tube defects was among those 10 topics.

In the Federal Register of November 27, 1991 (56 FR 60537), in conformity with the requirements of the 1990 amendments, the agency proposed to establish general principles that would govern the appropriateness and validity of health claims on dietary supplements as well as on foods in conventional food form. The agency also proposed to authorize four health claims and to not authorize six others, including a claim on folate and neural tube defects.

2. The Dietary Supplement Act of 1992 (DS Act)

In October of 1992, the Dietary Supplement Act (DS Act; Title II of Pub. L. 102-571) was enacted. It imposed a moratorium until December 15, 1993, on FDA implementation of the 1990 amendments with respect to dietary supplements. The DS Act directed FDA to issue proposed rules to implement the 1990 amendments with respect to dietary supplements by June 15, 1993, and to issue final rules based on these proposals by December 31, 1993.

The DS Act also amended the so-called "hammer" provision of the 1990 amendments to provide that, if the agency did not meet the established December 31, 1993, timeframe for issuance of final rules, the proposed regulations would be considered final regulations.

Accordingly, when FDA issued its final rules on health claims in the Federal Register of January 6, 1993 (58 FR 2478), they did not cover dietary supplements.

3. The 1993 Final Rules

On January 6, 1993, FDA published its final rules on general principles for health claims (58 FR 2478) and the 10 nutrient disease-relationships (58 FR 2537 through 2849). The general principles regulation provides that FDA will issue regulations authorizing health claims only when it determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner that is consistent with generally recognized scientific procedures and principles) that there is significant agreement, among experts qualified by training or experience to evaluate such claims, that the claim is supported by the scientific evidence.

On January 6, 1993, the agency also issued regulations announcing its

decisions with respect to conventional foods for each of the 10 nutrient-disease relationships that the 1990 amendments directed it to consider. The agency authorized claims on all foods, including dietary supplements, on seven nutrient-disease relationships: Calcium and osteoporosis; sodium and hypertension; fat and cancer; saturated fat and cholesterol and coronary heart disease (CHD); fiber-containing grain products, fruits, and vegetables and cancer; fruits, vegetables, and grain products that contain fiber and risk of CHD; and fruits and vegetables and cancer.

Because of the DS Act, FDA took no final action with respect to the use on dietary supplements of health claims on dietary fiber and cancer; dietary fiber and CHD; omega-3-fatty acids and CHD; zinc and immune function in the elderly; antioxidant vitamins and cancer; and folic acid and neural tube defects.

With respect to folic acid, the agency explained that, while the Public Health Service (PHS) had recommended that all women of childbearing age in the United States consume 0.4 milligram (mg) of folic acid daily to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects, PHS had also identified several issues that remained outstanding, including the appropriate level of folic acid in food and safety concerns regarding increased intakes of folic acid. Sections 403(r)(3)(A)(ii), 402(a), and 409 of the act (21 U.S.C. 342(a) and 348) establish that the use of a substance in food must be safe. Questions raised in the PHS recommendation (see 58 FR 2606 at 2609) included the safety of high intakes of folate by the target population as well as by other segments of the population who may unintentionally be exposed to high intakes if overfortification of the food supply with folic acid were to occur as a result of the PHS recommendation. FDA concluded that it could not authorize a health claim on folic acid until the questions regarding the safety of the use of this nutrient, as well as other concerns raised by PHS, were satisfactorily resolved (58 FR 2606 at 2614).

4. The Dietary Supplement Proposals

In the Federal Register of June 18, 1993 (58 FR 33700), FDA published a proposal on health claims on dietary supplements. FDA proposed to revise its food labeling regulations to make dietary supplements of vitamins, minerals, herbs, or other similar nutritional substances subject to the same general requirements that apply to

all other types of food with respect to health claims.

In the Federal Register of October 14, 1993 (58 FR 53296), FDA published a proposal not to authorize health claims on the labels of dietary supplements on five nutrient-disease relationships: Dietary fiber and cancer; dietary fiber and CHD; antioxidant vitamins and cancer; omega-3 fatty acids and CHD; and zinc and immune function in the elderly. However, in the same issue of the Federal Register (58 FR 53254), the agency did propose to authorize the use on the labels and labeling of conventional foods and dietary supplements of a health claim on the relationship between folate and risk of neural tube defects and to provide for safe use of folic acid in foods by amending several of its regulations that permit use of folic acid in foods (see also 58 FR 53305 and 58 FR 53312).

#### 5. The Dietary Supplement Health Claim Final Rule

In the Federal Register of January 4, 1994 (59 FR 395), FDA announced that it was amending its food labeling regulations to make dietary supplements subject to the same general requirements that apply to all other types of food with respect to the use on the label or in labeling of health claims that characterize the relationship of a substance to a disease or health-related condition.

Also in the Federal Register of January 4, 1994 (59 FR 433), the agency announced that, in accordance with the 1990 amendments, as amended by the DS Act, the regulation on folate and neural tube defects that it proposed on October 14, 1993 (58 FR 53254), was considered a final regulation for dietary supplements of vitamins, minerals, herbs, and other similar nutritional substances (dietary supplements). In its notice, the agency stated that the document was part of a separate rulemaking contemplated by Congress if a final regulation on the proposal issued on October 14, 1993, was not issued by December 31, 1993, and noted that the notice bore a separate docket number (i.e., No. 93N-0481) to distinguish it from the one assigned to the October 14, 1993 rulemaking (i.e., No. 91N-100H), which, the agency said, was ongoing.

In this document, FDA is finalizing its October 14, 1993, proposal to authorize health claims on the relationship between folate and neural tube defects. This final rule pertains to conventional food as well as to dietary supplements. Elsewhere in this issue of the Federal Register, FDA is proposing to revoke the regulation on this nutrient-disease

relationship that became final by operation of law.

#### 6. The Dietary Supplement Health and Education Act of 1994

The President signed the Dietary Supplement Health and Education Act of 1994 (Pub. L. 103-417) (hereinafter referred to as the DSHEA) into law on October 25, 1994. Among other things, the DSHEA defines "dietary supplements" (in section 3(a)).

In the October 14, 1993, proposal, FDA used the terms "dietary supplements of vitamins, minerals, herbs, and other nutritional substances" and "food in conventional food form." Under the changes effected by the DSHEA (see sections 3 (a) and (c) of the DSHEA), the form of a product is no longer determinative of whether the product is a dietary supplement. Accordingly, with the exception noted below, FDA will use the terms "food" or "foods" in this document to reflect this change and the act's definition of "dietary supplements." FDA will use the terms "conventional food" and "dietary supplement" in response to comments dealing with the bioavailability of folate, for which a distinction needs to be made between foods and dietary supplements. Where other terminology was used in the regulatory language of the October 14, 1993, proposal, FDA has modified that language to conform to the changes effected by DSHEA.

#### B. Relationship Between Folate and Neural Tube Defects

The agency reviewed and updated the scientific literature on the relationship between folate and neural tube defects in the Federal Register of November 27, 1991 (56 FR 60610), January 6, 1993 (58 FR 2606), and October 14, 1993 (58 FR 53254), and provides only a brief summary here.

**Folate.** The term "folate," as used in this document, includes the entire group of folate vitamin forms: That is, folic acid (pteroylglutamic acid), the form of the vitamin added to dietary supplements and to fortified foods, and the naturally- occurring folylpolyglutamates (pteroylpolylglutamates) which are found in foods. "Folate" is thus the general term used to include any form of the vitamin, without reference to the state of reduction, degree of substitution, or number of glutamates. As a vitamin, folate functions metabolically in the synthesis of amino acids and nucleic acids. Insufficient quantities of folate in the diet lead to impaired cell multiplication and alterations in protein synthesis (Ref. 1).

These effects are most noticeable in rapidly growing or dividing cell populations (Ref. 1). Pregnancy increases the need for folate and many other nutrients because of the need of the mother to maintain adequate nutrition and to meet the nutritional requirements of the developing fetus.

**Neural tube defects.** Neural tube defects are serious birth defects that can result in infant mortality or serious disability. The birth defects anencephaly and spina bifida are the most common forms of neural tube defects and account for about 90 percent of these defects. These defects result from failure of closure of the covering of the brain or spinal cord during early embryonic development. The neural tube forms between the 18th and 20th days of pregnancy and closes between the 24th and 27th days. Because the neural tube forms and closes during early pregnancy, the defect may occur before a woman realizes that she is pregnant.

Each year, about 2,500 cases of neural tube defects occur among about 4 million births in the United States (i.e., in approximately 6 of 10,000 births annually). Recent data from State-based birth defects surveillance systems show declining trends for neural tube defects in the United States for about the last 30 years (Ref. 2). The Maternal and Child Health Bureau of the Health Resources and Services Administration reported that the neural tube defect rate in the United States has declined from 1.3 per 1,000 live births in 1970 to 0.6 per 1,000 live births in 1989 (Ref. 3).

The majority of neural tube defects are isolated defects and are believed to be caused by multiple factors. About 90 percent of infants with a neural tube defect are born to women who do not have a family history of these defects. Neural tube defects have been reported to vary with a wide range of factors including genetics, geography, socioeconomic status, maternal birth cohort, month of conception, race, nutrition, and maternal health, including maternal age and reproductive history (Ref. 4). Women with a close relative (i.e., sibling, niece, nephew) with a neural tube defect, with insulin-dependent diabetes mellitus, and with seizure disorders who are being treated with valproic acid or carbamazepine are at significantly increased risk compared with women without these characteristics. Rates for neural tube defects also vary within the United States, with lower rates observed on the west coast than on the east coast.

Several lines of evidence led to the hypothesis that nutritional factors might be associated with some human neural

tube defects (see 56 FR 60610, 58 FR 2606, and 58 FR 53254). Among the nutrients that were hypothesized to play a role in reducing the risk of neural tube defects, folate, a B vitamin, received the greatest attention because of associations between folate intake and reduced risk of neural tube defects found in observational studies in humans and because of the well-recognized role of folate in cell division and growth. Because the neural tube forms early in embryonic development, interventions aimed at reducing the risk of these defects must occur periconceptionally (i.e., during the interval extending from at least 1 month before conception and continuing through the first 6 weeks of pregnancy).

In the folate health claim proposal (58 FR 53254), FDA tentatively concluded that the available data show that folate alone may reduce the risk of recurrence of neural tube defects when given periconceptionally at high-dose levels (i.e., 4 mg/day) to women at high risk of such a recurrence. Additionally, based on a synthesis of information from several observational studies that reported periconceptional use of multivitamins containing 0 to 1,000 micrograms (mcg or µg) of folic acid, FDA inferred that folic acid intake at levels of 0.4 mg (400 mcg) per day may reduce the risk of occurrence of neural tube defects. Protective effects measured by reduction in incidence of neural tube defects have been found in several observational studies that reported periconceptional use of multivitamin supplements containing about 400 mcg folic acid.

*Public health significance.* Reduction in adverse pregnancy outcomes such as birth defects is an important public health goal. Because most neural tube defects occur in women without a history of such outcomes, interest in reducing the risk of first occurrences has been very high. PHS has inferred that if all women of childbearing age consumed 0.4 mg (400 mcg) folic acid daily throughout their childbearing years, there might be a reduction in neural tube defects of about 50 percent (i.e., about 1,250 cases per year) (Ref. 5).

#### *C. Regulatory and Other Activities Related to Folate and Neural Tube Defects*

Since the passage of the 1990 amendments in November 1990, the rapidly evolving nature of the science relative to folate and the risk of neural tube defects and a number of PHS activities have intertwined with the regulatory process on the question of whether a health claim should be authorized on this topic. These

developments have resulted in a dynamic process that began with the publication of a proposed rule not to authorize a health claim on folic acid and neural tube defects (56 FR 60610); saw PHS issue a recommendation that all women of childbearing age in the United States should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other neural tube defect (Ref. 5); included meetings of FDA's Folic Acid Subcommittee and Food Advisory Committee (Refs. 6 and 7); and was marked by FDA publishing a final rule that noted that, while the PHS recommendation evidenced that significant scientific agreement exists regarding the relationship between folate and neural tube defects, there were significant unresolved questions about the safe use of folic acid in food (58 FR 2606). In its January 6, 1993, Federal Register document, the agency concluded that it could not authorize a health claim for folate until the questions regarding the safe use of this nutrient, as well as other concerns raised by PHS, were satisfactorily resolved.

The process proceeded to the point where, in October 1993, FDA stated that it had tentatively concluded that the safety questions had been resolved, and that there is significant scientific agreement about the validity of the relationship between folate and neural tube defects (58 FR 53254). The agency also tentatively concluded that, based on its discussions with the Folic Acid Subcommittee and its analyses of food intake data, daily folate intakes can be maintained within safe ranges by allocating fortification with folic acid to specific foods in the food supply through an amendment to the food additive regulation for folic acid.

The agency therefore proposed to authorize a health claim relating diets adequate in folate to a reduced risk of neural tube defect-affected pregnancies (58 FR 53254). In companion documents published in the same issue of the Federal Register, the agency also proposed to provide for the safe use of folic acid in foods by amending the food additive regulations for folic acid (58 FR 53312) and to amend the standards of identity for specific enriched cereal-grain products to require the addition of folic acid (58 FR 53305).

The agency convened the Folic Acid Subcommittee and the Food Advisory Committee on October 14 and 15, 1993 (Ref. 8). Members were asked to comprehensively review the October 14, 1993, proposals and to provide comments. The agency requested that

the Folic Acid Subcommittee give priority to the health claim issue because the DS Act required that health claim regulations be finalized by December 31, 1993. The agency treated the discussions of the Folic Acid Subcommittee as comments. A summary of the discussions that occurred during the meetings is provided in the summary of comments below.

As stated above, in January 1994, FDA announced (59 FR 433) that, by operation of law, the regulation that it proposed on October 14, 1993 (58 FR 53254), to authorize the use of a health claim about the relationship between folate and the risk of neural tube defects was a final regulation applicable to the label and labeling of dietary supplements only. The agency also advised that, given the PHS recommendation and the results of the agency's review of the evidence on this claim, in addition to authorizing the claim on dietary supplements, it had no intention of taking action against conventional foods that are naturally high in folate that bear a claim on this nutrient-disease relationship, so long as the claim fully complies with the provisions of the regulation that became final for dietary supplements by operation of law.

#### *D. Scope of This Document*

In the Federal Register of October 14, 1993 (58 FR 53254), the agency posed a series of questions for itself. These questions, and the agency's proposed answers, provided the outline for the October 14, 1993 document. The questions were: (1) Is a health claim on the relationship between folate and neural tube defects appropriate on food labels? (2) If the agency concludes that a health claim can be safely implemented, what should such a claim say about folate and neural tube defects? (3) Should the food supply be fortified with folic acid to ensure that women have adequate folate intakes? If so, is it necessary to limit the foods to which folic acid can be added and the levels at which it can be added to those foods? (4) If there are to be limitations on the foods that can be fortified with folic acid, which foods are most appropriate for fortification, and at what levels should they be fortified?

During the development of this final rule, data on the folate status of the U.S. population obtained during Phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III, Phase 1, 1988-1991) became available. The agency anticipated evaluating red blood cell (RBC) and serum folate data, and data on folate intake from foods and

dietary supplements from this survey. Additionally, because the NHANES III folate consumption data are more current than the data used by the agency in developing its October 14, 1993, proposals for food fortification and for amending the agency's food additive regulation for folic acid (58 FR 53305 and 58 FR 53312, respectively), the agency considered delaying completion of these rulemakings until evaluation of the newer data was complete.

However, in late 1993, FDA became aware of a methodological problem associated with the radioassay kits used in NHANES III (1988 to 1994) that affected serum folate and RBC folate values and, consequently, data interpretation. FDA's Center for Food Safety and Applied Nutrition requested that the Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), review, under a contract with FDA, the issues and report its findings to the agency. FDA requested that LSRO/FASEB: (1) Examine the analytical bases of the discrepancies associated with serum folate and RBC folate values derived from use of certain analytical kits used in NHANES III (1988 to 1991); (2) evaluate the scientific basis and validity of procedures proposed by the Centers for Disease Control and Prevention (CDC) to make corrections to serum folate and RBC folate values obtained in NHANES III Phase 1 (1988 to 1991); (3) reexamine current "cutoff" values used for estimation of "deficient," "low status," etc., in light of the need for application of a correction factor; and (4) determine whether these approaches are still useful for estimating the prevalence of inadequate folate nutriture in the U.S. population.

A full description of the problem, the analytical issues involved, the issues that arose that are related to the interpretation of NHANES III Phase 1 (1988 to 1991) data, and LSRO/FASEB's conclusions are presented in "Assessment of Folate Methodology Used in the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1991)" (Ref. 9). A major conclusion of LSRO/FASEB was that neither adjustment of the serum folate or RBC folate data from NHANES III Phase 1 (1988 to 1991) to correct for the analytical problem, the use of the data without adjustment, nor the use of either data set with adjusted criteria for normalcy and deficiency, by themselves, can predict the prevalence of inadequate folate nutriture of the U.S. population.

Based on LSRO/FASEB's report and its own review of the data, the agency

has concluded that while there is a need for further evaluation of the NHANES III (1988 to 1991) serum folate and RBC folate data set, the agency will not delay this rulemaking until such evaluation is complete.

The complete data from NHANES III (1988 to 1994) on folate intake from food and dietary supplements are not yet publicly available. Therefore, the agency cannot evaluate total folate intakes from foods and from dietary supplements from this survey data. The agency has concluded that it will also not delay the fortification and food additive rulemakings until the expected availability of these data in 1996.

## II. Summary of Comments and the Agency's Responses

The agency received nearly 100 comments in response to its October 14, 1993, proposed rule on a health claim on folate and neural tube defects. In addition, as stated above, FDA submitted the transcript of the October 14 and 15, 1993, meetings of the Folic Acid Subcommittee and Food Advisory Committee, in which the proposed rule was discussed, to the docket 91N-100H as a comment (Ref. 8). Comments were received from individual members of FDA's Folic Acid Subcommittee and Food Advisory Committee and invited guest consultants; other Federal agencies; a foreign government; State departments of agriculture, consumer services, or health; health care professionals; consumers; consumer advocacy groups; national organizations of health care professionals; State and territorial public health nutrition directors; manufacturers and suppliers of vitamins to the conventional food industry and the dietary supplement industry; manufacturers of finished foods including breakfast cereals, frozen foods, and bakery products; and trade associations of dietary supplement manufacturers, bakers, millers, and food processors. A number of comments were received that were more appropriately answered in other dockets, and these were forwarded to the appropriate dockets for response.

FDA has considered all of the comments on a health claim on folate and neural tube defects that it received. The agency reviewed all of the documents, including letters, press releases, scientific articles and data supporting these articles, review articles, and recommendations, that were included in the comments. A summary of the comments that the agency received and the agency's responses follow.

### A. *Advisability of Authorizing Health Claims*

1. Some comments endorsed health claims because of their potential educational benefits, while other comments stated that health claims on foods that focus on single nutrients are a bad idea because combinations of foods, not single nutrients, build health. The advisability of health claims was also discussed at the October 14 and 15, 1993, meeting of the Folic Acid Subcommittee (Ref. 8).

The agency notes that the issue of whether health claims should be permitted in food labeling is moot because the 1990 amendments authorized claims on the relationship between substances and diseases or health-related conditions if the scientific validity standard is met.

### B. *Advisability of Authorizing a Health Claim for Folate and Neural Tube Defects*

In § 101.79(c)(2)(i)(A) (21 CFR 101.79(c)(2)(i)(A)), FDA proposed to authorize health claims on labels or in labeling of conventional foods and dietary supplements on the relationship between folate and neural tube defects in women of childbearing age.

#### 1. Scientific Validity Standard: Adequacy of the Scientific Data

2. Many comments supported FDA's tentative decision to authorize a health claim on the relationship between folate and neural tube defects but did not provide any specific reasons for their support. Several comments noted that the scientific basis for the claim was as strong as that used to authorize other claims (e.g., those relating calcium and osteoporosis and saturated fat and heart disease). Members of the Folic Acid Subcommittee who supported a health claim noted that such claims would provide information to the target population, and that such claims tend to be more effective than educational programs alone.

Other comments opposed the health claim, identifying specific concerns with the quality and quantity of the data used to develop the PHS recommendation and to support the proposed health claim. Members of the Folic Acid Subcommittee who opposed a health claim cited the weakness of the data supporting the relationship, including the very small number, and observational nature, of studies relating intake of folate at levels attainable from usual diets to reduced risk of neural tube defects and the many issues associated with the interpretation of these studies (58 FR 53265).

