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Folic Acid and the American Food Supply*

A historical account of the FDA's creation of the current folic acid regulations

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Abstract

During the 1980s, scientific studies began to uncover a link between the B-vitamin folic acid and a reduction in the prevalence of neural tube defects, including spina bifida and anencephaly. When Congress passed the Nutrition Labeling and Education Act of 1990, it included a command that the FDA consider the link between folic acid and neural tube defects to determine whether the evidence was strong enough to permit food manufacturers of products containing folic acid to make a claim that their products may help prevent neural tube defects. Although the FDA initially rejected the use of such a claim, faced with mounting pressure from the scientific community and other government agencies, it reversed course and allowed manufacturers to make certain health claims regarding folic acid. It also required that certain products be fortified with folic acid, while banning its addition to other products. This paper details this process in an attempt to show its complexity and the very serious issues it presents. Since the process is largely complete, the paper also attempts to evaluate the process, as a whole, to determine what the FDA did well and what, if anything, the FDA should have done differently.

Introduction

In the past, many Americans probably thought little about the ingredients in many of the foods they consumed. Certainly, in these more health conscious times, consumers are more attentive than ever to the foods they eat and to the nutritional value of those foods. But, that attention to the foods and their nutritional values probably consists more of noting the calories, fat, and cholesterol contents than some of the more mysterious nutrients like Thiamin, Riboflavin, Niacin, and Folic Acid. Many consumers probably have no idea what those nutrients are or why or how they came to be included in many of the foods purchased today. Interestingly, these nutrients are among those that are often present in foods not because they naturally occur in them or because they are necessary to make the specific food item, but because their inclusion is required by the United States Food and Drug Administration ("FDA"). The FDA requires manufacturers of some food products to include in those products several specific ingredients if they want to label their product in a certain way. For example, if the Borden Foods Corporation wants its Prince brand pastas to say "enriched macaroni product" on the label, the manufacturer must add certain nutrients in specific quantities. Similarly, if General Mills Cereals, LLC, wants its Cheerios to say "As Part of A Heart-Healthy Diet, the Soluble Fiber in Cheerios Can Reduce Your Cholesterol!" it must meet certain other FDA requirements.

This paper will explore how one specific nutrient, folic acid, created a controversy for the FDA and is, today, a required ingredient for certain foods. Folic acid, which is a B vitamin, received little attention until the mid 1980s, when studies began to uncover evidence of a link between folic acid and the prevention of certain birth defects, called neural tube defects. As the evidence grew, Congress ordered the FDA to examine the link and possibly create a rule which would allow manufacturers of food products containing folic acid to place on the products' labels a claim stating that consumption of the product may reduce the risk of having

a child with neural tube defects. The FDA, after numerous delays and several changes in course, ended up adopting a three-part plan which not only allowed manufacturers to include on their products a health claim regarding folic acid, but also required certain products to contain folic acid, while banning the addition of folic acid to others. This paper details that process. It begins with an overview of folic acid and neural tube defects, then discusses the various scientific studies which led Congress to take note of folic acid. Only those studies which were published prior to the FDA taking action are included, as those make up the body of evidence with which the FDA had to work when it undertook the various folic acid-related programs. The paper then details the lengthy rulemaking process the FDA went through before arriving at the current rules. Discussions of recent litigation resulting from the rules, as well as the effects of the rules on the prevalence of neural tube defects, follow to conclude the paper. The goal of this paper is not to be entirely comprehensive, but rather to illuminate the various steps and processes which occurred to lead to the present day rules and requirements regarding folic acid.

Description of Folate[1]

Folate is the more common term for vitamin B_9. The vitamin is found naturally in a variety of foods, including green vegetables (such as spinach, broccoli, and Brussels sprouts), fruits (such as oranges and grapefruits), dried beans, and liver, among other things. While folate is a term generally used to describe this naturally occurring version of the vitamin, the vitamin's synthetic version, found in dietary supplements and fortified foods, is called folic acid. In humans, folate and folic acid are essential during the cell division and multiplication process, which is why diets lacking in them could lead to impaired cell function. Folate and folic acid function the same way once absorbed by the body, but the natural folate found in foods is typically not absorbed as easily as the synthetic form. Some estimates are that 100% of folic acid in foods

[1]The contents of this section are factual in nature and can be found, except where specifically noted, throughout the body of nutritional literature.

is absorbed by the body, while only 50% of natural folate is so absorbed.[2] Both are water soluble, so excess is excreted from the body, requiring that adequate folate be ingested each day. Excessive folic acid intake thus results in few side effects although, as will be discussed later, it has been shown to potentially mask symptoms of a vitamin B_{12} deficiency. In addition to neural tube defects, which are the issue here, folic acid has been linked to the prevention of several other diseases, including cardiovascular disease and Alzheimer's Disease.[3] It has also been shown to help lower levels of homocysteine in the blood, which helps reduce the risk of heart attacks and strokes. Most of the research and the resulting rules and regulations issued by the FDA refer to the synthetic form, so for the most part the term folic acid, rather than folate, will be used.

Description of Common Neural Tube Defects

A neural tube defect is a malformation of the brain or spinal cord that occurs during fetal development.[4] During normal fetal development, the covering for the brain and spinal cord forms approximately 18 to 20 days after conception and closes between 24 and 27 days after conception.[5] Therefore, because this initial development and closure of the neural tube occurs within the first month after conception, and because 50% of all pregnancies in the United States are unplanned, the proper closure of the neural tube often occurs before a woman realizes she is pregnant.[6] It is during this development and closure of the neural tube that neural tube defects occur, most of which occur when the neural tube fails to close.[7]

[2]MayoClinic.com, *Folate vs. Folic Acid: What's the difference?* At http://www.mayoclinic.com/invoke.cfm?id=HQ00703
[3]Marian Burros, *Eating Well; One More Reason to Eat Your Greens*, N.Y. Times, May 16, 2001, at F5.
[4]Ronald J. Lemire, *Neural Tube Defects*, 259 JAMA 558 (1988).
[5]Food Labeling: Health Claims and Label Statements; Folate and Neural Tube Defects, 61 Fed. Reg. 8752, 8753 (March 5, 1996).
[6]*Id.*
[7]Lorenzo D. Botto, et al., *Neural Tube Defects*, 341 New Eng. J. Med. 1509 (1999).

The most common types of neural tube defects, accounting for 90% of these defects in the United States, are anencephaly and spina bifida.[8] In anencephaly, the defect is in the brain, with brain tissue being "exposed to the surface through a defect in the scalp and skull."[9] Children born with anencephaly do not have a forebrain or a cerebrum, and any portion of the brain that does develop is often not covered with bone or skin.[10] This results in an infant who is blind, deaf, unconscious, and unable to feel pain.[11] Although reflex action such as breathing and responses to touch and sound may occur, the infant's lack of a cerebrum precludes any possibility that it will gain consciousness.[12] Therefore, children born with anencephaly are either stillborn or die soon after birth.[13] Approximately 18.38 babies per 100,000 live births were affected by anencephaly in 1991, and 10.33 per 100,000 live births had this condition in 2000[14]. An unknown number of cases of anencephaly occur in fetuses which are spontaneously aborted, and an unknown number are detected through fetal testing and are voluntarily aborted.

While anencephaly occurs when the neural tube fails to close at the head end, spina bifida is a defect which occurs lower along the spinal column. Two forms of spina bifida are typically included in neural tube defect studies and statistics, namely meningocele and myelomenigocele.[15] Meningocele is sometimes referred to as a postneurulation defect, or a closed neural tube defect, because it occurs after the neural tube closes and is covered by skin.[16] This type of spina bifida "is a saccular herniation of meninges and cerebrospinal fluid through a bony defect of the spine."[17] In contrast, myelomenigocele is an open neural tube defect, or neurulation defect, because it occurs before the neural tube has closed and is, therefore, usually uncovered.[18]

[8] Food Labeling, *supra* note 4, at 8753.
[9] Lemire, *supra* note 3, at 558.
[10] The National Institute of Neurological Disorders and Stroke Information Page, *at* http://www.ninds.nih.gov/health_and_medical/disorders/anencephaly_doc.htm.
[11] *Id.*
[12] *Id.*
[13] Botto, *supra* note 6, at 1511.
[14] Centers for Disease Control ("CDC"), *Spina Bifida and Anencephaly Prevalence – United States, 1991-2001*, 51 Morbidity and Mortality Weekly Report ("MMWR") 9 (Sept. 13, 2002).
[15] Botto, *supra* note 6, at 1511.
[16] Lemire, *supra* note 3, at 559.
[17] Botto, *supra* note 6, at 1511.
[18] Lemire, *supra* note 3, at 558.