Several comments noted that because of the variety of micronutrients in addition to folic acid contained in supplements whose use was reported in several case-control studies, and because foods high in folate are also important sources of other micronutrients, it is not possible to isolate an independent role for folate in reduction in risk of first occurrences of neural tube defects. Other comments also expressed concern regarding the lack of folate-specific data at intakes of 400 mcg daily and noted that studies showing a positive impact of use of multivitamins containing 400 to 1,000 mcg of folic acid may have been showing a combined effect of folic acid and vitamin B12 or of folic acid and other components of the multivitamin preparations.

A comment noted that there is little knowledge about biological mechanisms that would explain the role of folate in reduction in risk of neural tube defects. The comment stated that it was inappropriate to conclude that, because folic acid alone at a supraphysiologic dose (i.e., 4,000 mcg/day; 4 mg/day) is effective in reducing the risk of neural tube defects among women at recurrent risk, it would also reduce the risk of such defects among women at much lower risk of a first occurrence when consumed at lower doses (i.e., at 400 mcg/day; 0.4 mg/day). Another comment expressed the opinion that the agency should not authorize a claim because there is not significant scientific agreement that the evidence supports the claim.

Section 101.14(c) (21 CFR 101.14(c)) states that the agency will issue a regulation authorizing a health claim when it determines, based on the totality of the publicly available scientific evidence, that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

For folate and neural tube defects, the agency evaluated all of the available scientific evidence, consulted with the Folic Acid Subcommittee and Food Advisory Committee about this evidence, and considered all the information contained in the comments. Based on this review, FDA has concluded that there is significant scientific agreement that the data associating folate intake and reduced risk of neural tube defects support a health claim on this relationship.

The strongest evidence for this relationship comes from the randomized controlled Medical Research Council intervention study (Ref. 14) that showed

that women at risk of a recurrence of a neural tube defect-affected pregnancy who consumed a supplement containing 4 mg (4,000 mcg; 10 times the reference daily intake (RDI) folic acid daily throughout the periconceptional period had a significantly reduced risk of having another child with a neural tube defect. This study demonstrated, for the first time, that there was a significant reduction in recurrence of neural tube defects with high levels of folic acid but not with other vitamins and minerals. This study identified a specific role for folic acid in reducing the risk of recurrence of neural tube defect-affected pregnancies in women with a history of this defect and thus established the scientific basis for a relationship between folate intake and the occurrence of neural tube defects.

In addition, protective effects against occurrence of neural tube defects were found in a Hungarian randomized controlled trial that used a multivitamin/multimineral preparation containing 0.8 mg folic acid daily (Ref. 15). Four of five observational studies have also reported a reduced risk of neural tube defects among women who reported consuming 0.4 to 1.0 mg folate daily from multivitamin supplements (Refs. 10, 11, 13, and 16). Several of these studies (Refs. 11, 13, and 16) have also reported beneficial effects against occurrence of neural tube defects of dietary folate intakes of 100 to 250 mcg or more daily.

Based on its review of all of these studies, the agency has concluded that their results are consistent with the conclusion that folate, at levels attainable from usual diets, may reduce the risk of occurrence of neural tube defects.

The agency agrees that there are still significant gaps in our knowledge about the etiology of neural tube defects; about how folate, either alone or in combination with other nutrients, reduces the risk of neural tube defects; about dose-response relationships between folate intake and reduction in risk of neural tube defect-affected pregnancies; and about the role of other essential nutrients in the etiology of neural tube defects. However, the randomized controlled Medical Research Council trial (Ref. 14) clearly established the specific effectiveness of increased folate intake in reducing the risk of recurrence of some neural tube defects, and the findings of most of the studies cited above (Refs. 9, 10, 11, 13, and 16) are consistent with the conclusions drawn from the results of the Medical Research Council trial.

Because of the consistency between the results of the Medical Research

Council trial and the results of the smaller observational studies, PHS has inferred that folate alone, at levels attainable in usual diets, may reduce the risk of neural tube defects (Ref. 5). FDA participated in the development of the PHS recommendation and noted in the folate health claim proposal (58 FR 53266) that the recommendation evidenced that significant scientific agreement exists regarding the validity of an association between folate intake and risk of neural tube defects.

FDA has therefore concluded, based on its own review of the scientific literature, that there is significant scientific agreement regarding the validity of the relationship, and that the statutory requirements for authorizing a health claim in this topic area have thus been met. Therefore, the agency is adopting § 101.79(c)(2)(i)(A) as proposed.

## 2. Appropriateness of Providing for a Claim

In addition to comments addressing the scientific validity of a health claim on folate and neural tube defects, the agency received comments questioning the advisability of authorizing a claim on this topic.

### a. *General comments.*

3. Some comments stated that it was advisable to provide for a folate/neural tube defects health claim because such a claim can serve to broaden public knowledge of the relationship between folate and neural tube defects. A comment noted that the folate/neural tube defect claim might be especially beneficial for women who had previously had a child with a neural tube defect. One comment suggested that a health claim for folate and neural tube defects would increase intake of folate by women of childbearing age.

Others expressed concern by noting that consumers will find it difficult to understand the claim and will begin to associate folate-containing foods with an effect on birth defects in general. A comment noted that, given that many occurrences of neural tube defects will not be affected by folate intake, the claim will give a false hope of avoidance of the defect. A comment expressed concern that publication of the claim might cause unnecessary alarm among women who are pregnant. Other comments noted that neural tube defects are not the result of folate deficiency per se or noted the lack of evidence that there is a need in the general U.S. population for an increase in folate intake. Another comment, in considering the agency's proposed model health claims, noted that FDA

was trying to make the food label do more than it can.

Another comment emphasized that the context in which data from the major controlled intervention trial of effects of folic acid at levels approaching those obtainable from diets (i.e., the Hungarian trial; Ref. 15) were obtained (e.g., women who volunteered for the trial gave up drinking and smoking, consumed healthful diets before pregnancy, and in general pursued good health practices in the periconceptional interval) is not the same context in which women in the general population will receive folate.

The agency agrees with the comments above that a health claim for folate and neural tube defects may have an educational benefit and has the potential for increasing folate intake among women in the target population by informing them of the importance of folate intake during their childbearing years. The agency also recognizes the importance of informing women of childbearing age of the need to ensure that their diets include adequate folate throughout this time of their lives and notes that providing information at the point of purchase of food by means of health claims and nutrient content claims can be an effective means of getting the information to consumers and of helping consumers to maintain healthful diets. Given that about half of all pregnancies are unplanned, many women in the general population can benefit from the information provided in the health claim because it will motivate them to increase their folate intake, even if they are not anticipating a pregnancy in the near future.

The agency recognizes that women in the Hungarian trial (Ref. 15) were advised to adopt specific health conscious practices before attempting to become pregnant, and that women in the general population may not adopt such practices before becoming pregnant. The agency notes, however, that there are no data to indicate that the outcome of the Hungarian trial was related to or dependent upon the adoption of those practices, and that all women in the trial were urged to adopt those practices, not only those receiving folate-containing supplements. The agency finds no basis to deny the claim based on such a consideration. In addition, although emphasis is frequently placed upon estimates that about half of all pregnancies in the United States are unplanned, the agency notes that the large numbers of women who do plan their pregnancies (i.e., about 50 percent) may be adopting health-conscious practices before conception and thus may receive folate

in a context similar to that employed in the Hungarian trial.

The agency recognizes that there is the potential for the health claim to be misleading and has addressed that potential by requiring that all claims contain specific information that informs women about the effect that adequate intake of folate during their childbearing years may have on their risk of a specific type of birth defect, without implying that adequate folate intake will provide 100 percent protection against that, or any other, birth defect. The agency recognizes that many nutrients, as well as attention to overall diet and healthful lifestyles, are important for obtaining the best possible outcome of pregnancy and has incorporated these concepts into the language of the health claim.

Specifically, in this health claim regulation, the agency identifies the target population for the claim as women during their childbearing years (§ 101.79(c)(2)(i)(A)); describes the effect of folate intake on the risk of neural tube defects, a very specific type of birth defect (§ 101.79(c)(2)(i)(C)); requires that claims not imply that folate intake is the only recognized risk factor for neural tube defects (§ 101.79(c)(2)(i)(D)); summarizes the significance of appropriate folate intake relative to reduction in risk of neural tube defects in the total dietary context by requiring that claims state that healthful diets are also needed (§ 101.79(c)(2)(i)(H)); and provides for optional (voluntary) identification of a variety of sources of folate in the claim (§ 101.79(c)(3)(vii)). In describing the requirements for foods to bear the claim, the agency has defined characteristics that will qualify a food for bearing the folate/neural tube defect health claim with an eye to ensuring that such foods will be good sources of folate (§ 101.79(c)(2)(ii)(A)).

Provision of such information will assist women in understanding the relationship of folate intake to the risk of neural tube defects and the significance of the information in the context of the total daily diet. Thus, the claim includes facts essential for consumer understanding of the conditions and circumstances under which the claimed effect is more likely to be obtained.

*b. Small size of the population at risk.*

4. Some comments disagreed with the agency's proposal to authorize a health claim for folate and neural tube defects because other authorized claims are different from this one. They pointed out that the folate claim deals with a problem that affects a very small number of people, while other authorized claims deal with reducing

the risk of long-developing conditions affecting very large segments of the population (e.g., calcium and osteoporosis; fat and heart disease). Another comment noted that there have been large unexplained declines in neural tube defects in the United States since the 1930's. Another comment noted that neural tube defects constitute only a small fraction of all birth defects and stated that the proposed claim could lead to a false sense of security regarding protection from risk of all birth defects. Another comment noted that despite their distressful nature, because neural tube defect-affected births are a relatively rare phenomena, they should be attacked at a medical level.

The agency disagrees with comments that it should not authorize a folate/neural tube defect health claim on the basis that the affected population is small in number. The eligibility requirements for a health claim do not limit such claims solely to disease or health-related conditions affecting significant portions of the population. Rather, the general eligibility requirements for health claims require that for a substance to be eligible for a health claim, the substance must be associated with a disease or health-related condition for which the general population or an identified U.S. population subgroup (e.g., the elderly) is at risk (see § 101.14(b)(1)).

As FDA explained in the final rule establishing § 101.14(b)(1) (58 FR 2478 at 2499), the agency will interpret this provision flexibly and will disqualify few claims under it. However, the agency also advised that if the affected population is small in size or is not readily identifiable, information on prevalence in the U.S. population will be a material fact that must be disclosed to avoid misbranding the product.

FDA agrees that the prevalence of pregnancies affected by neural tube defects in the United States is low. However, because it is not currently possible to predict when a pregnancy will be affected, the U.S. subpopulation potentially at risk is large (i.e., women capable of becoming pregnant). The agency, consequently, disagrees that this health claim should not be authorized because a large subpopulation is potentially at risk of a neural tube defect-affected pregnancy.

*c. Potential impact of new data.*

5. Several comments expressed concern that results of research in progress on the potential role of factors other than folate could lead to revisions of the current PHS recommendation that all women consume 0.4 mg of folate daily throughout their childbearing

years to reduce their risk of neural tube birth defects. A comment noted that, based on testimony presented at the April 15 and 16, 1993, meeting of the Folic Acid Subcommittee, data from ongoing studies in South Carolina and Texas will be available soon and should provide information on the effectiveness of folate-containing supplement intervention programs in these areas. Another comment noted that data reported at the recent meeting of the American Public Health Association suggested that while reported intake of folate-containing supplements appeared to be associated with a reduced incidence of neural tube defect-affected pregnancies overall, the association was not statistically significant for Hispanic women who have a higher risk for neural tube defects than many other women.

Some members of the Folic Acid Subcommittee questioned whether new data on vitamin B<sub>12</sub> (summarized in section II.E.6. of this document) should influence the agency's position on the relationship between folate and neural tube defects. Another Folic Acid Subcommittee member stated that regardless of the new findings, the agency should move ahead with the folate/neural tube defect health claim.

The agency is aware that data from several ongoing studies have been discussed at national meetings, but until these data and detailed descriptions of study designs, methodologies, and full results are publicly available, the agency cannot act on them. New data that have become publicly available during this rulemaking are reviewed in Section II.E.6 of this document. The agency notes, however, that the validity of the relationship between folate and neural tube defects has been established by the Medical Research Council trial (Ref. 14). New findings are not likely to detract from the validity of that relationship.

### C. Issues Regarding the Substance/Disease Relationship That Is the Basis of the Claim

#### 1. Identifying the Substance (Folic Acid Versus Folate)

In developing its proposed regulation, the agency considered how best to describe the relationship between folate and neural tube defects. In the proposed statement of the substance/disease relationship (§ 101.79(c)(2)(i)(A)), FDA described the substance that is the subject of the claim as "folate." FDA also used this term in proposed § 101.79(a)(2), (b)(1), (b)(3), (c)(2)(i)(B), (c)(2)(i)(F), (c)(2)(ii)(A), (c)(2)(ii)(B), (c)(2)(iv), (c)(3)(ii), and (d). The agency's use of this term differed from the

wording of the 1990 amendments which required that FDA evaluate the relationship between "folic acid" and neural tube defects.

Based on its review of the available studies, the agency in its October 14, 1993, proposed rule (58 FR 53254 at 53280) described its rationale for broadening the topic by noting that the term "folates" is used broadly to represent the entire group of nutritionally active folate vitamin forms and includes both synthetic folic acid and the folylpolyglutamates that occur naturally in foods.

In reviewing the scientific evidence on the relationship between folate and neural tube defects, the agency noted that some studies reported effects of use of supplements of folic acid in combination with intakes of food folates (Ref. 10), while other studies reported effects of dietary intakes of food folates alone (Refs. 11, 13, and 16). Based on its review of these studies, the agency tentatively concluded that the diet/disease relationship is more accurately described as being related to all of the biologically active vitamin forms of folate rather than just to the synthetic form of the vitamin (i.e., folic acid). Thus, in its review of the substance/disease relationship, FDA considered the effect of all of the nutritionally active forms of this vitamin (i.e., folates) on neural tube defects and not just the effect of the form of the vitamin specified in the 1990 amendments (i.e., folic acid). Use of the term "folate" in proposed § 101.79(a)(2), (b)(1), (b)(3), (c)(2)(i)(B), (c)(2)(i)(F), (c)(2)(ii)(A), (c)(2)(ii)(B), (c)(2)(iv), (c)(3)(ii), and (d) was consistent with the scope of the agency's review.

6. A comment stated that FDA had unjustifiably changed the demonstrated efficacious form of the vitamin from "folic acid" to "dietary folate," and that because dietary food folate has not been demonstrated to reduce the incidence of neural tube defects, such a change is not justified. Several comments stated that FDA, in its health claims proceedings, had departed from the PHS recommendation, which uses the term "folic acid" in its title and in describing dietary change associated with reduced risk of neural tube defects, and that FDA, instead, concentrated inappropriately on food folate.

FDA does not agree with these comments and concludes that it was justified in expressing the food substance/disease relationship as "folate and neural tube defects" rather than as "folic acid and neural tube defects." FDA also disagrees with the comments that folic acid is the only substance that was appropriately the subject of FDA's

review, and that dietary food folate has not been demonstrated to reduce the incidence of neural tube defects.

a. *Efficacy of food folate.* In reviewing the scientific evidence on the relationship between folate and neural tube defects, the agency noted that one study attributed all observed effects to consumption of dietary supplements of undefined composition without quantifying contribution of folate either from the supplements or from food (Ref. 10), while other studies attempted to specifically quantify intakes of folate from food as well as from dietary supplements (Refs. 11, 13, and 16).

Some studies reported protective effects of use of supplements containing folic acid in combination with intakes of food folates (Refs. 11, 13, and 16), while other studies reported protective effects from dietary improvement in general (Ref. 17) or from intakes of food folates alone (i.e., without supplement use) (Refs. 11 and 13).

Milunsky et al. (Ref. 11), Bower and Stanley (Ref. 16), and Werler et al. (Ref. 13) presented data on the relationship of dietary folate to risk of neural tube defects among nonusers of dietary supplements. Each of these studies found reduced risk of neural tube defects associated with increasing dietary intake of food folate. In the prospective study of Milunsky et al. (Ref. 11), the relative risk of neural tube defects was 0.42 for those women ingesting more than 100 mcg folate per day compared with those ingesting less than 100 mcg folate per day. Bower and Stanley (Ref. 16), in a study in Western Australia, found reduced risk of neural tube defects among women consuming more than 240 mcg food folate per day versus community controls. Werler et al. (Ref. 13) reported a significant trend of reduced occurrence of neural tube defects with increasing dietary food folate.

Laurence et al. (Ref. 17) performed a trial of dietary education without prescribing supplements and found that improvement in women's diets from "poor" to "good" led to a 50 percent reduction in recurrence of neural tube defects in women at high risk of this complication. Dietary improvement is assumed to increase intake of folate and many other nutrients by unspecified amounts. Specifically, these authors reported no cases of neural tube defects among women who were judged to have eaten "good" or "fair" diets (Ref. 17). All recurrences occurred among the 30 of 186 women who were judged to have eaten "poor" diets. "Poor" diets were defined as those considered to be deficient in first-class protein, usually no fruits and vegetables, and generally

with excessive amounts of carbohydrates. "Good" diets were defined as those providing good intakes of all essential foods, including protein, and with no excessive amounts of refined carbohydrates, sweets, and soft drinks (see 58 FR 53253, October 14, 1993).

The studies of Milunsky et al. (Ref. 11), Bower and Stanley (Ref. 16), Werler et al. (Ref. 13), and Laurence et al. (Ref. 17) have all demonstrated that food folates provide protective effects against risk of neural tube defects.

b. *Interchangeability of the terms "folate" and "folic acid" in common usage and in nutrition labeling.* FDA notes that, in common usage, the terms "folic acid" and "folate" are frequently used interchangeably to describe the biologically active forms of the vitamin. Foliates are ubiquitous in nature, being present in nearly all natural foods (Ref. 18), and occurring in a wide range of forms (Ref. 19). Human nutritional requirements for folate can be met by a variety of naturally occurring forms of the vitamin from many sources as well as by pteroylglutamic acid, the form of the vitamin added as a fortificant to breakfast cereals and other foods, and the form present in dietary supplements.

In nutrition labeling, "folic acid," "folate," and "folacin" are allowable synonyms (§ 101.9(c)(8)(iv) and (c)(7)(iv)). All of these terms provide a way to describe the nutritional value of folate vitamin forms, although the term "folacin" is now rarely used.

c. *Interchangeability of the terms "folate" and "folic acid" in the PHS recommendation.* FDA disagrees that the PHS statement emphasizes synthetic folic acid, the form of the vitamin used as a fortificant in conventional foods and in dietary supplements. In point of fact, the PHS statement, consistent with lay information and with nutrition labeling regulations, uses the terms "folic acid" and "folate" interchangeably (Ref. 5). For example, the PHS recommendation states that "folate intake  $\geq$  0.4 mg/day can be obtained from the diet through careful selection of foods," that improvement in dietary habits is one potential approach "for the delivery of folic acid to the general population in the dosage recommended," and that "women should be careful to keep their total daily folate consumption at < 1 mg per day" (Ref. 5).

That some ambiguity with respect to use of the terms "folic acid" and "folate" was present in the PHS recommendation was recognized during finalization of the recommendation at a CDC-sponsored meeting held in Atlanta

on July 27, 1992. At that meeting, CDC staff noted that the ambiguity was deliberate (Ref. 20):

INVITED SPEAKER WALD: There is an ambiguity here over whether it's total or extra, unless you have a particularly kind of astute legal perspective on this. \* \* \* I have a question, though. Was the ambiguity deliberate?

CDC's ERICKSON: Yes.

INVITED SPEAKER WALD: You see, I think I would have probably inserted the same ambiguity myself. Because the intention is to get something going. \* \* \* And one has the 0.4 mg figure from the previous RDA \* \* \* at least that is a psychological fixing point.

Thus, there was some ambiguity in the PHS recommendation from the time of its development, and the recommendation does not identify synthetic folic acid as the sole active form of the vitamin.

d. *Conclusion.* Based on its review of the available studies, the agency tentatively concluded in the proposed rule that the food substance/disease relationship is most accurately expressed as "folate and neural tube defects" rather than as "folic acid and neural tube defects" because the term "folate" encompasses all forms of the vitamin from any source. In addition, at intakes attainable from usual diets, both folate from foods and folic acid from fortified foods or dietary supplements are converted into the same functional, metabolically active, reduced coenzyme vitamin forms in the body (Ref. 19). Thus, nutritional requirements are met by a variety of forms of folate, and, with respect to reduction in risk of neural tube defects, the utility of increased folate intake, whether achieved through improved food choices or through use of dietary supplements, has been shown.