In this, the more common type of spina bifida, the spinal cord, nerves, or both may protrude through a defect in the spine.[19] These two types of spina bifida occurred in 24.88 out of every 100,000 live births in the United States during 1991, and in 20.85 out of 100,000 in 2000[20]. As with anencephaly, an unknown number of spina bifida cases occur in fetuses which are not carried to term. Unlike anencephaly, which is always fatal at or immediately after birth, infants born with spina bifida can often survive the birthing process and live for quite some time. Although fatality rates are higher elsewhere, in the United States, 90% of infants with spina bifida survive, with over half living into their 20s.[21]

Causes of Neural Tube Defects

Although neural tube defects are horrifying and/or deadly, little is known about their cause and, until recently, little was known about their prevention. Although a few studies in the 1960s and 1970s began to take note of possible common trends in neural tube defect cases, it was not until the 1980s that researchers began to make serious progress. Most of the work during the 1980s occurred in the United Kingdom, before spreading around the world. By the 1990s, research results were being published in the United States, Hungary, China, and elsewhere. Although many of the studies were subject to possibly bias criticisms and other flaws, the vast majority pointed to one major factor in the prevention of high numbers of neural tube defects: folic acid. However, the link between folic acid and neural tube defects is still somewhat of a mystery today. In fact, it took years for many in the scientific community to be convinced that such a link even existed. For example, in one article discussing neural tube defects, published in the *Journal of the American Medical Association* in 1988, the author notes that nutrition seems to be a factor in the incidence of neural tube defects, but lists protein, vitamins, and folic acid all as possible candidates, while not completely ruling out theories that nitrite-cured meats, blighted potatoes, salicylates, hard water, and

[19]Botto, *supra* note 6, at 1511.
[20]CDC, *supra* note 13.
[21]Botto, *supra* note 6, at 1511.

certain medications might also be the cause.[22] Even the FDA was unwilling to officially associate folic acid with the prevention of neural tube defects until 1993. Until that point, the FDA refused to authorize the use health claims regarding a link between folic acid and neural tube defects, and refused to include folic acid in the requirements for standardized food types.[23] What follows is a survey of the different types of studies conducted and published prior to the FDA's proposal of folic acid measures in late 1993. Although new studies analyzing the links between folic acid and neural tube defects are still being published today, this paper examines only the major studies published prior to 1993, as those were the studies upon which the FDA based its decision to propose the various folic acid measures it eventually adopted.

Although a potential link between folic acid and neural tube defects was first discussed in 1965,[24] modern conclusions regarding the link seem to stem more from research reported in *The Lancet* in 1980.[25] This study ("Smithells 1980") focused on the use of several vitamins, not just folic acid, in prevention of neural tube defects. This is not unexpected, as early research in the area of neural tube defects noted links between increased likelihood of the defects in lower socioeconomic levels, which led to speculation that a more general nutrition element may be at issue.[26] Therefore, the Smithells 1980 study worked from a hypothesis that "subclinical deficiencies of one or more vitamins contribute to the causation of [neural tube defects]."[27]

The Smithells 1980 study was conducted using as subjects women living in Northern Ireland, South-East England, Yorkshire, Lancashire, and Cheshire who previously had at least one pregnancy affected by a neural tube defect. The women who participated were planning another pregnancy, but were not yet pregnant. This group consisted of 185 women who were given a vitamin (Pregnavite forte F) daily, beginning at least 28 days before conception and continuing until after the second missed menstrual period, at which point closure

[22] Lemire, *supra* note 3 at 559.

[23] Food Labeling: Health claims and Label Statements; Folic Acid and Neural Tube Defects, 56 Fed. Reg. 60610 (Nov. 27, 1991).

[24] E.D. Hibbard & R.W. Smithells, *Folic acid metabolism and human embryopathy*, 1965 The Lancet 1254.

[25] R.W. Smithells, et al., *Possible prevention of neural-tube defects by periconceptional vitamin supplementation*, 1980 The Lancet 339.

[26] *See, e.g.*, Lemire, *supra* note 3, at 559, and Smithells, *supra* note 24, at 339.

[27] Smithells, *supra* note 24, at 339.

of the neural tube should have occurred. The Pregnavite forte F supplements administered provided the women with vitamin A, vitamin D, thiamine, riboflavin, pyridoxine, nicotinamide, ascorbic acid, ferrous sulphate, and calcium phosphate, at various dosages. The supplements also included 0.36 mg of folic acid.[28] Women who missed more than one day of taking the supplement or who became pregnant before taking the supplement for 28 days were not included in the study. The study used as a control group 264 women who previously had a pregnancy affected by a neural tube defect but who either declined to participate in the study or who were pregnant prior to beginning the supplement program.