The comments summarized above do not provide a basis for the agency to change the relationship statement because they are inconsistent with the scientific data, and they do not provide data that demonstrate that "folic acid" performs nutritional functions different from those performed by naturally occurring food folates. Thus, making a distinction between "folate" and "folic acid" when all forms of the vitamin are capable of conversion to active vitamin coenzymes and metabolic function is artificial and inappropriate.

Therefore, in § 101.79, FDA is authorizing a health claim on labels and in labeling of conventional foods and dietary supplements about the relationship between folate and neural tube defects in women of childbearing age. The agency is retaining this terminology throughout the codified language. However, § 101.79(c)(2)(i)(B) states that any one of several synonyms

may be used, including "folic acid" and "folate," when specifying the nutrient in a health claim.

FDA notes that in proposed § 101.79(c)(2)(i)(F), the term "folic acid" was used instead of the intended term "folate," which was otherwise consistently used throughout the proposed codified language. FDA is correcting this terminology in the final codified language, which for other reasons described in this preamble is redesignated as § 101.79(c)(2)(i)(E).

## 2. Issues of Source and Amount

In § 101.79(c)(2)(i)(H), the agency proposed to prohibit statements in the health claim that a specified amount of folate (e.g., 400 mcg (100 percent of the Daily Value (DV)) in a dietary supplement) is more effective in reducing the risk of neural tube defects than a lower amount (e.g., 100 mcg (25 percent of the DV) in a breakfast cereal or from diets rich in fruits and vegetables). The agency proposed this limitation because it is consistent with scientific data showing that reduced risk of neural tube defects has been associated with general dietary improvement, which is assumed to increase folate intake by unspecified amounts. In response to this proposed limitation, the agency received comments addressing the separate issues of source of folate and amount of folate.

### a. Source.

7. Several comments agreed with the agency's proposal, stating that health claims should not contain statements that adequate diets cannot provide sufficient folate, or that only fortified foods or supplements can provide adequate folate. Other comments disagreed, stating that FDA should require claims to state that the evidence that folate reduces the risk of neural tube defects is stronger for supplements than for food. Other comments stated that evidence that folate-rich diets reduce the risk of neural tube defects is only suggestive, while evidence that folic acid containing-supplements reduce the risk of neural tube defects is conclusive.

The agency agrees with comments that health claims should not contain statements that diets cannot provide sufficient folate to affect the risk of a neural tube defect because such statements are inconsistent with the available scientific evidence.

The studies of Milunsky et al. (Ref. 11), Bower and Stanley (Ref. 16), Werler et al. (Ref. 13), and Laurence et al. (Ref. 17) were summarized in response to comment 6, above. Milunsky et al. (Ref.



11), Bower and Stanley (Ref. 16), and Werler et al. (Ref. 13) all presented data on the relationship of dietary folate to risk of neural tube defects among nonusers of dietary supplements. Each of these studies found reduced risk of neural tube defects associated with increasing intakes of dietary folate. Laurence et al. (Ref. 17) found fairly strong protection against recurrence of neural tube defects associated with improvement in overall diets.

FDA concludes, based on its review of the scientific literature, that the proposed limitation in § 101.79 on statements that specific sources are superior to others is appropriate because the scientific literature does not support the superiority of any one source over others. As noted above, both folate from conventional foods and folic acid from fortified foods or dietary supplements are converted into functional, metabolically active coenzyme forms for use in the body (Ref. 19). Thus, in the absence of the limitation, manufacturers would be free to put statements that would be false and misleading in their labeling. The agency's conclusion is consistent with PHS's recommendation that advises that careful selection of foods is one means by which women can increase their folate intakes.

**b. Amount.**

8. Several comments agreed with the agency that the claim should not state that a specific amount of folate is more effective than another amount. Several comments noted that dose/response data to justify such statements do not exist, and that scientists do not yet know the requisite folate level that will protect the fetus from a neural tube defect. Other comments disagreed, stating that claims should state that experts recommend 400 mcg per day or 100 percent of the DV when referring to adequate amounts of folate. Another comment stated that while the 400 mcg level is admittedly imprecise, it is the recommendation of PHS. Another comment stated that consumers need to be reminded that a reduction in neural tube defects will only occur if all women consume 400 mcg folate per day throughout their childbearing years.

The agency agrees with comments that dose/response data are insufficient to provide a basis for stating that a specific amount of folate is more effective than another amount. The quantitative results from the studies of Milunsky et al. (Ref. 11), Bower and Stanley (Ref. 16), and Werler et al. (Ref. 13) suggest that amounts *lower* than the current recommendation of 400 mcg may be protective.

After reviewing the comments above and the available scientific literature,

FDA concludes that the comments do not provide a basis for the agency to change its position regarding prohibition of statements in the claim that imply that specific amounts of folate are superior to other amounts because such statements are inconsistent with the scientific data. FDA's conclusion is consistent with information provided in the PHS recommendation that states that amounts of folate lower than 400 mcg may reduce the risk of neural tube defects, and that additional research is needed to establish the minimum effective dose (Ref. 5). Again, a contrary position by the agency would permit false statements to appear on the label.

In the final codified language, the agency is redesignating proposed § 101.79(c)(2)(i)(H) as § 101.79(c)(2)(i)(G) and, for the reasons stated above, is prohibiting in § 101.79(c)(2)(i)(G) claims that a specified amount of folate per serving from one source is more effective in reducing the risk of neural tube defects than a lower amount per serving from another source.

**c. Restriction of claims to specific products.**

9. Several comments stated that the health claim should be limited to supplements containing 400 or 800 mcg of folate or limited to dietary supplements or breakfast cereals containing 400 mcg of folate. Other comments stated that health claims should not be allowed for naturally occurring food folates. Another comment stated that to allow health claims solely on supplements or fortified foods would undermine the need for women to learn to eat more healthfully and to obtain a full array of nutrients found in a balanced diet.

The agency disagrees with comments that recommended that it limit claims to dietary supplements or to dietary supplements and fortified breakfast cereals that contain 400 mcg or more of folate. The agency's review of the scientific literature, summarized in response to comments 6 to 8 above, provides no basis for making a distinction in source or in amount between folate from conventional foods and folic acid from dietary supplements or fortified cereals because the available evidence shows that increased folate intake, rather than the source of the folate, is what is of importance in reducing the risk of neural tube defects (Ref. 5). Increasing total folate intake among women of childbearing age, rather than emphasis on one source versus another, is what is of importance. This conclusion is consistent with PHS's recommendation, which states that improvement in dietary habits and

use of dietary supplements are both appropriate approaches by which women may increase their folate intake.

d. *Target intake goal.* The agency proposed in § 101.79(c)(3)(iv) to include as optional information in the health claim a statement that the DV level of 400 mcg of folate is the target intake goal.

10. Several comments stated that all health claims should refer to the likely effectiveness of 400 mcg of folate, or that claims should be required to state that experts recommend 400 mcg per day. Other comments stated that 400 mcg is the PHS recommendation, and without this information, women may assume that lower amounts are adequate.

The agency disagrees with these comments. FDA chose not to propose to require that claims identify 400 mcg as the target intake goal because it tentatively concluded that there is uncertainty as to the optimal intake of folate with respect to reduction in risk of neural tube defects (Ref. 5). As noted above, several studies (Refs. 11 and 13) have found reductions in risk of neural tube defect-affected pregnancies at folate intakes below 400 mcg per day. None of the comments provided evidence that showed that these findings were not valid. Thus, FDA concludes that a requirement that claims state that women must consume 400 mcg folate per day to achieve a reduction in risk of a neural tube defect-affected pregnancy would be inconsistent with the available scientific data.

However, because 400 mcg is the reference daily intake (RDI), because PHS recommends a 400 mcg/day intake, and because the Folic Acid Subcommittee supported the 400 mcg/day intake goal, the agency has concluded that it may be helpful to some consumers if the health claim were to include information that the RDI of 400 mcg per day is the target intake goal. Therefore, FDA is adopting § 101.79(c)(3)(iv) to allow for optional inclusion of this information, with the target intake goal (400 mcg; 0.4 mg) expressed as 100 percent DV. Claims may identify 100 percent of the DV (400 mcg folate) as the target intake goal and may state the PHS recommended daily intake (400 mcg folate, 0.4 mg).

**3. Focusing on the Periconceptional Interval**

In proposed § 101.79(a)(1), the agency defined neural tube defects as serious birth defects of the brain or spinal cord. The agency noted that these defects result from a failure of the covering of the brain or spinal cord to close during

early embryonic development and further noted that, because the neural tube forms and closes during early pregnancy, the defect may occur before a woman realizes that she is pregnant. In proposed § 101.79(a)(2), the agency described the relationship between adequate folate intake and reduced risk of a neural tube defect-affected pregnancy and summarized the studies whose results provide the basis for the health claim.

11. A number of comments stated that studies have shown that folic acid added to the diet before pregnancy reduces the risk of neural tube defects, and that the relationship statement should be corrected to reflect this fact.

The agency agrees that the studies that provide the basis for the relationship between folate and neural tube defects focused on improved folate nutriture before conception and continuing into early pregnancy. Therefore, the agency is modifying several of the statements in § 101.79(a)(2) to more precisely describe the results of these studies. Specifically, FDA is modifying the second sentence of § 101.79(a)(2) to state that in the studies described, folate was consumed daily "before conception and continuing into early pregnancy \* \* \*," and the fourth sentence to state that the study involved reported periconceptional use of multivitamins that contained folic acid.

12. A comment suggested that claims be allowed to be more precise in describing the period during which adequate folate is needed. The comment noted that the statement relating to daily consumption of folate throughout the childbearing years implies that body folate stores must be built up over decades, while studies have shown that it is sufficient to consume folate during the weeks before the neural tube closes. The comment proposed that a statement that women who consume adequate amounts of folate during the month before and after becoming pregnant may reduce their risk of a neural tube defect would convey this information. Another comment criticized the model health claims provided by the agency because they failed to alert women to the critical periconceptional period.

The agency recognizes that the scientific data support the need for specific attention to folate intake in the periconceptional interval and has modified § 101.79(a)(2) to reflect this fact by specifically mentioning periconceptional use.

The agency notes that one of the purposes of health claims is to assist women in recognizing the importance of healthful diets, including adequate

folate nutriture throughout their childbearing years (see H. Rept. 101-538, 101st Cong., 2d Sess. 9-10 (1990)). Given that about 50 percent of pregnancies are unplanned, and that many women may not recognize that they are pregnant until after the critical period of neural tube closure, it is important for women to maintain healthful diets throughout their childbearing years. While some women who plan their pregnancies might benefit from the more specific information suggested in the comment, the agency concludes that the more general wording in the model claims will reach a wider group of women and provide them with useful and important information.

FDA is adopting § 101.79(c)(3)(ii), which states that health claims may include statements from paragraphs § 101.79 (a) and (b). Through the use of statements derived from § 101.79(a)(2), manufacturers will be able to provide information that alerts women to the importance of the periconceptional period.

#### 4. "Will Reduce" Versus "May Reduce"

13. One comment stated that proposed § 101.79(a)(2), which stated that available data show that diets adequate in folate may reduce the risk of neural tube defects, was misleading and recommended that this section be reworded to state that "studies have shown that folic acid added to the diet before a pregnancy occurs will reduce the risk of neural tube defects."

The agency disagrees with the assertion that adequate folate intake *will* reduce the risk of neural tube defects. The available data show that in an area of low prevalence of neural tube defects, folate intake from dietary supplements or from fortified cereals was not associated with reduced risk of neural tube defects (Ref. 12). The agency did not receive any data or information challenging this data.

The agency notes that use of the term "will reduce" is overly promissory to the individual and is misleading because it is not consistent with the available data. Prevalence rates for neural tube defects vary with a wide range of factors including genetics, socioeconomic status, maternal health, and race. The agency has discussed the multifactorial nature of neural tube defects (and will do so again below (see comment 36 of this document)). It has concluded that claims need to reflect this aspect of the nature of these defects because folate intake is not the only risk factor for them. Use of the term "will reduce" in the claim is not consistent with the multifactorial nature of neural

tube defects. Thus, FDA finds no basis to change the wording of § 101.79(a)(2), and it is including the sentence "The available data show that diets adequate in folate may reduce the risk of neural tube defects" in the final regulation without change.

#### 5. Need for Healthful Diets

14. Some members of the Folic Acid Subcommittee expressed concern about a single nutrient approach to the problem of neural tube defects because nutrients function together in the body. Another comment felt that a health claim for folic acid could be misinterpreted to mean that folic acid could prevent all birth defects. One comment noted that, because nutrients function synergistically in the body, increasing a single nutrient is unwise. Another comment stated that by focusing on the relationship between a single nutrient and a single outcome, opportunities to improve overall health are missed. Another comment expressed concern about singling out one vitamin for a health claim when the major sources of the vitamin (e.g., fruits and vegetables) are being promoted for good health. Other comments noted that in pregnancy it is the total diet, not a single nutrient, that is related to health outcome.

The agency agrees with the comments that expressed concern about the problems in focusing on a single-nutrient, particularly in women of childbearing age. Many nutrients affect healthy pregnancy, and the claim should not lead women to focus undue attention on one nutrient, or on a single dietary factor, instead of on overall healthful diets and health conscious behaviors.

In addition, because healthy pregnancies and good pregnancy outcomes are dependent upon an overall good diet, adequate in protein, vitamins and minerals, and many other nutrients, women should not be misled into believing that folate is the only nutrient about which they need to be concerned in preparing for a pregnancy. With respect to neural tube defects, FDA in its proposed rule (58 FR 53254) reviewed evidence that nutrients other than folate (e.g., methionine, vitamin B<sub>12</sub>, pantothenic acid) have roles in reducing the risk of neural tube defects, and additional evidence is summarized in section II.E.6. of this document. Thus, normal fetal development requires many nutrients in addition to the nutrient that is the subject of the health claim.

Based on these considerations, the agency has concluded that information regarding overall improvement in a woman's diet and nutrition in the

periconceptional interval, as well as throughout her childbearing years, is of considerable importance because pregnancy outcome depends upon adequate intakes of a wide range of nutrients. This concern needs to be balanced against the fact that the available evidence provides the basis for significant scientific agreement that dietary intakes of folate may reduce the risk of neural tube defect-affected pregnancies.

Therefore, in response to these comments, FDA is including in § 101.79(c)(2)(i)(H) in the final regulation a requirement that the claim state that folate needs to be consumed as part of a healthy diet. This requirement will ensure that, while highlighting the role of adequate folate intake, the health claim will not cause women to place undue emphasis on consumption of this nutrient. Thus, this information is necessary to ensure that the claim is properly balanced.

#### *D. Requirements for Foods Bearing the Claim*

##### 1. Qualifying Amounts

In § 101.79(c)(2)(ii)(A), FDA proposed that the food or dietary supplement meet or exceed the requirements for a "good source" of folate as defined in § 101.54 (i.e., containing  $\geq 10$  percent of the RDI). In proposing this eligibility requirement, FDA considered that folate is ubiquitously distributed in the U.S. food supply. While a number of foods (e.g., some legumes, okra, broccoli, spinach, turnip greens, asparagus, Brussels sprouts, endive, lentils) contain more than 80 mcg of folate/serving (the amount that is greater than or equal to 20 percent of the RDI (i.e., that amount that would be required for a claim of a "rich" source)), the great majority of foods contain folate at lower levels. For example, oranges, grapefruit, many berries, peas, many vegetable juices, beets, and parsnips contain folate at levels of 40 to 80 mcg/serving (i.e., at or above 10 percent of the RDI or at levels that meet the requirement of a claim of a "good" source) (Ref. 22).

##### *a. General comments.*

15. Many comments and the Folic Acid Subcommittee and Food Advisory Committee were generally satisfied with the eligibility requirements and supported FDA's proposal to allow claims on foods that were at least a good source of folate. These comments supported the criterion because it would accommodate a wide variety of fruits and vegetables that would be excluded if the eligibility requirement was set at a higher level. One comment, however, suggested that the proposed amount was

too high and might exclude some commonly consumed foods such as peas.

A third group of comments thought that the proposed amount was too low. Some of the comments said that claims should not be permitted unless the food provides at least 20 percent of the RDI (i.e., 80 mcg folate/serving), arguing that it was poor policy to make exception to the general health claims requirements regulations, and that if the goal is to maximize intake of folate, then 20 percent of the RDI should be the minimum amount allowed for the claim. Others felt strongly that the claim should be limited to those foods or supplements that provide 100 percent of the RDI per serving or per dose.

The agency is concerned that if it required (in accord with § 101.14(d)(2)(vii)) that the food contain 20 percent or more of the RDI for folate (i.e., 80 mcg or more folate per reference amount customarily consumed; an amount sufficient to qualify for a "high" or "excellent source of" nutrient content claim) to bear a health claim, many good food sources of folate would not qualify without fortification.

One of Congress' purposes in providing for health claims was to enable Americans to maintain a balanced and healthful diet (H. Rept. 101-538, supra, pp. 9-10). Given this fact, and given that the evidence demonstrates that the risk of neural tube defects can be affected by consuming foods that, while good sources of this nutrient, do not provide the high level that is provided by supplements and highly fortified foods (see Refs. 11, 13, 16, and 17), FDA concludes that it would not be consistent with the intent of the 1990 amendments to set requirements that would limit eligibility to bear a health claim to the foods that are high in folate.

Use of a qualifying criterion for the health claim that is consistent with the "good source" definition (i.e., 10 to 19 percent of the DV; 40 to 76 mcg folate/serving) provides for an amount of the nutrient that allows a wide variety of fruits, vegetables, and whole grain products to qualify to bear the health claim, is consistent with current Federal guidelines for general dietary patterns, and yet is still likely to result in a daily dietary intake of folate that the data show may reduce the risk of neural tube defects. For example, current Federal dietary guidelines recommend five or more servings of fruits and vegetables and six or more servings of grain products per day. Consumption of fruits, vegetables, and grain products in the recommended amounts would likely result in daily intakes of folate of 0.4 mg

(400 mcg) or more, even though individually many of the foods consumed contain less than 20 percent of the RDI for folate per reference serving (Ref. 22).

Accordingly, FDA is adopting § 101.79(c)(2)(ii)(A), which provides that conventional foods and dietary supplements can bear a folate/neural tube defect health claim if they contain 10 percent or more of the RDI for folate per reference amount customarily consumed (i.e., meet the definition for a "good source" claim in § 101.54 (21 CFR 101.54)). The availability of the claim for a wide variety of products will provide flexibility to women in deciding how to individually achieve the target intake by selecting from among foods that naturally contain folate, dietary supplements, and highly fortified foods.

##### *b. Higher qualifying amounts for dietary supplements than for foods.*

16. Several comments stated that to qualify to bear the claim, each food should provide at least 25 percent of the RDI, and each supplement should provide 100 percent of the RDI. However, these comments did not provide any support for the levels that they suggested or for why supplements should have to have a higher level of the nutrient than a conventional food.

Having dealt with the level necessary to qualify to bear the claim in response to the previous comment, the agency will deal here with the question of whether, to qualify for a claim, dietary supplements should be required to provide more folate than foods. The agency concludes that there is no reason why they should. In response to comment 7 of this document, the agency concluded that the available scientific evidence establishes that sources of folate are equivalent in their ability to provide folate. Thus, there is no basis for requiring that either dietary supplements or conventional foods provide more than 10 percent of the RDI for folate per reference amount customarily consumed to qualify for the claim.

##### 2. Disintegration and Dissolution of Dietary Supplements

FDA proposed in § 101.79(c)(2)(ii)(C) to disqualify dietary supplements from bearing a health claim if they fail to meet the United States Pharmacopeia (USP) standards for disintegration and dissolution. The agency tentatively concluded that the benefits of folate intake from food and dietary supplements can only be obtained if the folate is available for absorption and metabolism by the body. The agency noted that a dietary supplement that does not disintegrate and dissolve

clearly does not provide the nutrient in an assimilable form, and that a claim for such a supplement would be misleading because the supplement would not provide the nutrient that is the subject of the health claim (58 FR 58283).