The 185 study group mothers gave birth to 188 babies (as a result of three sets of twins), which broke down along the following categories: 140 babies were born without a neural tube defect, 1 baby was born with a neural tube defect, 11 fetuses were spontaneously aborted (none had a neural tube defect), 26 pregnancies were still ongoing (but with normal amniotic-fluid α-fetoprotein values, indicating no neural tube defect), and 10 were not examined. This yields a neural tube defect recurrence rate of 0.6% (1 in 178). The 264 control mothers produced 269 babies (including five sets of twins), of which 12 had a neural tube defect, 192 had no neural tube defect, 1 was spontaneously aborted and was affected by a neural tube defect, 17 were spontaneously aborted but had no neural tube defect, 38 remained unborn but had normal amniotic-fluid α-fetoprotein values, and 9 were not examined. This yields a neural tube defect recurrence rate of 5.0% (13 in 260). Therefore, the results of this early study showed a potential link between vitamin use and neural tube defects rates, with mothers taking vitamins having approximately 1/8 the rate of neural tube defect recurrence as mothers not taking the vitamins. Nearly two years later, the same researchers published the results of a second study conducted the same way as the first, yielding similar results.[29] In this second study ("Smithells 1981"), there were two cases of neural tube defects among the 202 mothers receiving supplements (.99%) and ten cases among the 198 mothers not receiving supplements (5.05%).

[28]The amount of folic acid is provided here for comparison with amounts used in later studies.

[29]R.W. Smithells, et al., *Vitamin Supplementation and Neural Tube Defects*, 1981 The Lancet 1425.

Perhaps because of such a stark difference between the two groups' rates of neural tube defect recurrence, the Smithells 1980 study received much commentary. The authors, themselves, noted several possible problems with a conclusion that the vitamins were responsible for the reduced rate, including a potential for women with a low probability of recurrence somehow self-selecting into the supplementation group and a potential that something other than the vitamins was causing the lowered rate.[30] Although they do not fully explore it, the authors' self-selection argument does present an interesting potential problem with the study. The problem arises because the participants in this study, unlike later trials examined below, were not randomized. Women were able to choose whether or not they wanted to take the vitamin. There is, therefore, a potential that the women electing to take the vitamin may have led healthier lifestyles overall, by perhaps eating better diets, not drinking, not smoking, getting adequate rest and/or exercise, etc. Therefore, the study may potentially be skewed by more health conscious women electing to take the vitamin.

In addition to criticism, the study also received praise from some commentators. For example, J. H. Edwards called the results "compelling evidence of a major effect comparable with that relating cigarette smoking and lung cancer."[31] He noted that the results make it "clear that all women who have an affected child should receive supplementation for further pregnancies."[32] While Edwards was unwilling to make any recommendations regarding women who have not had neural tube defect-affected pregnancies, he did think the study's results were strong enough to consider fortification of the food supply or provision of vitamin supplements with oral contraceptives with instructions for women to begin taking the vitamins if they stop taking the contraceptives.[33]

[30] Smithells, *supra* note 24, at 340.
[31] J. H. Edwards, *Vitamin Supplementation and Neural Tube Defects*, 1982 The Lancet 275.
[32] *Id.*
[33] *Id.*

However, not all commenting researchers were convinced with the Smithells studies. For example, Renwick noted that the results do not mean that neural tube defects are caused by vitamin deficiencies, noting that the vitamin supplements may correct a problem caused by something else, such as toxicity from blighted potatoes.[34] Chalmers and Sacks also criticized the Smithells studies because 27% of the originally supplemented women were eventually excluded for a variety of technical reasons, even though 300 of the 301 original control women were allowed to proceed. Perhaps more importantly, however, it is their opinion that the "studies are far too undersized and too short-term to rule out potentially serious and unexpected side effects of the supplement."[35] Similarly, Meier criticized the studies as being potentially similar to the study which showed that giving diethylstilboestrol ("DES") to pregnant women reduced fetal mortality, but later was shown to cause vaginal cancer in the daughters of women who took DES during pregnancy. Meier, therefore, believes the potential costs of the results of these studies may be much greater than anticipated.[36] Following the published results and criticisms of the Smithells studies, a number other researchers conducted studies through the 1980s, leading to several more publications during the years immediately surrounding 1990. In 1988, Joseph Mulinare, M.D., along with three other doctors, published the results of a study they conducted during the mid-1980s ("Atlanta study").[37] The Atlanta study involved the researchers reviewing, in an after-the-fact way, the records of women who had been part of the Atlanta Birth Defects Case-Control ("ABDCC") Study. The researchers then used records of women who had had pregnancies affected by neural tube defects and who had participated in the ABDCC to form a case group for the Atlanta study. The Atlanta study used two control groups. One, the normal control group, was made up of randomly chosen women who had given birth to children without birth defects and who matched certain demographic characteristics (race, time of birth, location of birth, etc.) of specific case group women. The second control

[34] J.H. Renwick, *Vitamin Supplementation and Neural Tube Defects*, 1982 The Lancet 748.
[35] Thomas C. Chalmers & Henry Sacks, *Vitamin Supplements to Prevent Neural Tube Defects*, 1982 The Lancet 748.
[36] Paul Meier, *Vitamins to Prevent Neural tube Defects*, 1982 The Lancet 859.
[37] Joseph Mulinare, et al., *Periconceptional Use of Multivitamins and the Occurrence of Neural Tube Defects*, 260 JAMA 3141 (1988).

group, the abnormal group, was made up of women who had given birth to babies with serious birth defects other than neural tube defects, and who matched certain demographic characteristics of specific case group women. All three of the groups consisted of women who had been pregnant between 1968 and 1980, and the case group consisted of 347 women while the control groups consisted of a combined 2829 women.