17. Several comments agreed with the agency's proposed requirement and urged the agency to require all dietary supplements to meet such quality standards. Another comment proposed that the agency use the USP standards that are currently under development, and that the dissolution requirement become effective when the USP proposal becomes effective. The USP commented and proposed wording for use in § 101.79(c)(2)(ii)(C): "Folic acid present in dietary supplement dosage forms (e.g., tablets, capsules) shall meet the requirements of the United States Pharmacopeia as defined in Section 201(j) of the act."

Another comment stated that in making this proposed requirement effective for dietary supplements, the agency would accord the same claim to foods (i.e., conventional foods) without similar requirements for bioavailability, and that excluding foods from this requirement was scientifically unjustified. The comment did not identify conventional foods from which folate had been demonstrated to be unavailable or elaborate on the concern.

The agency proposed that dietary supplements meet USP standards for dissolution and disintegration, and that bioavailability under conditions of use stated on the label be shown *only* if there are no applicable USP standards for disintegration and dissolution. Thus, the agency proposed that a demonstration of bioavailability would be required *only* if there were no USP method available to check for dissolution and disintegration.

The comment that stated that in making the requirement proposed in § 101.79(c)(2)(ii)(C) effective for dietary supplements, the agency would accord the same claim to conventional foods without similar requirements, may have misread the agency's proposed requirement. "Bioavailability" includes, but is not limited to, dissolution and disintegration. Dissolution and disintegration are necessary preconditions for absorption and subsequent metabolism. Digestive processes ensure that conventional foods are digested, and that components are liberated for absorption. With respect to the bioavailability of folate from conventional foods, the agency is aware that the bioavailability of folate varies widely but is not aware of any foods from which folate has been shown to be unavailable.

However, dietary supplements, including folate-containing supplements, can be manufactured in a manner that prevents dissolution and disintegration (e.g., extremely compressed preparations), and the digestive processes may be insufficient to ensure the liberation of the components for absorption. The components of such a supplement would not be available for absorption and utilization by the body. A claim on a dietary supplement that does not disintegrate or dissolve would be misleading because the supplement would not meet the preconditions necessary to ensure that the nutrient that is the subject of the claim is available for absorption.

The agency did not receive other comments contending that dietary supplements should not meet USP standards for disintegration and dissolution, or that bioavailability should not be demonstrated when applicable USP disintegration and dissolution standards are not available. The agency is adopting § 101.79(c)(2)(ii)(C) as proposed and is redesignating it as § 101.79(c)(2)(ii)(B).

### 3. No Health Claim on Foods or Supplements Containing More Than 100 Percent of the RDI for Preformed Vitamin A or Vitamin D

In § 101.79(c)(2)(iii), FDA proposed that a health claim for folate and neural tube defects be prohibited on conventional foods and on dietary supplements that contain more than 100 percent of the RDI for vitamin A as retinol or preformed vitamin A or vitamin D per serving or per unit. The agency proposed this limitation because of the recognized toxicity of high intakes of these vitamins for the fetus and the teratogenic effects of these nutrients at levels not greatly in excess of the RDI.

18. Several comments agreed with FDA's proposal, noting that many dietary supplements currently contain more than 100 percent of the RDI for vitamin A, and that such levels are unnecessary and potentially harmful. Another comment misread the proposed requirement regarding vitamin A and noted that since manufacturers were now increasing the  $\beta$ -carotene content of supplements because of health benefits, these supplements should not be excluded from carrying a folate/neural tube defect claim because of their high  $\beta$ -carotene content.

The agency is aware that folate is often combined with other nutrients, particularly vitamins and minerals, in dietary supplement formulations or in highly fortified foods. In light of the

expectation that the presence of a health claim on the label of such products is likely to result in increased intake of these products, FDA is concerned that some consumers may try to increase their folate intake by consuming multiple doses of dietary supplements or multiple servings of highly fortified foods. The agency was concerned that, for some fortified foods and dietary supplements that contain both folate and preformed vitamin A or vitamin D, consumers could be exposed to excessive vitamin A or vitamin D intakes in their attempts to obtain increased amounts of folate. The agency, however, did not propose similar requirements for  $\beta$ -carotene because the agency is not aware of data on potential teratogenic or other adverse effects of  $\beta$ -carotene on the fetus.

This limitation is consistent with other recent recommendations. In 1991, the CDC recommendation for increased intake of folate by women with a history of a neural tube defect-affected pregnancy (Ref. 23) warned against overconsumption of multivitamins because of the potential for excessive intakes of vitamins A and D from such preparations and the known adverse effects of these vitamins on the health of the fetus. In addition, recent recommendations in Canada for women of childbearing age regarding folic acid and neural tube defects recognized the teratogenicity of high levels of vitamin A and cautioned against excessive intakes of this nutrient (Ref. 24).

With the exception of the comment regarding  $\beta$ -carotene discussed above, the agency received no comments objecting to this requirement. Thus, the agency is adopting § 101.79(c)(2)(iii) as proposed. The agency advises that the limitation contained in this provision pertains only to conventional foods or to dietary supplements that contain more than 100 percent of the RDI for vitamin A as retinol or preformed vitamin A or vitamin D.

## E. Label Information

### 1. Mandatory Nutrition Labeling

In § 101.79(c)(2)(iv), FDA proposed to require that the nutrition label of conventional foods or dietary supplements bearing the folate/neural tube defect health claim provide information about the amount of folate in the food or dietary supplement. This proposed requirement is consistent with § 101.9(c)(8)(ii) (21 CFR 101.9(c)(8)(i)), which states that the declaration of vitamins and minerals on the nutrition label shall include any of the vitamins

and minerals listed in § 101.9(c)(8)(iv) when a claim is made about them.

19. One comment agreed with the proposed requirement for mandatory nutrition labeling on products bearing the folate/neural tube defects health claim. Another comment noted that use of multiple terms such as "micrograms," "milligrams," etc., would probably confuse lay persons.

The agency agrees with the comments and is adopting, with the modifications noted below, the requirement in § 101.79(c)(2)(iv) that products bearing the health claim include in the nutrition labeling information about the amount of folate in the food.

FDA adopted the 1980 Recommended Dietary Allowance (RDA) values as RDI values, with folate values expressed on the label in milligrams (mg) and percent of the DV (58 FR 2206, January 6, 1993). In the Federal Register of January 4, 1994 (59 FR 427 at 431), FDA proposed to amend § 101.9 by revising paragraph (c)(8)(iv) to state, among other things, the RDI for folate in micrograms (i.e., 400 micrograms; 400 mcg). The agency stated that changing the current unit of measure for folate will facilitate consumer comprehension of quantitative nutrient information because consumers are more familiar with this nutrient being expressed in microgram units.

In § 101.79(c)(2)(i)(F) and (c)(3)(iv), FDA has modified the codified language so that all references to folate intake in the health claim will be required to be expressed as percent DV with the option of adding the microgram equivalent in parentheses. That is, values for folate will be expressed as percent of the DV (i.e., the percent of the RDI as established in § 101.9(c)(8)(iv)). FDA has modified the codified language in § 101.79(c)(2)(i)(F) so that reference to the safe upper limit of daily folate intake in the health claim will also be required to be expressed as percent DV with the option of adding the microgram equivalent in parentheses (see comment 32 of this document). Thus, in response to the comment's concern about the confusion that would result if multiple terms are used to describe the level of folate, FDA has modified the regulations to provide for consistent terminology.

## 2. Identifying the Nutrient

In proposed § 101.79(c)(2)(i)(B), FDA considered the use of synonyms for "folate" and the need to aid consumers in understanding this nutrient. The agency provided for the use of synonyms and for additional description of this term through phrases such as "folate," "folic acid," "folacin,"

"folate, a B vitamin," "folic acid, a B vitamin," and "folacin, a B vitamin."

20. Several comments agreed that the agency's proposed synonyms are appropriate. Other comments urged that a single term, for example, "folic acid," "folic acid, a B vitamin," "folate," or "folate, a B vitamin," be used throughout all claims. Other comments agreed with the use of the agency's proposed synonyms to encourage the consumption of healthy diets but recommended that claims be worded in such a way as to demonstrate that "folic acid" is the effective form. Several comments disagreed with use of the term "folacin," noting that it was rarely used.

The agency notes that the descriptive term "a B vitamin" in conjunction with "folate," "folacin," or "folic acid" is commonly used in lay information for consumers and may be useful for consumers in indicating the nutritive function of folate as a vitamin. FDA is thus retaining the provision for its optional use in § 101.79(c)(2)(i)(B).

FDA recognizes that current regulations for nutrition labeling in §§ 101.9 and 101.36 do not include the term "folic acid" as an allowable synonym for folate. This omission was an oversight when the agency amended § 101.9 (58 FR 2079 at 2178, January 6, 1993), and when it promulgated § 101.36 (59 FR 373, January 4, 1994). Before it was amended, § 101.9 had listed folic acid as the preferred term, with folacin as an allowable parenthetical synonym. When it proposed amendments to § 101.9 in 1990 (55 FR 29847, July 19, 1990), the agency explained why the term "folate" was preferable to "folacin". However, an explanation for use of "folic acid" was inadvertently omitted in that document, as was inclusion of the term "folic acid" as an allowable synonym.

The agency has advised firms that it would have no objection to the use of the term "folic acid" in nutrition labeling. In light of common usage and FDA policy, and for consistency among nutrition labeling and health claim regulations, the agency is making a technical amendment to §§ 101.9 and 101.36 in this final rule to include "folic acid" as an allowable synonym for folate.

The agency notes that, as discussed in comment 6, above, the terms "folic acid" and "folate" are both used in the PHS recommendation (Ref. 5). By allowing the use of these terms, the PHS recommendation can be quoted directly on the label if all other requirements for the health claim are met. The inappropriateness of limiting the term to "folic acid" to describe the relationship

has been discussed in response to comment 6 of this document. Therefore, FDA is adopting § 101.79(c)(2)(i)(B) as proposed.

## 3. Identifying Diets Adequate in Folate

In § 101.79(c)(2)(ii)(B), the agency proposed to require that health claims relating folate to neural tube defects identify sources of folate by stating that adequate amounts of folate may be obtained by making specific dietary choices of folate-rich foods, as well as through use of dietary supplements or fortified breakfast cereals. The purpose of this proposed requirement was to assist women in obtaining adequate amounts of folate in their diets by providing information on sources of folate. In proposed § 101.79(c)(2)(ii)(B), the agency provided examples of the types of phrases that could be used to meet this requirement (e.g., "Adequate amounts of folate, a B vitamin, can be obtained from diets rich in fruits, dark green leafy vegetables and legumes, enriched grain products, fortified cereals, or from dietary supplements").

21. Many comments agreed with the proposal to require statements that dietary sources such as fruits, vegetables, and grains may contribute folate to the diet, although some comments disagreed with providing specific details, such as recommended numbers of servings. Other comments supported the agency's proposed approach, emphasizing that the health claim must help consumers understand that, in pregnancy, it is the total diet, not a single food, that is related to health outcome, and that there is good evidence for dietary claims regarding increased folate intake and reduced risk of neural tube defects. Another comment stated that health claims should not reveal a bias against food forms, fortificants, or dietary supplements.

Other comments disagreed with the proposal to identify healthful dietary patterns on the basis that many women will not change their eating habits, and that it is therefore important to point out the importance of use of dietary supplements. Other comments noted that the statements regarding beneficial diets were overly focused on food and should be made optional, that adding dietary information to the health claim reduces its educational effectiveness, and that inclusion of such information was neither required by law nor consistent with other authorized health claims such as that for calcium and osteoporosis. Several comments recommended that statements regarding diets adequate in folate be made optional because such information is

better presented in educational materials.

The agency disagrees with the comments that stated that the proposed statements regarding sources of folate were overly focused on food. Such comments imply that FDA was biasing the statements against dietary supplements. In fact, each example included dietary supplements in the list of sources of folate (e.g., fruits, vegetables, enriched grain products, fortified cereals, and dietary supplements). The agency also disagrees that the educational effectiveness of the claim is reduced by inclusion of the proposed statement because statements of this type provide, in an abbreviated form, information on sources of folate about which a consumer may be unaware.

In the context of a total diet, the consumer needs flexibility in deciding how to increase folate intake. Provision of this information is consistent with section 403(r)(3)(B)(iii) of the act, which states that the claim shall be stated in a way that enables the public to understand the relative significance of the claim in the context of the total daily diet. Awareness of the food sources of folate, including dietary supplements, will assist women in recognizing the significance of the claim in the context of the total diet. Provision of information on sources of folate in the health claim will assist consumers by making them aware that specific foods and dietary supplements contain folate.

However, FDA recognizes that while there has been a noticeable increase in the use of health claims over the last 2 years, the number of products that bear health claims is not as great as the agency had anticipated. The agency is therefore interested in simplifying claims to facilitate their increased use. The agency is particularly interested in removing so-called "required" elements that are not necessary to ensure that the claims are truthful, not misleading, and scientifically valid. While the agency agrees with the comments that supported inclusion of information on the dietary sources of folate, and while it supports health claim statements that include examples of dietary sources of this nutrient, the agency is concerned that requiring such specific information will increase the length of the claim and may dissuade manufacturers from including it in their labeling.

In comment 14 of this document, the agency concluded that information regarding overall improvement in a woman's diet and nutrition throughout her childbearing years is of considerable importance because pregnancy outcome

depends upon adequate intake of a wide range of nutrients. The agency is adopting § 101.79(c)(2)(i)(H), which requires that the health claim state that there is a need for a healthful diet as well as adequate folate intake. FDA has concluded that this information is necessary to ensure that the claims have proper balance.

The agency is persuaded that shorter claims that state the need for a healthful diet, without reference to specific foods, will meet the objective of encouraging broader use of the claim while alerting women to the importance of overall diet during the childbearing years. Therefore, FDA is requiring that claims state that adequate folate needs to be consumed as part of a healthful diet (see section II.C.5. of this document, and new § 101.79(c)(2)(i)(H) without identifying specific sources. The appearance of the claim on a wide range of qualifying foods will itself convey information about the variety of sources of folate available to women as part of a healthful total diet.

Therefore, the agency is removing proposed § 101.79(c)(2)(ii)(B) in its entirety and is adding in the codified language a provision (§ 101.79(c)(3)(vii)) for optionally including in the claim information that identifies sources of folate. Because of these changes, FDA has adopted proposed § 101.79(c)(2)(ii)(C) as § 101.79(c)(2)(ii)(B).

#### 4. Identifying the Health-Related Condition

In developing proposed § 101.79(c)(2)(i)(C), FDA considered whether women might be confused or not understand the term "neural tube defect" and provided for some qualification of this term through use of alternate phrases such as "the birth defect spina bifida," "the birth defects spina bifida and anencephaly," "spina bifida and anencephaly, birth defects of the brain or spinal cord," and "birth defects of the brain or spinal cord, spina bifida and anencephaly."

22. The agency received several comments regarding these proposed synonyms. A comment agreed with the agency that the health-related condition must be specified and stated that the agency's proposed synonyms were appropriate. Another comment noted that "anencephaly" is not a familiar term, and that a phrase such as "certain serious birth defects, neural tube defects" is preferable. Another comment recommended that only the statement "neural tube defect" be allowed because it is the more appropriate and accurate term, and because consumers will benefit from seeing the same identifying

statements in health claims on many products. Several comments, however, asserted that consumers will not understand "neural tube defects" and stated that a more understandable term might be "birth defects of the brain and/or spinal cord."

The agency has considered these comments and concludes that the term and qualifiers provided in its proposed rule, i.e., "neural tube defects," "the birth defect spina bifida," "birth defects spina bifida and anencephaly," "spina bifida and anencephaly, birth defects of the brain or spinal cord," and "birth defects of the brain or spinal cord anencephaly or spina bifida," will allow manufacturers considerable flexibility in crafting claims and in educating consumers. The agency is also persuaded to include the option of using the simpler terms "birth defects of the brain or spinal cord" or "brain or spinal cord birth defects" and has modified § 101.79(c)(2)(i)(C) accordingly. The agency accepts the suggestion that use of the latter terms will make the claims simpler and more useful to consumers because the phrase may be more understandable than phrases that include medical terms such as "neural tube defects" or "anencephaly".

The agency also considered whether use of the very general terms "some birth defects" or "some serious birth defects" would be appropriate. As discussed in its January 1993 final rule on folate and neural tube defects (58 FR 2606 at 2610), the act requires that claims on foods be truthful and not misleading. The agency recognizes that, based on the results of the Medical Research Council trial, the association between folate intake and birth defects is limited to neural tube defects. The Medical Research Council trial found that folic acid, while significantly reducing the risk of neural tube defects in women at high risk of recurrence of this complication, did not significantly alter the incidences of a wide variety of other birth defects in the population studied (Ref. 14). Similarly, Czeizel et al. (Ref. 15) reported that the results of the Hungarian trial that studied use of a multivitamin/multimineral supplement containing 0.8 mg of folic acid showed no reduction in incidences of birth defects other than neural tube defects.

FDA also points out that the prevalence of neural tube defects in the United States has been steadily declining in recent decades, and that the estimated incidence is presently about 1 in 1,600 births (Ref. 25). Currently, estimated incidences of other serious birth defects are considerably higher than that for neural tube defects. For

instance, estimated incidences are 1 in 115 for birth defects involving the heart and circulation, 1 in 130 for those involving the muscles and skeleton, 1 in 135 for those involving the genital and urinary tract, 1 in 235 for those involving the nervous system and eye, 1 in 735 for club foot, and 1 in 635 for chromosomal syndromes (Ref. 25).

Because neural tube defects constitute a relatively small fraction of all birth defects, women should not be misled into a false sense of security that they can affect their risk of all birth defects through diets adequate in folate. The agency has therefore decided not to include use of the more general terms "some birth defects" or "some serious birth defects" because use of such terms would fail to disclose the material fact that the food substance/disease relationship is specifically between folate and neural tube defects. Use of such general terms can create the impression that adequate folate intake will reduce a woman's risk of other serious birth defects, and women might, as a result, discount risk factors for other birth defects (e.g., alcohol use, drug abuse).

#### 5. Safe Upper Limit of Daily Intake

Sections 403(r)(3)(A)(ii), 402(a), and 409 of the act establish that the use of a substance in a food must be safe. Based on concerns discussed in the Federal Register of January 6, 1993 (58 FR 2606), the agency concluded that it could not authorize a health claim on folate and neural tube defects at that time. The agency was concerned that the possibility exists that folic acid itself could be a substance that increases the risk of a disease or a health-related condition in persons in the general population (see section 403(r)(3)(A)(ii) of the act).

Recognizing the potential for adverse effects from high intakes of folate, PHS included a caution statement in its recommendation that "because the effects of higher intakes are not well known but include complicating the diagnosis of vitamin B<sub>12</sub> deficiency, care should be taken to keep total folate consumption at <1 mg per day, except under the supervision of a physician" (Ref. 5).

In § 101.79(c)(2)(i)(G), FDA proposed to require a statement as part of the health claim on fortified foods in conventional food form and on dietary supplements containing more than 25 percent of the RDI for folate per unit or per serving that 1 mg of folate per day is the safe upper limit of intake. The agency noted that the availability of the health claim would likely encourage increased intakes of health-claim

labeled foods, and that, if intakes of highly fortified foods and dietary supplements were increased, it could result in folate intakes above the level known to be safe.

The agency received comments addressing two issues related to safe use of foods bearing health claims: (1) Is there a need for concern about a safe upper limit of daily intake? (2) If so, should a statement identifying a safe upper limit of intake be included in a health claim, and how should such a statement be worded?

a. *Need for concern about a safe upper limit of daily intake.* FDA tentatively concluded that, under certain circumstances, there was a need to disclose the safe upper limit of intake in the health claim and tentatively decided to use 1 mg per day (1,000 mcg; 250 percent of the DV) of total folate as the upper limit for such intake (58 FR 53254 at 53273).

The agency noted in the final rule of January 6, 1993 (58 FR 2606 at 2612), and the proposed rule of October 14, 1993 (58 FR 53254 at 53266), that there is a general paucity of evidence on the safety of daily folate intakes above 1,000 mcg (1 mg). The agency noted that there may be risks attendant upon increased consumption of folate for some groups in the population. The agency stated that, at the present time, the potential adverse effect that has been most extensively documented is a masking of anemia in persons with vitamin B<sub>12</sub> deficiency, while irreversible neurologic damage progresses. Other groups at risk from excessive intakes of folate include pregnant women, persons on antiepileptic (i.e., antiepileptic) medications, and those on antifolate medications. There were no data to identify the magnitude of other possible risks of increased folate intake or to establish safe use at daily intakes above 1,000 mcg.