Using the records, the researchers conducted telephone interviews with the women to determine the level of vitamin use by each woman prior to and after conception of the specific baby at issue. The researchers discovered that 7% of the women in the case group had taken multivitamins during the entire pre- and post-conception period, while 15% of the control mothers had taken multivitamins during the applicable period. Forty-six percent of the case mothers and 39% of the control mothers reported no multivitamin use during the period. Using these results and the incidence of neural tube defects, the Atlanta study yielded a relative risk of neural tube defects of between 0.41 and 0.51, showing that women who did not use multivitamins were more likely than women who used multivitamins to have a pregnancy affected by a neural tube defect. These results are in contrast with a somewhat similar study conducted by James L. Mills, et al. ("Mills study"), using data from California and Illinois.[38] Like the Atlanta study, the Mills study used after-the-fact questioning, rather than concurrent monitoring and observation. Researchers in the Mills study formed three groups of women who were pregnant between mid-1985 and mid-1987: case mothers (whose pregnancies were affected by neural tube defects), abnormal control mothers (whose pregnancies were affected by major malformations other then neural tube defects) and normal control mothers (whose pregnancies were not affected by neural tube defects or major malformations). Each group consisted of approximately 550 women of very similar demographic characteristics, determined through a matching procedure. When a woman with a neural tube defect-affected pregnancy was discovered (and the researchers examined 82% of the affected

[38] James L. Mills, et al., *The Absence of a Relation Between the Periconceptional use of Vitamins and Neural-Tube Defects*, 321 New Eng. J. Med. 430 (1989).

women in Illinois and 65% of the affected mothers in California), researchers matched a normal and abnormal control woman of similar characteristics (location, stage of birth, race, date of diagnosis, etc.) to the woman in the neural tube defect group and included the matched women in the abnormal or normal control group. Each woman was then interviewed by telephone twice within five months of delivery or diagnosis: once by a researcher to confirm the details of the woman's pregnancy, then a second time by a second researcher who did not know to which of the three groups the woman belonged. The second interview asked the women about vitamin use during the month prior to the first date of their last menstrual period and the approximately 45 days later. Women who reported vitamin use were asked to identify the type of vitamin used. Women were then separated based on how frequently they took the vitamins. Using this data, the researchers, using the three groups women (which were virtually identical in all characteristics, due to the matching procedure described above), determined that the use of vitamins across the three groups was not statistically dissimilar, and that among vitamin users, the odds of having an infant with a neural tube defect was also not statistically dissimilar. Therefore, the researchers concluded that the use of multivitamins does *not* reduce the risk of neural tube defects.

Noting that their study produced results in contrast with that of the Atlanta study and the British studies discussed above, the authors of the Mills study offered some analysis as to why they considered their results to be superior. As compared to the British studies, the Mills study authors noted that those studies have been criticized in numerous ways (as discussed above). Also, the British studies looked only at recurring cases of neural tube defects and did so in the United Kingdom, which has a much higher rate of neural tube defects than the United States. The Mills study authors also criticized the Atlanta study, noting that differences in results could have been the product of the differing time periods of the two studies (1968-1980

for the Atlanta study versus 1985-1987 for the Mills study) and the differing locations for the two studies (Atlanta, Georgia, versus Illinois and California). However, the authors of the Mills study also noted several differences between the studies which might, in fact, make the Mills study superior to the Atlanta study. First, the authors noted that in the Atlanta study, women were interviewed from two to 16 years after the pregnancy at issue, leading to a larger potential for recall bias than in the Mills study, where the interviews occurred no more than 5 months after the pregnancy. Also, this time difference made it more difficult for the Atlanta researchers to determine what type of multivitamin the women took, leading the Mills researchers to believe their results to be more accurate.