In its proposal of October 14, 1993 (58 FR 53254 at 53266), the agency described how it had reached its tentative decision that 1 mg of total folate per day was the safe upper limit of intake. Based on its review of the scientific literature and its discussions with the Folic Acid Subcommittee, the agency tentatively concluded that: (1) For those with vitamin B<sub>12</sub> deficiency, there was little likelihood of problems at daily intakes lower than 1 mg (58 FR 53254 at 53268 to 53270); (2) an upper limit of intake of 1 mg of folate per day was safe for pregnant women and for persons with epilepsy; (3) doses of folic acid of up to 1 mg per day have not been reported to reduce the effectiveness of medications that interfere with folate metabolism; (4) effects of long-term continuous exposures of body tissues to

elevated blood levels of folic acid, which occur when the body's capacity to metabolize folic acid is exceeded, have not been evaluated; and (5) there have been no long-term studies to quantitate the effects, if any, of increased folate intake on the metabolism of other nutrients.

The agency stated (58 FR 53254 at 53268) that it knew of no data that would support the long-term safety of continuous daily folate intakes of more than 1 mg. The agency, noting that the value of 1 mg for a safe upper limit of daily folate intake could be modified if data were available to support such a decision, solicited comments and data on this point.

In addition, the agency described how it had reached its tentative decision that a statement that 1 mg of total folate per day was the safe upper limit of daily intake should be required on products bearing the health claim and fortified above 25 percent of the RDI for folate. The agency's tentative conclusion was based on, among other considerations: (1) The scientific evidence, and the view expressed by experts, that there are no data to ensure that adverse effects are not likely to occur at daily intakes above 1 mg (Refs. 6, 7, 8, and 26); (2) the PHS recommendation that folate intake of women of childbearing age should not exceed 1 mg per day (Ref. 5); and (3) the support by the Folic Acid Subcommittee of FDA's use of 1 mg of total folate per day as a safe upper limit guide when considering fortification strategies. The upper safe limit of intake that FDA proposed was based on its best scientific judgment at the time. The agency solicited comments and data on its tentative judgment.

Some comments expressed uncertainty regarding an amount that would represent a safe upper limit of daily intake of folate, while other comments strongly agreed or strongly disagreed with FDA's proposal that 1,000 mcg of total folate per day is the safe upper limit of intake.

The agency did not receive any data relating to safety of long-term intakes of folate at levels above 1 mg per day for any of the groups considered at potential risk from increased intakes.

23. Several comments noted that the agency should not misconstrue the absence of safety data on folate intakes of 1 to 4 mg (1,000 to 4,000 mcg) per day as evidence of the absence of harm; that because daily intakes for the general population are well below 1 mg, it has never been established that 1 mg per day of folate from all sources is a safe daily upper limit; and that the upper safe limit of intake for African-Americans, and perhaps Hispanic

Americans, is not known. Several comments noted that pernicious anemia has an earlier age-at-onset among African-Americans than among Caucasians, and that vitamin B<sub>12</sub> deficiency is not rare in persons with sickle cell anemia. Another comment noted that the level of folate that will accelerate the neurologic disorders of vitamin B<sub>12</sub> deficiency is unknown, and that physicians see patients who have been taking folic acid supplements who present with neuropsychiatric disturbances. Another comment noted that there were uncertainties regarding effects of chronic exposures of children, whose requirements for folate are lower than those of adults, to increased intakes of folic acid. Uncertainties regarding safety of increased intakes of this nutrient were the major factor in the opposition in the Folic Acid Subcommittee/Food Advisory Committee to FDA's proposed rules (Ref. 8).

Many comments agreed with FDA's estimate of 1 mg of folate as an upper safe limit of intake given the paucity of information concerning the possible risks of excess folate intakes. Other comments noted that the masking of pernicious anemia is real, but that there is no evidence for folate toxicity at daily intakes of 1 mg/day or less. The comments said that the value of 1 mg/day has, therefore, emerged as being safe. Other comments recognized that overconsumption of folate may complicate the diagnosis of vitamin B<sub>12</sub> deficiency, but that there is limited evidence regarding effects of intakes of folic acid between 400 mcg and 5,000 mcg per day.

FDA notes that a major factor in both the Folic Acid Subcommittee's and the Food Advisory Committee's concern about FDA's proposals was the fundamental issue of lack of documentation of safety of long-term daily intakes at levels above 1,000 mcg (Ref. 8). The agency is also aware that the Committee members expressed considerable concern about the lack of information on the size of the population potentially at risk from increased intakes of folate. Specifically, the agency did not receive data regarding potential adverse effects of increased folate intakes in African-American women or in children. The agency notes that the absence of data on long-term effects of increased folate intakes does not allow the agency to adequately identify those potentially at risk.

As stated above, the agency is not aware of any data that establish the safety of long-term intakes of folate above 1,000 mcg per day. The absence

of any data that allow systematic evaluation of intakes above this level means that potential risks and at-risk groups cannot be adequately defined or described. FDA notes that some members of the Folic Acid Subcommittee and most folate and vitamin B<sub>12</sub> experts submitting comments (Ref. 8) were concerned about the lack of documentation of safety of daily long-term intakes of folate above the level of 1 mg/day. In addition to concerns regarding those with low vitamin B<sub>12</sub> status, other safety concerns included uncertainties of effects of increased folate intakes by young children and the unknown physiological significance of circulating free folic acid in the blood, particularly in pregnant women. In its proposed rule (58 FR 53254 at 53269), the agency summarized evidence from the scientific literature that high levels of free folic acid are not normally found in the circulation, and that folic acid is concentrated in crossing the placenta and accumulates in fetal tissues. The agency also noted that no information is available to ascertain whether developing neural tissue is protected from the neurotoxic effects of very high circulating levels of free folic acid. None of these issues were addressed in comments that the agency received.

Comments that disagreed with FDA's proposal to consider 1,000 mcg folate/day as the safe upper limit of intake raised several issues which are considered below:

i. *Basis for a safe upper limit: Synthetic folic acid versus total folate.*

24. A comment stated that the limit should be based on supplemental synthetic folic acid only because only this form has been associated with masking of the anemia of pernicious anemia. This issue of whether the upper limit should be based on total folate or on synthetic crystalline folic acid was raised in several comments, with some comments of the opinion that it was appropriate to use estimated consumption of folate from all sources in defining the safe upper limit of intake and others recommending use of "crystalline folic acid" only.

The agency disagrees that the safe upper limit of daily intake should be based on "crystalline folic acid" rather than total folate from all sources. FDA notes that the distinction between "synthetic folic acid," referring only to crystalline folic acid, and "folate," referring only to naturally occurring food folates, with respect to the 1,000 mg/day estimate of safe daily intake, is an artificial one and is not consistent with what is known about the nutritional interrelatedness of a variety

of folate vitamin forms in providing coenzyme forms of the vitamin for meeting the body's needs for this essential nutrient. Issues relating to "folic acid" versus "folate" are discussed in response to comment 6 of this document.

Metabolic needs for folate are met from body pools of reduced coenzymes, regardless of whether these coenzymes are derived from synthetic folic acid or from naturally occurring food folates. While it is true that evidence relative to the masking of the anemia of vitamin B<sub>12</sub> deficiency has been obtained from persons who consumed or were treated with synthetic folic acid, such individuals were also consuming unknown quantities of folate from foods. Thus, total daily folate exposures associated with the masking have not been quantified, and the effect of food folates on adverse effects is not known. It is also not known whether the variable responses, in terms of masking effects, to low levels of folic acid in supplements are the result of differences in folate intakes from background diets or of other factors that are currently not understood. For these reasons, it is not possible to attribute all adverse effects solely to crystalline folic acid.

In addition, high intakes of food folates can have adverse effects in persons with poor vitamin B<sub>12</sub> status. With respect to nonpernicious anemia-related vitamin B<sub>12</sub> deficiency, Sanders and Reddy (Ref. 27) noted that megaloblastic anemia is rarely encountered in Caucasian vegetarians and vegans because of their high intakes of folate. These authors reported that, for example, the folate content of diets of vegan children aged 6 to 13 years was twice as high as that of omnivorous children aged 7 to 12 years (Ref. 27). Because the high folate intakes would at least temporarily improve the associated anemia, vitamin B<sub>12</sub> deficiency usually presents with neurological signs and symptoms in infants (Ref. 27). Herbert reported that studies over several decades have all indicated that major myelin synthesis damage from vitamin B<sub>12</sub> deficiency with only minor hematopoietic (i.e., hematologic) damage reflects better folate status because folate improves hematologic, but not neurologic, manifestations of the deficiency (Ref. 28). He also found generally higher red cell folate in persons with greater myelin damage (that only vitamin B<sub>12</sub> deficiency produces) than in persons with greater hematologic damage (which deficiency of either folate or vitamin B<sub>12</sub> produces) (Ref. 28).

The observations above suggest that a safe upper limit of daily intake is more



accurately based on total folate intake than on just intake of crystalline folic acid because under conditions in which vitamin B<sub>12</sub> utilization or intake is limited (i.e., in pernicious anemia or in nonpernicious anemia-related vitamin B<sub>12</sub> deficiency), either crystalline folic acid or food folate may cause adverse effects when consumed in excess.

The agency noted in response to comment 6 of this document, that use of a distinction between "folic acid" and "folate" is inconsistent with the PHS recommendation, which uses these terms interchangeably (Ref. 5), and with advice provided by FDA's and CDC's advisory panels. Moreover, use of such a distinction is not supported by recent statements from experts on folate and vitamin B<sub>12</sub> (Refs. 7, 8, and 26). Therefore, the agency concludes that the safe upper limit of daily intake should be based on total folate intake (i.e., on consumption of folate from all sources).

ii. *Lack of evidence of untoward effects of increased intakes.*

25. Several comments that disagreed with the agency's tentative conclusion that 1 mg folate per day from all sources is the safe upper limit of intake stated that there is no evidence that maximum intakes of 1,500 mcg to 2,000 mcg will result in any untoward effects. Another comment reviewed the literature describing the effects of intakes of 1,000 to 5,000 mcg folic acid per day in persons with vitamin B<sub>12</sub> deficiency and concluded that the literature did not reveal any substantial safety concerns. Another comment stated that 5,000 mcg/day should replace 1,000 mcg/day as the upper limit of safe intake.

The agency is aware that the literature describing the effects of intakes of folic acid between 1,000 and 5,000 mcg per day is very limited but disagrees that there is no evidence of untoward effects of daily folate intakes of 1,500 to 2,000 mcg per day, and that 5,000 mcg per day should be identified as the safe upper limit of intake.

The literature describing the effects of daily intakes of 1,000 to 5,000 mcg folic acid includes three uncontrolled intervention trials involving 15 persons (Refs. 29, 30, and 31) and 16 case reports (Refs. 32, 33, 34, 35, 36, and 37). These reports represent a very small data base, with information from a total of only 31 individuals. Moreover, the agency notes that, among these data, exposures of 9 individuals to daily intakes of 1,000 to 5,000 mcg folic acid lasted for less than 30 days (e.g., Refs. 30, 31, 32, and 33). Therefore, these reports are not useful in assessing the safety of life-long exposures. However, hematological responses that could lead to a delay in the diagnosis of vitamin

B<sub>12</sub> deficiency were observed in 9 of the 16 patients (i.e., in more than 50 percent) whose daily oral intakes of folic acid were in the range of 1,000 to 5,000 mcg and continued for 1 month or more (Refs. 29, 32, 33, 35, and 37). Thus, the limited scientific literature shows that approximately half of the patients with pernicious anemia associated with vitamin B<sub>12</sub> deficiency will respond to folate at doses between 1,000 and 5,000 mcg per day when they are given the vitamin for relatively short periods of time (e.g., several months).

In addition, in discussing safety issues in its proposed rule (58 FR 53254 at 53267), the agency noted that, although there was a lack of systematic evaluation of the effect of folic acid on the anemia of vitamin B<sub>12</sub> deficiency at intakes of less than 5,000 mcg per day, several case reports have described hematologic improvement in pernicious anemia patients with doses of folic acid lower than 1,000 mcg/day (e.g., at 200 to 500 mcg/day; Refs. 38, 39, 40, 41, 42, 64 through 65, and 72 through 74). Thus, adverse effects have been reported at daily doses of less than 1,000 mcg, at doses of 1,000 to 5,000 mcg, and at doses greater than 5,000 mcg.

iii. *Lack of evidence of toxic effects of increased folate intakes in pregnant women.*

26. Another comment that disagreed with the agency's tentative conclusion noted that millions of pregnant women have taken prenatal vitamins containing 1,000 mcg folic acid, that folic acid at dosages of 4,000 mcg per day has been extensively studied in pregnant women, and that no toxic effects have been shown in healthy individuals.

The agency disagrees with the comment that folic acid at doses of 4,000 mcg per day have been extensively studied in pregnant women and are without toxic effects. The agency recognizes that pregnant women take prenatal supplements which usually contain 800 mcg of folic acid, and that such supplements have been in use for many years. FDA notes that, while there is no evidence that 800 mcg of folic acid per day (i.e., the RDA level for pregnant or lactating women) is unsafe for this group, such dosages are usually taken only during the second and third trimesters of pregnancy or during lactation to meet specific nutritional needs for limited periods of time and are usually taken under physician supervision. The Institute of Medicine in *Nutrition During Pregnancy* stated that the safety of large doses of folic acid in pregnant women has not been systematically determined (Ref. 43).

The agency notes also that the comment that folic acid at doses of 4,000 mcg per day has been extensively studied in pregnant women, and that such doses are without toxic effects, is not substantiated by the scientific data. In the only study utilizing 4,000 mcg folic acid/day, the Medical Research Council (MRC) trial, about 910 women took supplements containing 4,000 mcg of folic acid from the time of randomization into the trial until the 12th week of pregnancy (Ref. 14). At the conclusion of the study, the author stated that, although the MRC trial had sufficient statistical power to demonstrate the efficacy of the intervention, it did not have sufficient power to answer the question of safety for public health purposes.

Consequently, this study does not provide a basis on which to determine whether the use of 4,000 mcg/day of folic acid by pregnant women is safe.

Thus, the agency has not received any data or information that would persuade it that any level other than 1 mg (1,000 mcg) folate per day is the appropriate safe upper limit of intake for pregnant women.

iv. *Adverse effects in those with vitamin B<sub>12</sub> deficiency can be detected with clinical care.*

27. Another comment disagreed with the proposed 1,000 mcg safe intake limit and noted that adverse effects of high intakes of folate with respect to vitamin B<sub>12</sub> deficiency can be detected with clinical care. Other comments stated that the issue of masking of vitamin B<sub>12</sub> deficiency was overstated and predated modern clinical nutrition.

FDA is aware that, in many instances, the adverse effects of increased folate intake associated with the masking of the anemia of vitamin B<sub>12</sub> deficiency can be detected with clinical care but disagrees that this fact provides adequate justification for increasing the safe limit of daily intake. The agency notes that measurements of vitamin B<sub>12</sub> status are not performed on a routine basis by physicians. Currently, there are no population-based data on how many people in the United States have undiagnosed vitamin B<sub>12</sub> deficiency and thus might be at risk from increased intakes of folate. The agency noted in the January 6, 1993 final rule (58 FR 2606 at 2615), that significant percentages of the elderly, demented patients, acquired immune deficiency syndrome (AIDS) patients, and patients with malignant diseases have subnormal vitamin B<sub>12</sub> levels without having any of the classical manifestations of vitamin B<sub>12</sub> deficiency. Lindenbaum et al. recently reported that the prevalence of vitamin B<sub>12</sub> deficiency was greater than

12 percent in a large study (n=548) of free-living elderly Americans (Ref. 44). In addition, 5 to 10 percent of all patients, regardless of age or clinical status, are found to have low serum vitamin B<sub>12</sub> levels (58 FR 2606 at 2615). Little is known about whether folate supplementation would have any adverse effect on such persons, who are far more numerous in the U.S. population than are persons with pernicious anemia.

The argument that adverse effects in persons with vitamin B<sub>12</sub>-related problems can be identified with clinical care fails to consider whether such persons, who may be unaware of their vitamin B<sub>12</sub> status, would recognize an adverse effect as being the result of increased folate intake, and whether they would seek medical attention if subtle adverse effects were experienced. Thus, the agency concludes that the argument that adverse effects in persons with vitamin B<sub>12</sub>-related problems can be identified with clinical care does not provide a sufficient basis for increasing the safe upper limit of intake for such persons or for other persons in the general population for whom there are currently no data to establish the effects, if any, of high intakes of folate. In developing its proposed rule,

FDA was aware of the contentious nature of a proposed upper limit and specifically asked for data on this issue. This topic was also extensively discussed by FDA's Folic Acid Advisory Committee and Food Advisory Committee (Refs. 7 and 8). No data were submitted in any of the comments that addressed the issue of the safety of intakes above 1,000 mcg per day either for persons in the general population or for any of the groups identified as potentially at risk from increased folate intakes. The agency also notes that its position regarding use of 1,000 mcg folate per day as the safe upper limit of daily intake was supported by all comments from individuals with known expertise in folate and vitamin B<sub>12</sub> metabolism and related diseases.

Because there are inadequate data and information on the safety of consuming more than 1,000 mcg folate per day, the agency is unable to conclude that there is a reasonable certainty of no harm to persons consuming more than 1,000 mcg folate per day. In the absence of data on high intakes of folate, the agency is unable to adequately define the nature or magnitude of potential risk from increased folate intakes. At this time, the agency has no data to support a conclusion of safe use of folate above 1,000 mcg per day or data that would provide a basis for a change from the proposed upper limit of 1,000 mcg per

day to an upper limit of 5,000 mcg per day. In addition, for the reasons explained above, the agency has not been persuaded by the comments that it should consider synthetic folic acid as the only active form of the vitamin and thus base its estimate of a safe upper limit of intake on this form of the vitamin only.

The agency therefore concludes that, because of the lack of evidence of safe use at intakes greater than 1,000 mcg folate daily, and the potential for serious harm to some persons from such intakes, daily intakes above 1,000 mcg by the general population should not be encouraged.

b. *Including a safe upper limit of daily intake in the claim.* In recognition of comments and safety concerns discussed in its proposal, FDA, in § 101.79(c)(2)(i)(G), proposed to require a statement on fortified foods in conventional food form and on dietary supplements that contain more than 25 percent of the RDI (i.e., more than 100 mcg per reference amount customarily consumed or, for supplements, per unit) about the maximum safe daily limit for folate consumption. The agency proposed that such a statement (e.g., "Folate consumption should be limited to 1,000 mcg per day from all sources.") was necessary to prevent the health claim from being misleading regarding potential risks from excessive intakes.

In the October 14, 1993 proposal (58 FR 53254 at 53282), the agency, noting that the safe upper limit of intake was 1 mg (1,000 mcg), stated that a fortified food that contains more than 100 mcg folate per serving contributes more than 25 percent of the RDI and more than 10 percent of the daily limit. Therefore, it continued, consumption of such foods should be monitored by the consumer, so that he or she will not consistently or significantly exceed the upper limit.

In its proposed rule (58 FR 53254 at 53282), the agency also noted that it was not proposing to require that this statement be included in claims on the relatively small number of conventional foods that contain more than 100 mcg of folate without fortification (e.g., dark green leafy vegetables, certain legumes). The agency stated that it believed that there is no need for the consumer to monitor intakes of these foods because their folate content consists of reduced pteroylpolyglutamates whose bioavailability is generally considered lower than that of the folic acid (i.e., pteroylmonoglutamate) added as a fortificant to foods. The agency received many comments on this aspect of the proposal.

c. *General comments.*

28. Comments supporting inclusion of a caution statement in health claims stated that an admonition regarding excessively high intakes is absolutely essential in the health claim, and that the agency must require a meaningful and useful disclosure regarding the risks of excess intake. One comment stated more specifically that health claims related to folate and neural tube defects should be balanced by a warning statement that increased intakes of folate may increase the frequency of irreversible neurologic damage from vitamin B<sub>12</sub> deficiency. A related comment stated that, among Black and Hispanic females, folic acid fortification or supplementation is likely to do more harm than good, and that a caution statement was important for such groups. One comment recognized the need to set upper limits of safe intake but noted that, in the absence of strong evidence, it is inappropriate to warn consumers about potential adverse effects and detract from the benefits of the health claim.

Other comments supported the use of a statement of a safe upper limit of intake but found FDA's proposed language in § 101.79(c)(2)(i)(G) and in the model health claims (§ 101.79(d)) unsatisfactory because the agency failed to provide specific information on the potential adverse effects of overconsumption and failed to identify the subpopulations at risk from high intakes (e.g., the elderly).

The agency does not agree that it is inappropriate to warn consumers about the potential adverse effects of increased folate intake because adverse effects have been documented in the scientific literature. The agency's responses to comments 23, 25, and 27 of this document make clear that, for some population groups, there are risks attendant upon increased folate intake. Such groups include those with vitamin B<sub>12</sub> deficiency and African-American women. As noted above, the agency did not receive data providing evidence rebutting the risks of folate intakes above 1 mg per day (1,000 mcg/day) for these and other at-risk groups, such as pregnant women, children, persons on antiseizure medications, or persons on antifolate medications.

Therefore, the agency agrees with the comments that stated that it should require that a useful statement regarding risks of excessive intakes be included in the health claim. In response to the comment that the model health claims were unsatisfactory because they failed to identify specific subpopulations at risk from increased intakes (e.g., the elderly), the agency is advising that it will not require identification of specific

at-risk groups in the caution statement because the limited data available from populations consuming folate at the level of 1 mg per day (1,000 mcg per day) and above do not allow an adequate identification of all such groups to be made. Identification in the claim of only some of the groups at risk (e.g., the elderly) would be misleading because persons in other at-risk groups that were not identified in the claim could conclude that because they were not mentioned, they were not at risk from high intakes.

*d. Inappropriate to include caution statement only on fortified foods and supplements.*

29. Other comments stated that it was inappropriate to single out only fortified foods or supplements that contain folate above 25 percent of the DV for carrying a warning statement.

The agency proposed not to require the caution statement in health claims on the relatively small number of conventional foods that contain more than 100 mcg of folate without fortification (e.g., dark green leafy vegetables, certain legumes) because many of these foods are not consumed on a daily basis, and even when consumed regularly, the bulk and energy value of such foods tends to limit their consumption.

The agency has reevaluated whether foods that are naturally high in folate (e.g., those containing more than 25 percent of the DV) should carry the caution statement proposed for fortified foods or supplements containing more than 25 percent of the DV. The agency agrees with the comment that it is inappropriate to single out fortified foods and supplements for a caution statement because there is no justification for distinguishing between added and naturally-occurring nutrients. This decision is consistent with the agency's conclusion (see comment 23 of this document) that total folate intake from all sources needs to be considered in arriving at a safe upper limit of daily intake. For this reason, FDA has decided to require that the modified caution statement described in comment 31 of this document appear on any conventional food or dietary supplement that meets the criteria set out in § 101.79(c)(2)(i)(F).

*e. Optional caution statement.*

30. Another comment advised the agency to permit the identification of the 1,000 mcg per day limit as optional information.

The agency rejects this comment. Given the point of the health claim message, it is unlikely that an optional caution statement would be included in most health claims. Therefore, most

consumers would not be alerted to the potential adverse effects of high levels of folate or might assume that claim-bearing products without the caution statement were safer than products that bore a claim that included the caution statement. Consumption of products bearing the caution statement might come to be associated with potential adverse effects, while consumption of other products with an identical folate content that did not bear the caution statement would not be associated with such potential adverse effects. Because potential adverse effects are related to increased intakes of folate from any source, it would be illogical for the agency not to require the caution statement on all products that carry the health claim and that meet the criteria for the caution statement. Claims on products that meet the criteria and that fail to carry the caution statement would be misleading because they would fail to alert consumers to the material fact that there may be risks attendant upon excessive folate intakes.

*f. Upper limit of safe intake expressed as percent DV.*

31. Another comment agreed with the use of a caution statement but felt that the safe upper limit of intake should be expressed as percent of the DV.

The agency agrees with this comment because this method of communicating the safe upper limit of intake will provide consistency with the nutrition label, thereby enhancing the comprehensibility of the information. The agency notes that, as stated in response to comment 19 of this document and in the codified language in § 101.79(c)(2)(i)(F), the upper limit of daily intake is to be expressed in the claim as percent of the DV, with manufacturers having the option of including the microgram equivalent in parentheses (e.g., 250 percent DV (1,000 mcg)).

*g. Limit caution statement to products with 100 percent DV.*

32. Several comments said that a warning statement should be limited to higher-dose foods or dietary supplements (those containing 100 percent or more of the DV) unless further research and monitoring demonstrate that the risks of increased folate intakes from lower-dose foods or supplements are also significant. Other comments argued that there is no need to include a warning statement and noted that supplements and cereals with 100 percent of the DV have never carried such a warning statement. Other comments expressed the opinion that the warning statement would discourage increased consumption of folic acid supplements.

The agency has considered whether requiring that the caution statement appear in claims on foods or dietary supplements that contain more than 25 percent of the DV is too restrictive. The agency recognizes that such a requirement would require that caution statements appear as part of health claims on a wide range of products that contain more than 100 mcg folate per serving (e.g., dietary supplements, breakfast cereals) that have not previously carried such a statement. The agency agrees with the comment that the result of such caution statements could well be to discourage consumption of such products. It was not the agency's intent to cause such a result because breakfast cereals and dietary supplements have traditionally been important sources of folate for consumers who use them. Additionally, in the case of many dietary supplements, a statement regarding daily consumption (e.g., "consume one per day") is already included in the labeling and serves to inform consumers as to the appropriate daily intake.

The agency notes, however, that the health claim is intended to encourage women to increase their intakes of folate, and that the claim is likely to encourage some women to consume more of particular products, particularly those bearing the claim that are very high in folate, than they might otherwise consume. Thus, a caution statement regarding excessive intakes is appropriate on foods that contain very high levels of folate because the possibility is created by the claim itself that some women will achieve high folate intakes.

The agency has concluded that a statement about high consumption of folate is necessary if a product contains more than 100 percent of the DV (i.e., 400 mcg when labeled for use by adults and children 4 or more years of age; 800 mcg when labeled for use by pregnant or lactating women; 58 FR 2206 at 2213, January 6, 1993; Food Labeling; Reference Daily Intakes and Daily Reference Values). Such an amount of folate would exceed not only the DV's but the PHS recommended folate intake for women of childbearing age. Thus, the caution statement is required only on products that contain more than current recommended daily intakes of folate per serving.

The agency has redesignated proposed § 101.79(c)(2)(i)(G) as § 101.79(c)(2)(i)(F) and has modified this provision to read that:

Claims on foods that contain more than 100 percent of the Daily Value (DV) (400 mcg) when labeled for use by adults and children 4 or more years of age, or 800 mcg

when labeled for use by pregnant or lactating women) shall identify the safe upper limit of daily intake with respect to the DV. The safe upper limit of daily intake value of 1,000 mcg (1 mg) may be included in parentheses.

*h. Upper limit useless without reference to intake goal.*

33. Other comments opposed including a reference to the upper limit of 1,000 mcg per day in any health claim because, they argued, consumers cannot determine their total daily intakes from all sources. These comments noted that stating an upper limit was useless unless all food types were labeled with their folate content. Another comment opposing the inclusion of a warning statement on foods or supplements containing more than 25 percent of the DV stated that inclusion of an upper limit was problematic if reference was not made to the 400 mcg/day intake goal.

The agency recognizes that there was an inconsistency in the way that proposed § 101.79(c)(2)(i)(G) was worded in that the safe upper limit of daily intake was expressed as 1,000 mcg rather than as a percent of the DV. The agency has corrected this inconsistency, as noted above in response to comment 32 of this document.

The agency disagrees that inclusion of the 400 mcg intake goal is necessary to make a caution statement understandable, and that a caution statement is useless unless all foods are labeled with their folate contents. The agency notes that diets that do not contain highly fortified foods and dietary supplements rarely provide daily folate intakes of more than 1,000 mcg. The likelihood of achieving daily intakes exceeding 1,000 mcg arises from consumption of highly fortified foods and dietary supplements, particularly those that contain more than the DV per unit or per serving. Under current labeling requirements, such foods and supplements must, or soon will have to, carry nutrition labeling. The safe upper limit of daily intake will thus appear on those products whose use provides the greatest potential for contributing to overconsumption (e.g., highly fortified foods and supplements whose label bears a health claim that explains a potential benefit of increased consumption). The agency concludes that it is necessary to require inclusion of the caution statement, with the safe upper limit of daily intake expressed as percent of the DV (percent DV), as part of the health claim on such products.

The agency also notes that the availability of the health claim may result in increased consumption of foods with high folate content that carry the claim. The expression of the folate

content as a percent of the DV will help consumers who select a health claim-labeled food that contains more than 100 percent of the DV and that is labeled with a statement that folate intakes should be limited to 250 percent of the DV, to recognize that the product provides more than the full amount of the DV while still leaving a considerable allowance for consumption of other foods of lower folate content. The percent DV labeling will also allow a consumer who selects four health claim-labeled foods that each contain more than 100 percent of the DV to quickly compute that these four products alone will provide more than 400 percent of the DV, an amount in excess of the safe upper limit of daily intake of 250 percent of the DV. Thus, the agency does not believe that explicit reference to the 400 mcg target intake goal is necessary to make the caution statement understandable. The agency advises, however, that manufacturers wishing to include reference to the 400 mcg intake goal may do so (§ 101.79(c)(3)(iv)).

*i. Caution statement on all products with >25 percent DV.*

34. One comment interpreted the proposed regulation to mean that the agency was proposing to require use of a caution statement on all products with more than 100 mcg folate/serving, whether or not they bore the health claim.

This comment misunderstood the proposal. The agency advises that it is requiring that the caution statement be used only on conventional foods or dietary supplements that bear the folate/neural tube defects health claim and that contain more than 100 percent of the DV (400 mcg when labeled for use by the general population or 800 mcg when labeled for use by pregnant or lactating women).

*j. Warnings on supplements without adequate vitamin B<sub>12</sub>.*

35. One comment suggested that the agency should require warnings on supplements that do not provide amounts of vitamin B<sub>12</sub> adequate to provide protection from the potential problem in nearly all cases.

This comment was based on the assumption that the greatest potential for adverse effects of high folate intake is the masking of the anemia of vitamin B<sub>12</sub> deficiency, with continued progression of neurologic damage, and that provision of oral vitamin B<sub>12</sub> will negate this concern. The comment did not provide data or information identifying the amount of oral vitamin B<sub>12</sub> that would protect nearly all persons from masking of a vitamin B<sub>12</sub> deficiency and, thus, the level below

which a warning statement would be required.

The agency disagrees with this suggestion. The agency is aware that very high doses of vitamin B<sub>12</sub> (e.g., about 1 mg; 500 times the RDI for this vitamin) without intrinsic factor (i.e., without the protein factor necessary for the absorption of vitamin B<sub>12</sub> and the factor whose lack causes pernicious anemia) have provided adequate treatment for some persons with pernicious anemia (Ref. 45). It has been suggested, based in part on observations that some patients with pernicious anemia can be maintained on oral vitamin B<sub>12</sub>, that high doses of vitamin B<sub>12</sub> be added to foods and dietary supplements fortified with folic acid to reduce the potential for adverse effects in persons with vitamin B<sub>12</sub> deficiency.

Several experts at a CDC meeting on surveillance for adverse effects of increased intakes of folate (Ref. 26) commented on this suggestion. One expert noted that in the presence of other nutrients (e.g., vitamin C, thiamin, iron), vitamin B<sub>12</sub> may be converted into analogs, some of which may have antivitamin B<sub>12</sub> activity.

In the proposal of October 14, 1993 (58 FR 53254 at 53280), the agency discussed the issue of whether high doses of vitamin B<sub>12</sub> should be added to foods or supplements fortified with folic acid to reduce the potential for adverse effects in persons with vitamin B<sub>12</sub> deficiency. The agency requested comments, specifically data, on the appropriateness, potential effectiveness, and safety of such fortification. The agency did not receive data or other information on this issue.

Given this lack of information, FDA finds no basis to require a warning statement on supplements based on their content of vitamin B<sub>12</sub> because there are no data on the effects of various folate/vitamin B<sub>12</sub> combinations on which to base a warning. In addition, relating a caution statement only to the vitamin B<sub>12</sub> content of a product would fail to recognize the potential adverse effects of increased folate intakes on other population groups, including, as discussed above, pregnant women, children, those on antiepileptic medications, and those on antifolate medications, because it would fail to recognize that potential adverse effects of increased intakes are not limited only to those with vitamin B<sub>12</sub>-related problems.

Because data are not available that address for the general population on the issue of simultaneous fortification of foods or dietary supplements with both folate and vitamin B<sub>12</sub>, the agency cannot establish a level of oral vitamin

B<sub>12</sub> that is sufficient to protect most persons with vitamin B<sub>12</sub>-related problems from the adverse effects of increased intakes of folate. In addition, questions regarding the appropriateness, potential effectiveness, and safety of such an approach remain unanswered. Vitamin B<sub>12</sub> deficiency, including pernicious anemia, is a serious condition, which, if untreated, can lead to irreversible neurological damage. Regardless of the widespread availability of oral vitamin B<sub>12</sub> preparations, patients with pernicious anemia, and others at risk of vitamin B<sub>12</sub> deficiency, should be diagnosed, treated, and monitored by a physician (Ref. 45).

#### 6. Multifactorial Nature of Neural Tube Defects

The general requirements for health claims for conventional foods (§ 101.14(d)(2)(iii)) provide that, where factors other than dietary intake of the substance affect the relationship between the substance and the disease or health-related condition, FDA may require that such factors be addressed in the health claim. FDA has decided that health claims on dietary supplements should be subject to the same requirement (see 59 FR 395 at 425).

It is well-recognized that neural tube defects have many causes, some of which are not related to folate status. Genetic and environmental factors contribute to the multifactorial nature of neural tube defects. Environmental factors associated with neural tube defects include, for example, maternal health, maternal family history of neural tube defects, and maternal use of certain antiepileptic medications (see 58 FR 53254 at 53258 for references).

FDA discussed the multifactorial nature of neural tube defects in several sections of its proposed rule. In proposed § 101.79(b)(1), FDA discussed the fact that neural tube defects are caused by many factors and also noted that a significant risk factor is a personal or family history of a pregnancy affected by a neural tube defect. In § 101.79(c)(2)(i)(D), FDA proposed to require that claims state that neural tube defects have many causes, and that claims not imply that folate intake is the only recognized risk factor for neural tube defects. The agency included language to this effect in the agency's proposed model claims (§ 101.79(d)).

The agency received several general comments and new data in response to the sections of the proposed codified language addressing the multifactorial nature of neural tube defects.

##### a. General comments.

36. Several comments agreed that the claim should include information on the multifactorial nature of neural tube defects to be consistent with claims for other diet-disease relationships. These comments asserted that the claims would be misleading if such information were not included. Other comments disagreed that the multifactorial nature of neural tube defects should be recognized in the claim because, for example: (1) Folate is the most important risk factor, or (2) there is no educational value in identifying the multifactorial nature of the condition. Another comment stated that only factors that can be controlled, or those on which women could take action, should be included in the claim.

FDA is in the process of reconsidering the need to include in health claims the fact that the disease that is the subject of the claim has many causes. In the January 1993 final rules on health claims, FDA included this fact as a required element of the claim. However, as discussed below, FDA has come to tentatively conclude, at least in part in response to a petition from the National Food Processors Association (Docket No. 94P-0390), that, at least for most claims, a statement about their multifactorial etiology adds length to the claim without conveying information that would directly affect the dietary choices of the consumers.

The agency is particularly concerned that manufacturers will be disinclined to use unnecessarily lengthy health claims on food labels, that additional verbiage may detract from the central consumer message of the claim, and that, as a result, health claims will be infrequently used, and the benefits of communicating information on diet-disease relationships to consumers through such claims will not be realized.

The issue of manufacturers' reluctance to use lengthy health claims is particularly significant in the case of the folate/neural tube defects health claim because this topic has received much less attention than has been given to chronic illnesses such as osteoporosis, heart disease, and cancer. The lower level of public familiarity with this topic was confirmed in a recent survey conducted for the March of Dimes Birth Defects Foundation regarding knowledge and practices of women of childbearing age in the United States with respect to consumption of folic acid from supplements and breakfast cereals (Ref. 53).

During January and February 1995, the Gallup Organization conducted for the March of Dimes a proportionate,

stratified random-digit-dialed telephone survey of a national sample of 2,010 women aged 18 to 45 years. The response rate was 50 percent. Estimates were statistically weighted to reflect the total population of women aged 18 to 45 years in the continental United States. In response to the question "Have you ever heard or read anything about folic acid?", 52 percent of women reported ever hearing of or reading about this nutrient. Of these, 9 percent answered that folic acid helps to prevent birth defects and 6 percent that folic acid helps to reduce the risk for spina bifida; 45 percent were unable to recall what they had heard or read. Fifteen percent of respondents reported having knowledge of the PHS recommendation regarding the use of folic acid; 4 percent reported that the recommendation was for prevention of birth defects and 1 percent, for the prevention of spina bifida (Ref. 52).

Respondents were also asked "From what you know, is there anything a woman can do to reduce her risk of having a baby with birth defects?" A total of 88 percent of respondents reported that a woman can help reduce the risk for having an infant with birth defects. The most common responses about how to reduce risk were avoiding alcohol and drugs (73 percent), and not smoking (63 percent); 1 percent of women reported that folic acid could reduce risk.

This study found that while most women interviewed recognized that there were a number of factors that might affect their risk of having a baby with a birth defect, there was a low level of awareness that consumption of folate from supplements, breakfast cereals, and other foods may specifically help to reduce their risk of a neural tube defect-affected pregnancy.

The results of the March of Dimes survey are consistent with recent findings by FDA. As part of FDA's ongoing review of its regulations governing health claims, the agency conducted six focus groups in May and June 1995 to evaluate consumer understanding of health claim messages. In a report on these focus groups, Levy (Ref. 54) noted that while almost all participants were aware of health effects of fat, calcium, and fruits and vegetables, very few had heard much about folic acid. Participants appreciated information provided in the folate/neural tube defects model claims but considered it insufficient to inform them as adequately as they wished to be informed.

Thus, recently available information suggests that there is a low level of awareness of the potential impact that

increased folate intake may have on the risk of a serious type of birth defect.

The agency has concluded, based in part on the studies mentioned above, that the need to provide a succinct health claim in this topic area is very important. Succinctness in the claim will increase the likelihood that firms will use it and thus will increase its educational value. To facilitate the use of such a claim by manufacturers, it needs to be no longer than necessary to convey the central consumer message.

With respect to the issue of whether explicit identification of the multifactorial nature of neural tube defects is necessary to prevent the folate/neural tube defects health claim from being misleading, the agency notes that use of the term "may reduce" in the claim describes the potential of folate to affect the risk of neural tube defects and serves to reflect the multifactorial nature of this birth defect. In addition, data obtained in the March of Dimes survey described above indicate that many women already recognize that birth defects in general may have many causes. The agency has therefore concluded that explicit reference to "may have many causes" is redundant when included with the phrase "may reduce."

The agency has concluded that it is not necessary to include explicit reference to the multifactorial nature of neural tube defects in the claim.

The agency notes, however, that the fact remains that neural tube defects are multifactorial in nature. This fact is confirmed by new data of which FDA has become aware and that are discussed in the following section. Because of this fact, the claim must not imply that folate intake is the only risk factor for these birth defects.

Therefore, the agency is modifying § 101.79(c)(2)(i)(D) by deleting the requirement that the claim state that neural tube defects have many causes but is retaining the requirement that claims shall not imply that folate intake is the only recognized risk factor for neural tube defects.

The agency is also advising that manufacturers who wish to do so may include, on an optional basis, information in the claim on additional risk factors for neural tube defects. Information that may be included is described in § 101.79(c)(3)(i).

b. *Data received in comments.* 1. The agency received new data from an Irish study that found that plasma levels of vitamin B<sub>12</sub>, as well as folate, were independent risk factors for neural tube defects (Ref. 51). These data were reviewed at the October 14 and 15, 1993, meeting of the Folic Acid

Subcommittee and are summarized here because the agency did not have the data in sufficient time to include them in its October 14, 1993, proposed rule. Kirke et al. (1993) (Ref. 51) compared values for plasma folate, plasma vitamin B<sub>12</sub>, and red blood cell folate in 81 women who had a neural tube defect-affected pregnancy and 247 control women. Values for all three parameters were significantly lower in case mothers than in control mothers. Plasma vitamin B<sub>12</sub> and red cell folate were both significantly positively correlated in case mothers but not in control mothers. Multiple regression analysis showed that plasma vitamin B<sub>12</sub> and plasma folate were independent predictors of red cell folate in case mothers but not in control mothers.