Approximately three months after the Mills study was reported in *The New England Journal of Medicine*, the results of another multivitamin-neural tube defect study were published in the *Journal of the American Medical Association*. This study ("Milunsky study") found a link between multivitamins, and specifically folic acid, and neural tube defects.[39] The Milunsky study examined women when they had a maternal serum α-fetoprotein (MSAFP) screen or an amniocentesis. These generally occurred during the first 15 to 20 weeks of the pregnancy. Of the participants, 86% of the women were from New England, with the remaining 14% from areas of the United States outside New England. Nurses contacted the women via telephone after the tests were conducted and prior to (in 93% of the cases) the women or the nurses receiving the results of the tests. The nurses questioned the women on "family, medical, and genetic history with special emphasis on diet, medication, and illness during the first trimester of pregnancy."[40] The questions allowed the researchers to determine multivitamin use during the three months prior to pregnancy as well as during the first three months of the pregnancy, and also provided detailed information about the women's diet during that time period, allowing the researchers to determine the amount of folic acid consumed as part of the diet during those same periods. Of the 24,559 women contacted, the nurses obtained complete interviews from 22,776.

[39] Aubrey Milunsky, et al., *Multivitamin/Folic Acid Supplementation in Early Pregnancy Reduces the Prevalence of Neural Tube Defect*, 262 JAMA 2847 (1989).

[40] *Id.* at 2848.

The researchers broke the data down in numerous ways, allowing them to determine the effects of folic acid and multivitamin intake for a variety of periods. Several pieces of data are of particular interest here. First, the study found 1.2 cases of neutral tube defects per 1000 pregnancies among women who used multivitamins at least once per week during the three months before and after pregnancy. This compares to a prevalence of 3.5 per 1000 in the women who used no multivitamins and 2.4 per 1000 in women who took multivitamins during the first trimester only. This yields a prevalence ratio of 0.36 for the women using multivitamins before and after conception compared to no multivitamins and 0.68 for women using multivitamins during the first trimester only compared with the women using no multivitamins. This implies a benefit to using multivitamins during the first trimester, and a greater benefit to using multivitamins before pregnancy and during the first trimester. Examining the data in a different way, women who used multivitamins during the first six weeks of pregnancy (prior to the closure of the neural tube) had 1.1 cases of neural tube defect per 1000 pregnancies, compared to 3.5 cases in women not using multivitamins and 3.2 cases in women using multivitamins after the seventh week of pregnancy, only. This implies that most of the benefits of multivitamin use result when use is during the first six weeks of pregnancy.

The Milunsky study also found that use of a multivitamin (during the first six weeks of pregnancy) containing folic acid yielded 0.9 cases of neural tube defect per 1000 pregnancies, where use of a multivitamin without folic acid resulted in 3.2 cases per 1000 and no multivitamin was 3.5 cases per 1000. This seems to imply that folic acid, rather than simply a multivitamin, is necessary for the benefits to occur. By examining the diets of women not using multivitamins, the researchers determined that in women whose diet during the first six weeks of pregnancy contained more than 100 micrograms of folic acid per day had 3.1 cases of neural tube defect per 100 pregnancies, compared to 7.3 per 1000 in women whose diets had less than 100 micrograms of folic acid per day. This implies that more than 100 micrograms of folic acid in the diet during early pregnancy can also yield a protective benefit.

The results of the Milunsky study seem to point toward a substantial benefit of folic acid intake prior to the sixth week of pregnancy. These results are perhaps more valuable than others discussed previously because of the sheer scope of this study, as it included over 22,000 pregnancies. The authors note that their results are similar to those of Smithells, examined above. They also note, though, an obvious limitation of their study, in that its sample is not representative of the general population. For example, of the 22,776 women in the study, 96% were white and 70% of the women had attended college. However, as the authors note, while the results of the study may not be transferable to the public at large, they "have no reason to hypothesize that the higher risk for NTD among [their] subjects should make their response to folic acid biologically different from that of other women."[41] Therefore, the authors predict that use of a multivitamin containing folic acid during the first six weeks of pregnancy could prevent 50% of the occurrences of neural tube defects.[42]

It is interesting to note that, as mentioned above, the Milunsky study was published three months after the Mills study, and yields completely contradictory results. The authors of the Milunsky study received the results of the Mills study as they published their own, and attached as an addendum their assessment of the contradiction between the two studies. The Milunsky authors note that in their study, the use of multivitamins was ascertained early in the pregnancies, and usually prior to the participants' or researchers' knowledge of whether the pregnancy was affected by a neural tube defect. This contrasts with the Mills study, where multivitamin use was determined after the birth of the baby or after a neural tube defect was identified. This delayed questioning leads, according to the Milunsky authors, to "substantial recall error that tends to lead to a null result."[43] Additionally, the Milunsky authors note that the Mills study classified as nonusers of multivitamins those women who began taking the multivitamins after they discovered they

[41] *Id.* at 2851.
[42] *Id.* at 2852.
[43] *Id.*

were pregnant. In the Milunsky study, 22% of women reported taking vitamins beginning during the first 6 weeks of pregnancy. This led the Milunsky authors to note that if such use does provide a protective effect, this would have been included in the nonusers, not the users, in the Mills study, also leading to an inaccurate result in the Mills study.

It is useful to pause here to note that the above-discussed studies provide a fairly comprehensive overview of the research available in 1990. This is noteworthy because 1990 is the year in which the FDA first became involved in the folic acid-neural tube defect issue in the United States. Although it will be discussed in greater detail below, Congress in 1990 passed the Nutritional Education and Labeling Act. As part of the legislation, Congress directed the FDA to consider whether there was enough evidence of certain nutrient-disease relationships, of which folic acid-neural tube defects was one, to allow manufacturers of foods to label their foods with health claims regarding the relationships. Therefore, in the years following 1990 when the FDA first began to review the issue in terms of health claims manufacturers might place on products containing folic acid, whether folic acid should be required as part of the food fortification program, and what restrictions, if any, needed to be placed on folic acid fortification, the previously described studies form the basis of the research available to it. Because these studies are in some ways flawed, non-comprehensive, and contradictory, the FDA's actions become more understandable. The studies described in the pages that follow are those the results of which were released as the FDA began to tackle the issue, and they provide more evidence on which the FDA could begin to base its actions.

Post 1990 studies

Although many of the earlier, above-detailed, studies were not actively-conducted, randomized studies yielding concrete results, and some were small in scope, one major randomized study was published in mid-1991.[44]

[44]MRC Vitamin Study Research Group, *Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study*, 338 The Lancet 131 (1991).

This randomized control trial study was conducted in the United Kingdom, and was praised by the U.S. Public Health Service as "one of the most rigorously conducted studies."[45] The study ("MRC study") ran from 1983 through 1991, and included over 1000 women from the United Kingdom, Hungary, Israel, Australia, Canada, the USSR, and France. All of the women already had a neural tube defect-affected pregnancy, were planning on becoming pregnant again, and were not taking vitamins. The women were randomly assigned to one of four groups and given capsules which contained: (a) 4 mg of folic acid only, (b) a multivitamin containing 4 mg of folic acid, (c) nothing or, (d) a multivitamin not containing folic acid. The women took one capsule each day through the 12th week of pregnancy, and it appears that women who became pregnant within two weeks of beginning the study were categorized separately.

By the time the study ended, 1195 women of the 1817 women randomized had a pregnancy which was examined for neural tube defects. In the 483 women in the MRC study who received folic acid, the recurrence rate of neural tube defects was 0.6%, compared with a recurrence rate of 3.6% in the 477 women who did not receive folic acid. Additionally, results were received from approximately the same number of women in each of the four groups (234-243 women), and the actual number of cases of neural tube defects was one in the group receiving only folic acid, 2 in the group receiving the folic acid and the multivitamin, 10 in the group receiving nothing, and 7 in the group receiving the multivitamin without folic acid. Taken as a whole, the results seem to indicate that 72% of neural tube defects were prevented in the groups taking folic acid. Although the study's participants were all women who were at an increased risk for neural tube defects pregnancies because they already had at least one affected pregnancy, the authors predict that the preventative effect of folic acid would apply similarly to women who had not previously had a neural tube defect pregnancy. They therefore suggested that all women should increase their folic acid intake.

[45]CDC, *Recommendations for the Use of Folic Acid to Reduce the number of Cases of Spina Bifida and Other Neural Tube Defects*, 41 MMWR 1 (Sept. 11, 1992).

Approximately one year later, another major study was published in *The New England Journal of Medicine* ("Hungarian study").[46] When the results of this study were announced (prior to publication) in the spring of 1992, they were perhaps the final piece of evidence necessary for many researchers to accept the link between folic acid and neural tube defects, according to Dr. James Mills, chief of pediatric epidemiology at the National Institute of Child Health and Human Development, and author of the previously described Mills Study.[47] This study, conducted by doctors in Hungary, was similar to the MRC study, except the subjects were women who had not previously had a neural tube defect-affected pregnancy. This is important, as 95% of pregnancies affected by neural tube defects occur in women who have not previously had a pregnancy affected by a neural tube defect.[48] In the Hungarian study, women who were planning to become pregnant were randomly assigned to either take a multivitamin (containing, among other things, 0.8 mg of folic acid) or a trace-element supplement. The women were to take the supplement daily for three months before attempting to conceive a child, then to continue daily intake of the supplement for the first three months of pregnancy. To be counted in the multivitamin group, the women had to take the vitamin daily for at least 28 days before conception and continue intake of the supplement until at least the date of the second missed menstrual period. Of the 7540 women entering the study, 4753 became pregnant and 4704 were studied.

The study noted rates of both congenital malformations and neural tube defects, with both being less prevalent in the multivitamin group. The rate of congenital malformations was 22.9 per 1000 in the trace-element group and 13.3 per 1000 in the multivitamin group. There were no cases of neural tube defects in the multivitamin group (consisting of 2394 women) and 6 cases in the trace-element group (of 2310 women).