The authors concluded that plasma vitamin B<sub>12</sub> and plasma folate were independent risk factors for neural tube defects and suggested that the enzyme methionine synthetase was involved directly or indirectly in the etiology of neural tube defects. They noted that the correlation between plasma vitamin B<sub>12</sub> and red cell folate, observed in case mothers only, was difficult to explain on a purely nutritional basis and favored the etiology of neural tube defects as being the result of some metabolic abnormality in the mother, and possibly in the embryo, interacting with maternal plasma levels of folate and vitamin B<sub>12</sub> (Ref. 50).

Mooij et al. (Ref. 46) measured levels of seven vitamins in blood of women who had a neural tube defect-affected pregnancy and reported that such measurements were not suitable for identifying women at high risk of another affected pregnancy. The authors hypothesized that the effect of folic acid was attributable, at least in part, to its overriding a metabolic disorder.

2. The agency received additional new data in a comment relating to a possible role of a deficiency of one or more antioxidant enzymes in the development of neural tube defects. The comment discussed the hypothesis that a genetic defect in antioxidant enzyme systems that protect neuronal membranes from excessive lipid peroxidation may play a role in the etiology of neural tube defects. The comment noted that abnormalities of the neural tube have been documented in cultured rat embryos exposed to oxygen radicals generated in vitro by xanthine plus xanthine oxidase. The severity of these abnormalities, which increases in a dose-responsive manner with exposure to xanthine oxidase, can be moderated by substances with known antioxidant activity such as glutathione,

catalase, L-ascorbic acid (vitamin C), or DL-alpha tocopherol (vitamin E).

This comment provided the results of a pilot study that tested the hypotheses in children with neural tube defects and their immediate families. In testing the hypothesis, the investigators assessed a number of red blood cell free radical-scavenging enzymes in eight families with one or more children with the neural tube defect meningocele. Seventeen healthy adults without a history of neural tube defects served as controls. All meningocele-affected children were found to be deficient in red blood cell glutathione peroxidase, with 5 in the range of moderately to severely deficient. At least one parent of seven of the eight affected children was deficient in red blood cell glutathione peroxidase activity, with four of seven in the moderately to severely deficient range. Nine additional children with meningocele or other neural tube defects (specifically, encephalocele and iniencephaly) were also studied. Red blood cell glutathione peroxidase activities were low in all of the nine additional affected children, with values in six of the nine in the moderately to severely deficient range.

The comment also noted that pterin aldehyde, a contaminant that may be present at a level of about 4 percent in commercially available folic acid preparations, may reduce exposure of the developing neural tube to toxic oxygen free radicals through its activity in inhibiting xanthine oxidase. The comment suggested (Comment 68H to docket 93N-100H) that a combination of genetic factors, deficient antioxidant enzyme capacities, exogenous or endogenous teratogens, periconceptional diets with inadequate amounts of free radical scavenging substances, or suboptimal concentrations of pterin aldehyde-like agents may provide further explanations for tissue-specific injury in some pregnancies.

The comment concluded that, while the mechanisms of neural tube defect formation likely fit into a complex ecogenetic model, a deficiency of one or more antioxidant enzymes may increase the risk for the development of neural tube defects. The comment recommended further study to determine whether reduced antioxidant activity predisposes the embryo to the development of neural tube defects.

c. *Data that were published after the close of the comment period.* 1. Mills et al. (1995) (Ref. 47) reported that women with neural tube defect-affected pregnancies had significantly higher levels of homocysteine than did vitamin B<sub>12</sub>-matched controls. Mills et al. (1995)

(Ref. 47) noted that their study showed that an abnormality of homocysteine metabolism, apparently related to methionine synthase, is present in many pregnancies that resulted in neural tube defects.

2. Mechanistic studies in cultured rat embryos have also provided insights into roles for nutrients in addition to folate in the etiology of neural tube defects. Chambers and coworkers identified autoantibodies (i.e., antibodies directed against tissue components of the same organism) to the extracellular basement membrane (i.e., the noncellular layer underlying the epithelium) protein laminin as an agent that caused neural tube defects in whole embryo cultures (see Ref. 48 for additional references). Such antibodies were found initially in the embryotoxic sera of monkeys with poor reproductive histories. Chambers et al. (1995) (Ref. 48) recently reported that methionine overcomes neural tube defects in rat embryos cultured on sera from monkeys immunized against laminin. The authors noted that the association of autoimmune diseases and fetal loss has received closer attention in recent years, but that neither the mechanisms of fetal loss nor treatments have been well defined (Ref. 48). The authors suggested that epidemiologic studies are needed to establish a possible role for autoantibodies in the etiology of neural tube defects and to determine the efficacy of methionine supplementation in overcoming such defects.

3. Data addressing the etiologic heterogeneity of neural tube defects were also derived from observations that infants and fetuses with isolated neural tube defects have different risk factors than those with neural tube defects occurring with other birth defects and from reported differences in recurrence risks for neural tube defects based on the level of the affected infant's defect (Ref. 49; Shaw et al., 1994, for references). Shaw et al. (1994) (Ref. 49), used population-based case ascertainment by the California Birth Defects Monitoring Program in an ethnically diverse population of more than 700,000 live births and fetal deaths to investigate whether heterogeneity existed among various anatomic and pathogenetic subclasses of neural tube defects for a variety of commonly collected child and parental characteristics. Among cases of anencephaly, increased risks were found for Hispanic white women with risk estimates highest for nonisolated cases. This population-based study showed increased risk for Hispanic women specifically among subclassifications of neural tube defects,

and provides some evidence that further classification of neural tube defects may reveal subgroupings of cases with different etiologies.

Shaw et al. (1995) (Ref. 50) used a case-control study design (549 cases and 540 controls) to investigate whether intake of supplemental folic acid or dietary folate reduced the risk of a neural tube defect-affected pregnancy (Ref. 50). The authors found that women with any use of a folic acid-containing vitamin in the 3 months prior to conception had a lower risk of having an NTD-affected pregnancy. Odds ratios were similar for average daily folic acid intakes of <400 mcg, 400 to 900 mcg, and >900 mcg/day, and thus, no dose-response pattern was apparent. Use of 400 to 900 mcg folic acid/day in the 3 months after conception was also associated with reduced risk of a neural tube defect-affected pregnancy. The authors also observed that women who did not begin using a folic acid-containing vitamin until the second trimester of pregnancy also had a reduced risk of neural tube defects and suggested that although the finding may be indicative of errors in reporting vitamin use in general, it also weakens the attribution of a direct preventive effect of folate on neural tube defects in the study population (Ref. 50).

When race/ethnicity were considered, nonHispanic white women who used a folic acid-containing vitamin in the 3 months before conception had a reduced risk of a neural tube defect-affected pregnancy. However, risk of a neural tube defect-affected pregnancy was not reduced in Hispanic women who consumed a folic acid-containing vitamin in the 3 months before conception. The overall results of this study are consistent with other studies showing associations between folate intake and reduced risk of neural tube defects. However, the data also suggest that the folate-associated reduction in risk may be specific to subsets of the population, primarily nonHispanic women (Ref. 50).

These recent studies are of significance for the insights that they provide into understanding the multifactorial etiology of neural tube defects. They support the hypothesis that neural tube defects are not the result of a wide-spread nutritional deficiency of folate in the U.S. population but may result from metabolic defects or other physiologic conditions affecting a small part of the population. These new data support FDA's decision to require that claims not imply that folate intake is the only recognized risk factor for neural tube defects.

## 7. Prevalence Statements

In § 101.79(c)(2)(i)(E), the agency proposed to require that the claim provide information that neural tube defects "while not widespread, are extremely significant." Because the affected population is few in number and not readily identifiable, FDA proposed to require that this information be disclosed to prevent women from being misled into believing that neural tube defects are very common birth defects, or that, lacking a personal or family history of such defects or other recognized risk factors, their risk of having a pregnancy affected with such a birth defect is very high.

37. The agency received a number of comments on the proposed prevalence statement. Some comments stated that the wording "while not widespread" was not clear, and one comment suggested use of "uncommon" rather than "while not widespread" in describing the prevalence of neural tube defects. One comment noted that statements indicating that neural tube defects had a low prevalence in the United States would discourage women from taking folic acid supplements because women would believe that the health claim is not applicable to them, and they would be misled into not taking the health claim seriously. One comment noted that there is no standard for the proposed term "not widespread." One comment noted that because the behavior intended to result from authorization of the health claim was to have women consume more folic acid, qualifiers regarding prevalence of the condition had no educational benefit. One comment, noting that statements regarding the extent of the disease-related conditions were optional in other approved health claims, and that the rarity of spina bifida and related birth defects is obvious to virtually all consumers, urged the agency to make prevalence statements optional in the folate/neural tube defect claim.

The Folic Acid Subcommittee also commented on issues of prevalence and demographics of neural tube defects at all of its meetings (e.g., Ref. 8). The Folic Acid Subcommittee discussed the decline in the rate of neural tube defects from a high in Boston in the 1930's of 5 per 1,000 births to the current overall U.S. rate of about 0.6 per 1,000 births (i.e., about 2,500 cases/year in the United States). In addressing the prevalence of neural tube defects among different ethnic groups, one Folic Acid Subcommittee member noted that African-American women have a rate lower than the overall U.S. rate, while Mexican-American women have a rate

about two and one-half times the national average. The participant also noted that there is about a two-fold higher rate among women in lower socio-economic groups than among those in higher socio-economic groups (Ref. 8).

The agency has reviewed the comments that it received and agrees that use of the proposed wording "while not widespread" is not clear because it is not quantitative. The agency notes that even though the occurrence of neural tube defect-affected pregnancies is low, the population at risk may be quite large because about half of pregnancies are unplanned. Therefore, the agency concludes that a statement of prevalence is not a material fact in light of the other statements made in the claim. For this reason, the agency concludes that it is not necessary to require that the claim state that the prevalence of neural tube defects is low to ensure that the claim is not misleading. Therefore, the agency is deleting the requirement proposed in § 101.79(c)(2)(i)(E) and redesignating subsequent sections as discussed below and as shown in the codified language.

However, given the other comments cited above and its discussions with the Folic Acid Subcommittee, the agency does not agree that there would be no educational benefit from providing prevalence information in the health claim. The agency concludes, based on the comments above, that prevalence information can be useful to consumers because it can provide a context that increases understanding of how frequently neural tube defects actually occur among pregnancies in the U.S. population.

The agency recognizes that it has provided for inclusion, on an optional rather than required basis, in other authorized health claims of information on the number of people in the United States who have the health-related condition (e.g., see saturated fat and cardiovascular disease claim and dietary fiber and cancer claims). Thus, in response to the comments above, and consistent with other authorized health claims, FDA, in § 101.79(c)(3)(v), is authorizing the use of optional statements to provide the estimated numbers on an annual basis of neural tube defect births among live births to women in the general U.S. population. Currently, this estimate is 0.6 cases per 1,000 live births, or 6 cases per 10,000 live births, or about 2,500 cases among 4 million live births, or about 1 case per 1,600 live births. These estimates are based on information for the U.S. population from PHS. FDA finds, based on a review of how such statistics are

generally presented, that expressing this information as the estimated annual number of neural tube defects per a specified number of births (e.g., per 1,000 live births or per 10,000 live births) will help to make this information as useful as possible. Section 101.79(c)(3)(v) provides for use of these estimates unless more current estimates from PHS become available, in which case, the newer estimates may be used.

#### 8. Quantifying Risk Reduction

In § 101.79(c)(2)(i)(F), the agency proposed that the claim contain a statement that some women may reduce their risk of a neural tube defect-affected pregnancy by maintaining adequate folate intake during their childbearing years. Such a statement is consistent with the estimate provided in the PHS recommendation that about half of neural tube defects (i.e., about 1,250 annually) might be averted if all women of childbearing age in the United States who are capable of becoming pregnant consumed 0.4 mg of folate daily throughout their childbearing years. FDA tentatively concluded that such a statement is necessary to ensure that women do not conclude on the basis of the claim that adequate intake of folate will prevent all occurrences of neural tube defects. The agency also proposed in § 101.79(c)(2)(i)(F) that the claim not attribute any specific degree of reduction in risk of neural tube defects to maintaining an adequate folate intake throughout the childbearing years.

38. Several comments agreed with the agency that a specific degree of reduction in risk should not be stated in the health claim. Other comments noted that while occurrence of neural tube defects will be averted by only some women, the risk of occurrence will be reduced for the population. Other comments objected to the proposal to prohibit use of the PHS estimated percent risk reduction of 50 percent. Some comments argued that the 50 percent estimate should be stated because it was a scientific finding, and that failure to include this estimate could have a negative effect on how much effort women make to ensure that they have adequate folate intake. Another comment stated that the estimate of 50 percent reduction should be included because it is preferable for women to know the exact benefit of folic acid rather than to be informed that "some but not all women may benefit."

The agency disagrees with comments that the PHS estimate of 50 percent is a scientific finding and represents an exact benefit achievable by all women who consume adequate folate daily

throughout their childbearing years. The PHS recommendation states that the 50 percent estimate was derived from studies that associated recalled use of folic acid-containing multivitamins with reduced risk of neural tube defect-affected pregnancies and states that "the protective effect found in the studies of lower-dose folic acid, measured by the reduction in neural tube defect incidence, ranged from *none* to *substantial*" (Ref. 5) (emphasis added). The PHS recommendation also noted that:

It is expected that consumption of adequate folic acid will avert some, but not all, neural tube defects. The underlying causes of neural tube defects are not known. Thus, it is not known what proportion of neural tube defects will be averted by adequate folic acid consumption. From the available evidence, CDC estimates that there is the potential for averting 50 percent of cases that now occur. However, until further research is done, no firm estimate of this proportion will be available (Ref. 5).

The agency also notes that there may be minimal or no effect of periconceptional use of folate in areas of low prevalence or in areas where other factors are contributing to an increased prevalence. This observation is consistent with scientific evidence that shows that, in an area of low prevalence in the United States, women who consumed folate from multivitamins or fortified breakfast cereals did not have a lower risk of having a neural tube defect-affected pregnancy than did women who did not consume multivitamins or fortified breakfast cereals (Ref. 12; Mills et al.).

Thus, the estimate of a potential for a 50 percent reduction in neural tube defect-affected pregnancies, if all women consumed adequate folate throughout their childbearing years, is not a scientific finding and may not be applicable to estimating potential risk reduction in areas of low prevalence. The agency notes further that the estimate of 50 percent is not applicable to risk reduction that might be experienced by individual women, whose personal risk factors are not fully understood. In addition, the estimated proportion may change with the availability of new scientific data and information. The agency recognizes, however, that manufacturers may wish to use the PHS recommendation, including the estimate of the potential for a 50 percent reduction in the incidence of neural tube defects, as labeling for folate-containing products. The agency also notes that there is considerable potential for making a misleading claim if such information is not presented in an accurate context.



The agency has concluded that an estimate of potential risk reduction can be included in the health claim because it may help some consumers better understand the potential population-based impact on neural tube defect-affected pregnancies if all women consumed adequate folate throughout their childbearing years. Therefore, FDA is providing in § 101.79(c)(2)(i)(E) that population-based estimates of risk reduction may be included in the claim so long as the claim makes clear that the estimate does not reflect risk reduction that may be experienced by individual women. Provision of such information will reduce the likelihood of women being misled that adequate folate intake will prevent an occurrence of a neural tube defect-affected pregnancy.

The agency has revised § 101.79(b)(3) to provide information from the PHS recommendation that explains how the estimate of a potential for reduction in incidence of neural tube defects of 50 percent was derived and provides the context in which the estimate can be understood by individual women.

FDA has also redesignated proposed § 101.79(c)(2)(i)(F) as § 101.79(c)(2)(i)(E) and revised this section to remove the prohibition against use of the PHS estimate. Section 101.79(c)(2)(i)(E) includes reference to new § 101.79(c)(3)(vi) which provides for optional inclusion of statements about population-based estimates of risk reduction. The requirement that claims state that some women may reduce their risk of a neural tube defect-affected pregnancy through adequate intake of folate throughout their childbearing years is retained in § 101.79(c)(2)(i)(E).

New § 101.79(c)(3)(vi) states that an estimate of the reduction in the number of neural tube defect-affected births that might occur in the United States if all women consumed adequate folate throughout the childbearing years (i.e., 50 percent) may be included in the claim if such an estimate is accompanied by information that states that it is a population-based estimate and does not reflect reduction in risk that may be experienced by individual women. New § 101.79(c)(3)(vi) also provides for use in the claim of information in revised § 101.79(b)(3).

#### 9. Optional Health Claim Information

In § 101.79(c)(3)(i), the agency proposed to permit manufacturers, in addition to including the fact that neural tube defects have many causes, to specifically identify risk factors for neural tube defects. The agency stated that specific examples of other risk factors include a personal history of such a defect, maternal diabetes

mellitus, use of the antiepileptic drug valproic acid, maternal febrile illness, or a close relative with a neural tube defect (§ 101.79(b)(1) and (b)(2)). The agency requested comments on whether such additional information would be useful to consumers.

##### a. *Identifying other risk factors.*

39. Some comments expressed the opinion that most of the optional information was helpful, while others stated that there was no educational value in identifying the multifactorial nature of neural tube defects, and that women cannot control other risk factors.

The agency disagrees with the comments that stated that identification of other risk factors would not be helpful to women. Certain conditions, such as diabetes mellitus, are known to increase a woman's risk of a neural tube defect-affected pregnancy. Identification of these risks in the claim may serve to alert some women to their higher risk and encourage them to seek advice from their health care providers before becoming pregnant.

The agency is providing in § 101.79(c)(3)(i) for the inclusion of optional information in the claim. Information in § 101.79(b)(1) or (b)(2) or drawn from other parts of § 101.79(c)(3) may be included in the claim. Use by manufacturers of factors listed in the regulation will ensure that claims will only include scientifically-based information and will not include information that has not been well-documented (e.g., "Birth defects of the brain or spinal cord may have many causes, such as exposure to pesticides \* \* \*").

b. *Consult a physician.* In § 101.79(c)(3)(iii), the agency proposed that a claim could include a statement that women with a history of a neural tube defect pregnancy should consult their physicians or health care providers before becoming pregnant. The agency tentatively concluded that such a statement would encourage such women to obtain medical guidance and thereby decrease their risk of a recurrence of a neural tube defect-affected pregnancy. The available data show that women with a history of a neural tube defect-affected pregnancy are at very high risk of another affected pregnancy (e.g., risk of a recurrence of a neural tube defect pregnancy is significantly greater than risk of an occurrence of this birth defect). The agency requested comments on whether provision of such information would be helpful to consumers.

40. The agency received several comments on this proposed optional information. All comments that addressed this issue recommended that

it be broadened to include all women rather than only those with a personal history of a neural tube defect-affected pregnancy. Comments stated that prenatal care was critical for all women and suggested that health claims should include a statement that all women planning a pregnancy should consult a physician or health care provider for information about adequate diets for their and their babies' health. Several comments suggested that such a statement be mandatory rather than optional.

FDA does not believe that it is appropriate, in general, for health claims to bear statements concerning the need to seek medical advice for treating the disease or health-related condition mentioned in the claim. The agency is concerned that the appearance of a statement concerning the treatment of a disease on the label of a food could mislead some consumers to believe that the food possesses therapeutic value for an existing disease or health-related condition (58 FR 2478 at 2514).

The agency originally proposed such a statement regarding women at recurrent risk of a neural tube defect-affected pregnancy because their risk of recurrence is very high, and because a specific recommendation from PHS has been made to such women when they are planning a pregnancy (i.e., they are advised to take 4 mg folic acid daily under a physician's supervision; Ref. 52).

Because all comments favored broadening the advice to include all women, and because the agency recognizes that it is important for all women to consult a health care provider before becoming pregnant, the agency is persuaded to modify § 101.79(c)(3)(iii) as suggested in the comments and to provide for claims to include, in addition to a statement regarding women at recurrent risk of a neural tube defect, a statement that all women should consult a health care provider before becoming pregnant (e.g., "Women, including those with a history of a neural tube defect pregnancy, should consult their health care provider when planning a pregnancy.").

However, because the length of claims has been consistently a concern of the comments, the agency is not persuaded that the information provided for in § 101.79(c)(3)(iii) should be required in all health claims, as suggested by one comment above. 10. Model Health Claims

FDA provided several model claims in the proposal that contained the elements described in its proposal. The agency included these model claims to

assist manufacturers in formulating appropriate claims.

a. *Toll-free number, pregnancy information symbol.*

41. Several comments stated that less detailed model claims were needed and proposed that the agency establish a toll-free 800 number through which women could obtain more information or recommended that the agency devise a uniform pregnancy information symbol for food labels that would alert women to look for products that bear the symbol.

The agency agrees that educational information is of great importance in increasing awareness among women of the need for adequate nutrition, including adequate folate intake, during their childbearing years. The agency is considering how best to evaluate consumer understanding of the health claim and is working with other PHS agencies to develop strategies to implement the PHS recommendation on folate intake.

With respect to the use of a pregnancy information symbol, the agency noted above that many pregnancies are unplanned, and for this reason, women need to be informed of the need for adequate nutrition throughout their childbearing years. While a pregnancy symbol might draw the attention of women who are already pregnant or who might be planning a pregnancy, it may not be helpful to women whose pregnancies are unplanned or to women whose pregnancies are too far advanced for folate intake to alter their risk of giving birth to a neural tube defect-affected infant. Such a symbol may also discourage other women from using the product because they do not think they will become pregnant.

The agency also notes that many of the foods that will bear the health claim will be consumed by the general population, and the appearance of a pregnancy symbol on the label might be incorrectly interpreted by some consumers to mean that the product is specifically intended for use in pregnancy.

For these reasons, the agency is not persuaded to use a pregnancy symbol with the health claim.

b. *General comments.*

42. Many comments criticized the length of the model claims and their required components. Comments stated that the model messages were too lengthy and complex and unwieldy, and that therefore manufacturers would be disinclined to use them. Other comments noted that the claims included unnecessary disclosures and requested that FDA remove the requirements relating to the

multifactorial nature of neural tube defects, sources of folate other than dietary supplements, and the caution statement. Several comments, stating that the model claims were overly focused on foods, urged the agency to develop a condensed claim for dietary supplements and suggested that such a claim should not need to identify other sources of folate or state a maximum daily limit on intake.

Another comment noted that in formulating the claim, the agency should be guided by the need to communicate the benefits of increased folate intake from food sources or dietary supplements, and that the message must also convey proper cautions, including the fact that increased folate intake will not prevent all birth defects or even all neural tube defects. Several comments praised portions of the model claims that required disclosure of the multifactorial nature of neural tube defects and the inclusion of information regarding sources of folate. One comment recommended that claims use the information in the PHS recommendation, including the warning statement, as closely as possible. Several comments noted that the model claims were not educationally strong enough, while others recognized the problem of providing the guidance that needs to be included in the claim without having the claim become so long as to be unusable. Some comments provided examples of shorter claims that they proposed as more appropriate than the agency's model claims.

As discussed in the proposal and elsewhere in this final rule, certain information is needed in the health claim, whether for conventional foods or for dietary supplements, for such claims to be truthful, scientifically valid, and not misleading to segments of the population that are not at high risk of having a neural tube defect-affected pregnancy or for whom no link between folate intake and risk of neural tube defect-affected pregnancies has been established.

The agency has addressed the issues of mandatory requirements relating to the multifactorial nature of neural tube defects, sources of folate other than dietary supplements, and the caution statement in response to comments 36, 21, and 32, respectively. The agency disagrees that all of these elements should be removed. Specifically, the agency has discussed in response to comment 36 why claims shall not imply that folate intake is the only risk factor for neural tube defects. In response to comments 28 through 34, the agency explained why a caution statement is

necessary, as well as its reasoning in limiting the requirement for such a statement to very narrow circumstances. The agency in response to comments has dropped the requirement that sources of folate be identified in the claim and instead has provided for optional inclusion of such information.

The agency also disagrees that its proposed model claims were overly focused on foods because each of the proposed claims specifically identified sources of folate as fruits, vegetables, whole grain products, fortified cereals, and dietary supplements.

The agency rejects the comments that urged it to develop a condensed claim for dietary supplements and not identify a safe upper limit of daily intake. Throughout its responses to the comments it received, the agency has been even-handed in considering conventional foods and dietary supplements (comments 29 and 32, above). Since increased folate intake is what is of importance, and since a variety of dietary sources of folate are available, it would be inconsistent with the available evidence for the agency to set different requirements for claims on dietary supplements than for claims on conventional foods.

Thus, the agency, in developing this final rule, has been guided by the need to communicate the effects on the risk of neural tube defects of increased folate intake while providing sufficient cautions to prevent claims from being misleading and to ensure that they are scientifically valid.

FDA has modified the model claims to reflect the changes that it has made in § 101.79 in response to the comments. The agency has sought to illustrate in the model claims that it is possible to fully comply with § 101.79 and still produce a claim that uses less than 30 words (see Examples 1 and 2 in § 101.79(d)). The agency also notes that in response to the petition from the National Food Processors Association, mentioned above, it is exploring the possibility of permitting a shortened version of the claim to appear on the front panel of the food label as long as the full claim appears on the label. FDA is considering how this can be accomplished while still ensuring that there is full compliance with section 403 (a) and (r) of the act. FDA anticipates publishing a proposal on these matters in the near future.

### III. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(11) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore,

neither an environmental assessment nor an environmental impact statement is required.

#### IV. Economic Impact

FDA has examined the impacts of this final rule to authorize the use on the labels and in the labeling of conventional food and dietary supplements of health claims on the relationship between adequate folate intake and risk of neural tube birth defects as required by Executive Order 12866 and the Regulatory Flexibility Act. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects; distributive impacts and equity). The Regulatory Flexibility Act (Pub. L. 96-654) requires analyzing options for regulatory relief for small businesses. FDA finds that this final rule is not a significant regulatory action as defined by Executive Order 12866. In compliance with the Regulatory Flexibility Act, the agency certifies that the final rule will not have a significant impact on a substantial number of small businesses.

On October 14, 1993, FDA published an analysis of the economic impact of the proposed rule under the previous Executive Order (E.O. 12291). In that analysis, the agency stated that folate health claims may result in increased demand for products containing folate, and that an increase in consumption of products containing folate is likely to result in health benefits in terms of fewer neural tube defects. The agency also stated that there would be no costs associated with folate health claims as use of these claims is voluntary.

The agency concluded that it was not able to estimate the number of products that will bear health claims, or the effect that folate health claims will have on consumer demand for products containing folate, and requested comments. As mentioned previously, the agency received nearly 100 comments in response to the proposed rule on health claims for folate and neural tube defects. None of the comments provided information that would alter the agency's economic impact conclusion.

#### V. Collection of Information

This rule contains no collection of information requirements under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 et. seq.).

#### VI. References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m. Monday through Friday.

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#### List of Subjects in 21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under the 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 101.9 *Nutrition labeling of food* is amended in paragraph (c)(8)(v) by revising the entry for folate to read as follows:

#### § 101.9 Nutrition labeling of food.

\* \* \* \* \*

(c) \* \* \*

(8) \* \* \*

(v) \* \* \*

Folate—either Folic acid or Folicin may be used.

\* \* \* \* \*

#### § 101.36 [Amended]

3. Section 101.36 *Nutrition labeling of dietary supplements of vitamins and minerals* is amended in paragraph (b)(3)(v) by removing the words "folate (folicin)," and by adding in their place the words "folate—either folic acid or folicin may be used."

4. Section 101.79 is revised to read as follows:

#### § 101.79 Health claims: Folate and neural tube defects.

(a) *Relationship between folate and neural tube defects—(1) Definition.* Neural tube defects are serious birth defects of the brain or spinal cord that can result in infant mortality or serious disability. The birth defects anencephaly and spina bifida are the most common forms of neural tube defects and account for about 90 percent of these defects. These defects result from failure of closure of the covering of the brain or spinal cord during early embryonic development. Because the neural tube forms and closes during early pregnancy, the defect may occur before a woman realizes that she is pregnant.

(2) *Relationship.* The available data show that diets adequate in folate may reduce the risk of neural tube defects. The strongest evidence for this relationship comes from an intervention study by the Medical Research Council of the United Kingdom that showed that women at risk of recurrence of a neural tube defect pregnancy who consumed a supplement containing 4 milligrams (mg) (4,000 micrograms (mcg)) folic acid daily before conception and continuing into early pregnancy had a reduced risk of having a child with a neural tube defect. (Products containing this level of folic acid are drugs). In addition, based on its review of a Hungarian intervention trial that reported periconceptual use of a multivitamin and multimineral preparation containing 800 mcg (0.8 mg) of folic acid, and its review of the observational studies that reported periconceptual use of multivitamins containing 0 to 1,000 mcg of folic acid, the Food and Drug Administration concluded that most of these studies had results consistent with the conclusion that folate, at levels attainable in usual diets, may reduce the risk of neural tube defects.

(b) *Significance of folate—(1) Public health concern.* Neural tube defects

occur in approximately 0.6 of 1,000 live births in the United States (i.e., approximately 6 of 10,000 live births; about 2,500 cases among 4 million live births annually). Neural tube defects are believed to be caused by many factors. The single greatest risk factor for a neural tube defect-affected pregnancy is a personal or family history of a pregnancy affected with a such a defect. However, about 90 percent of infants with a neural tube defect are born to women who do not have a family history of these defects. The available evidence shows that diets adequate in folate may reduce the risk of neural tube defects but not of other birth defects.

(2) *Populations at risk.* Prevalence rates for neural tube defects have been reported to vary with a wide range of factors including genetics, geography, socioeconomic status, maternal birth cohort, month of conception, race, nutrition, and maternal health, including maternal age and reproductive history. Women with a close relative (i.e., sibling, niece, nephew) with a neural tube defect, those with insulin-dependent diabetes mellitus, and women with seizure disorders who are being treated with valproic acid or carbamazepine are at significantly increased risk compared with women without these characteristics. Rates for neural tube defects vary within the United States, with lower rates observed on the west coast than on the east coast.

(3) *Those who may benefit.* Based on a synthesis of information from several studies, including those which used multivitamins containing folic acid at a daily dose level of  $\geq 400$  mcg ( $\leq 0.4$  mg), the Public Health Service has inferred that folate alone at levels of 400 mcg (0.4 mg) per day may reduce the risk of neural tube defects. The protective effect found in studies of lower dose folate measured by the reduction in neural tube defect incidence, ranges from none to substantial; a reasonable estimate of the expected reduction in the United States is 50 percent. It is expected that consumption of adequate folate will avert some, but not all, neural tube defects. The underlying causes of neural tube defects are not known. Thus, it is not known what proportion of neural tube defects will be averted by adequate folate consumption. From the available evidence, the Public Health Service estimates that there is the potential for averting 50 percent of cases that now occur (i.e., about 1,250 cases annually). However, until further research is done, no firm estimate of this proportion will be available.

(c) *Requirements.* The label or labeling of food may contain a folate/

neural tube defect health claim provided that:

(1) *General requirements.* The health claim for a food meets all of the general requirements of § 101.14 for health claims, except that a food may qualify to bear the health claim if it meets the definition of the term "good source."

(2) *Specific requirements—(i) Nature of the claim—(A) Relationship.* A health claim that women who are capable of becoming pregnant and who consume adequate amounts of folate daily during their childbearing years may reduce their risk of having a pregnancy affected by spina bifida or other neural tube defects may be made on the label or labeling of food provided that:

(B) *Specifying the nutrient.* In specifying the nutrient, the claim shall use the terms "folate," "folic acid," "folacin," "folate, a B vitamin," "folic acid, a B vitamin," or "folacin, a B vitamin."

(C) *Specifying the condition.* In specifying the health-related condition, the claim shall identify the birth defects as "neural tube defects," "birth defects spina bifida or anencephaly," "birth defects of the brain or spinal cord anencephaly or spina bifida," "spina bifida and anencephaly, birth defects of the brain or spinal cord," "birth defects of the brain or spinal cord;" or "brain or spinal cord birth defects."

(D) *Multifactorial nature.* The claim shall not imply that folate intake is the only recognized risk factor for neural tube defects.

(E) *Reduction in risk.* The claim shall not attribute any specific degree of reduction in risk of neural tube defects from maintaining an adequate folate intake throughout the childbearing years. The claim shall state that some women may reduce their risk of a neural tube defect pregnancy by maintaining adequate intakes of folate during their childbearing years. Optional statements about population-based estimates of risk reduction may be made in accordance with paragraph (c)(3)(vi) of this section.

(F) *Safe upper limit of daily intake.* Claims on foods that contain more than 100 percent of the Daily Value (DV) (400 mcg) when labeled for use by adults and children 4 or more years of age, or 800 mcg when labeled for use by pregnant or lactating women) shall identify the safe upper limit of daily intake with respect to the DV. The safe upper limit of daily intake value of 1,000 mcg (1 mg) may be included in parentheses.

(G) *The claim.* The claim shall not state that a specified amount of folate per serving from one source is more effective in reducing the risk of neural tube defects than a lower amount per serving from another source.

(H) The claim shall state that folate needs to be consumed as part of a healthful diet.

(ii) *Nature of the food—(A) Requirements.* The food shall meet or exceed the requirements for a "good source" of folate as defined in § 101.54;

(B) *Dietary supplements.* Dietary supplements shall meet the United States Pharmacopeia (USP) standards for disintegration and dissolution, except that if there are no applicable USP standards, the folate in the dietary supplement shall be shown to be bioavailable under the conditions of use stated on the product label.

(iii) *Limitation.* The claim shall not be made on foods that contain more than 100 percent of the RDI for vitamin A as retinol or preformed vitamin A or vitamin D per serving or per unit.

(iv) *Nutrition labeling.* The nutrition label shall include information about the amount of folate in the food. This information shall be declared after the declaration for iron if only the levels of vitamin A, vitamin C, calcium, and iron are provided, or in accordance with § 101.9 (c)(8) and (c)(9) if other optional vitamins or minerals are declared.

(3) *Optional information—(i) Risk factors.* The claim may specifically identify risk factors for neural tube defects. Where such information is provided, it may consist of statements from § 101.79(b)(1) or (b)(2) (e.g., Women at increased risk include those with a personal history of a neural tube defect-affected pregnancy, those with a close relative (i.e., sibling, niece, nephew) with a neural tube defect; those with insulin-dependent diabetes mellitus; those with seizure disorders who are being treated with valproic acid or carbamazepine) or from other parts of this paragraph (c)(3)(i).

(ii) *Relationship between folate and neural tube defects.* The claim may include statements from paragraphs (a) and (b) of this section that summarize the relationship between folate and neural tube defects and the significance of the relationship except for information specifically prohibited from the claim.

(iii) *Personal history of a neural tube defect-affected pregnancy.* The claim may state that women with a history of a neural tube defect pregnancy should consult their physicians or health care providers before becoming pregnant. If such a statement is provided, the claim shall also state that all women should consult a health care provider when planning a pregnancy.

(iv) *Daily value.* The claim may identify 100 percent of the DV (100% DV; 400 mcg) for folate as the target intake goal.

(v) *Prevalence*. The claim may provide estimates, expressed on an annual basis, of the number of neural tube defect-affected births among live births in the United States. Current estimates are provided in § 101.79(b)(1), and are approximately 6 of 10,000 live births annually (i.e., about 2,500 cases among 4 million live births annually). Data provided in § 101.79(b)(1) shall be used, unless more current estimates from the U.S. Public Health Service are available, in which case the latter may be cited.

(vi) *Reduction in risk*. An estimate of the reduction in the number of neural tube defect-affected births that might occur in the United States if all women consumed adequate folate throughout their childbearing years may be included in the claim. Information contained in paragraph (b)(3) of this section may be used. If such an estimate (i.e., 50 percent) is provided, the estimate shall be accompanied by additional information that states that the estimate is population-based and that it does not reflect risk reduction that may be experienced by individual women.

(vii) *Diets adequate in folate*. The claim may identify diets adequate in folate by using phrases such as "Sources of folate include fruits, vegetables, whole grain products, fortified cereals, and dietary supplements." or "Adequate amounts of folate can be obtained from diets rich in fruits, dark green leafy vegetables, legumes, whole grain products, fortified cereals, or dietary supplements." or "Adequate amounts of folate can be obtained from diets rich in fruits, including citrus fruits and juices, vegetables, including dark green leafy vegetables, legumes, whole grain products, including breads, rice, and pasta, fortified cereals, or a dietary supplement."

(d) *Model health claims*. The following are examples of model health claims that may be used in food labeling to describe the relationship between folate and neural tube defects:

(1) *Examples 1 and 2*. Model health claims appropriate for foods containing 100 percent or less of the DV for folate per serving or per unit (general population). The examples contain only the required elements:

(i) Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord birth defect.

(ii) Adequate folate in healthful diets may reduce a woman's risk of having a child with a brain or spinal cord birth defect.

(2) *Example 3*. Model health claim appropriate for foods containing 100

percent or less of the DV for folate per serving or per unit. The example contains all required elements plus optional information: Women who consume healthful diets with adequate folate throughout their childbearing years may reduce their risk of having a child with a birth defect of the brain or spinal cord. Sources of folate include fruits, vegetables, whole grain products, fortified cereals, and dietary supplements.

(3) *Example 4*. Model health claim appropriate for foods intended for use by the general population and containing more than 100 percent of the DV of folate per serving or per unit: Women who consume healthful diets with adequate folate may reduce their risk of having a child with birth defects of the brain or spinal cord. Folate intake should not exceed 250% of the DV (1,000 mcg).

Dated: February 26, 1996.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 96-5013 Filed 2-29-96; 1:12 pm]

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### 21 CFR Parts 136, 137, and 139

[Docket No. 91N-100S]

RIN 0910-AA19

#### Food Standards: Amendment of Standards of Identity For Enriched Grain Products to Require Addition of Folic Acid

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending the standards of identity for several enriched grain products and, by cross-reference, the standards of identity for enriched bromated flour, enriched vegetable macaroni, and enriched vegetable noodle products, to require the addition of folic acid. The agency is requiring that these products be fortified with folic acid at levels ranging from 0.43 milligrams (mg) to 1.4 mg per pound (mg/lb) or 95 micrograms (µg) to 309 µg/100 grams (g), of product. These values are based on a fortification level of 140 µg/100 g (0.635 mg/lb) of the cereal grain product. This action is

being taken to help women of childbearing age to reduce their risk of having a pregnancy affected with spina bifida or other neural tube defects (NTD's) and to comply with the recommendation of the U.S. Public Health Service (PHS) that they consume at least 0.4 mg (400 µg) of folic acid daily. This action also responds to a citizen petition submitted by Glenn Scott.

**EFFECTIVE DATE:** January 1, 1998.

**FOR FURTHER INFORMATION CONTACT:** Felicia B. Satchell, Center for Food Safety and Applied Nutrition (HFS-158), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-205-5099.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

Recent estimates state that there are approximately 4,000 pregnancies each year, including 2,500 live births, that are affected by spina bifida and other neural tube defects. In September 1992, PHS recommended that all women of childbearing age in the United States consume 0.4 mg (400 µg) of folic acid daily to reduce their risk of having a pregnancy affected with spina bifida or other NTD's (Ref. 1). Furthermore, PHS identified several possible approaches by which folate intake by the target population could be increased. These approaches included: (1) Improvement of dietary habits, (2) fortification of the U.S. food supply, and (3) daily use of folic acid supplements by women throughout their childbearing years. However, the PHS recommendation cautioned against daily intakes of folate above 1 mg. A recognized adverse effect of high intakes of folate is a masking of the anemia of vitamin B12 deficiency, allowing the neurologic damage to progress untreated. PHS noted that care should be taken to keep total folate consumption at less than 1 mg (1,000 µg)/day, except under the supervision of a physician (Ref. 1).

Following publication of the PHS recommendation, FDA convened a Folic Acid Subcommittee from its Food Advisory Committee (hereinafter referred to as the Folic Acid Subcommittee) to consider some of the issues raised by the recommendation. After consideration debate, the Folic Acid Subcommittee identified several approaches that might assist women of childbearing age to increase their daily folate intake. These approaches included: (1) Development of a fortification program such that 90 percent of women of childbearing age could receive at least 400 µg per day from all sources, while preventing