[46] Andrew E. Czeizel & István Dudás, *Prevention of the First Occurrence of Neural-Tube Defects by Periconceptional Vitamin Supplementation*, 327 New Eng. J. Med. 1832 (1992).
[47] Gina Kolata, *U.S. Backs a Vitamin to Foil Birth Defects*, N.Y. Times, Sept. 15, 1992, at C2.
[48] *Id.*

The number of neural tube defects in the trace-element group was consistent with the 5.7 cases expected, based on Hungarian records. Therefore, the authors note that the protective effect of multivitamins and folic acid noted in the above-described studies of women with previous neural tube defect pregnancies is also available to prevent first-time occurrences of neural tube defects. The Hungarian authors thus recommend, as did the authors of previous studies, that women planning to become pregnant should consume a vitamin supplement containing folic acid.

FDA scrambles to deal with Folic Acid

By the early 1990s, the publication of the above described studies made it fairly clear to the scientific community that there was a link between folic acid and the prevention of a high percentage of neural tube defects. However, to receive the protective effects of folic acid, it appears that a woman must be ingesting it prior to conception and during at least the first month of pregnancy. After this time, the neural tube should have formed and any defect would already be present and irreversible. This posed a potential problem, though, because often women do not realize they are pregnant until several weeks after conception. Also, in the United States 50% of pregnancies are unplanned.[49] Women not planning to become pregnant might have a further delay in discovering their pregnancy. This is complicated by the fact that very few women even knew of the helpful benefits of folic acid. For example, even by 1995, after the benefits of folic acid had been publicized in major media outlets, a March of Dimes survey determined that only 52% of women had ever heard of folic acid, only 9% of those women knew that folic acid helped prevent birth defects, and only 1% of all women listed folic acid intake as one way a woman could reduce the risk of birth defects.[50] Health officials were thus faced with the dilemma of how to ensure that women would receive adequate folic acid prior to becoming pregnant and during early pregnancy. A likely candidate to solve this problem was

[49] Food Labeling, *supra* note 4.
[50] *Id.* at 8772.

the FDA, and during the early 1990s it was prompted from two fronts to take action on this issue. First, Congress in 1990 passed the Nutrition Labeling and Education Act of 1990. Second, the Public Health Service in 1992 made a recommendation that all women receive folic acid as part of their diet and suggested that the FDA undertake a plan to assist in this.

On November 8, 1990, the first President Bush signed the Nutrition Labeling and Education Act of 1990 ("NLEA").[51] The NLEA amended the Federal Food, Drug, and Cosmetic Act ("FDC Act"), the main act which governs the FDA, in several ways. The first way the NLEA amended the FDC Act (through the addition of a new subsection (q) for section 403 of the FDC Act[52]) was by adding a provision classifying any food as misbranded unless it carries a nutrition label which specifies certain informational items, such as serving size, servings per container, number of calories per serving, and the amount of certain nutrients, vitamins, and minerals per serving. The NLEA requires that the Secretary of Health and Human Services (and by delegation, the FDA) issue proposed regulations implementing this section within 12 months and issue final regulations within 24 months.

The second main way the NLEA amended the FDC Act, and the way which is at issue here, was in the area of claims made by manufacturers on the label of food products. While the first amendment classified a food as misbranded if it failed to contain certain nutritional information, this new section (a new subsection (r) for section 403 of the FDC Act) classifies a food as misbranded if its label carries either of two claims. First, it is misbranded if its label carries a claim that "characterizes the level of any nutrient which is of the type required by" the new section (q) to be placed on the nutrition label. Second, it is misbranded if its label "characterizes the relationship of any nutrient which is of the type required by [the new (q) section] to be in the label or labeling of the food to a disease or a health-related condition." Both types of claims are thus banned from food packaging unless they meet the requirements of the new subsection (r). The first type

[51] Nutrition Labeling and Education Act of 1990, Pub. L. No. 101-535 (1990). For the discussion which follows, all references are to the NLEA Act unless otherwise noted.

[52] 42 U.S.C. § 343.

of claim (the "level of nutrient" claims) may be placed on food packaging if they comply with regulations promulgated by the Secretary of Health and Human Services (and, thus, the FDA). These types of claims are now governed by the FDA regulations defining such terms as "good source" or "high" or "rich in."[53] The "level of nutrient" claims are also restricted regarding when they may state the absence of a nutrient, the level of cholesterol, the level of saturated fat, and the level of dietary fiber. Also, the "level of nutrient" claims are restricted if food contains a nutrient which the FDA, through enacted regulations, has determined may cause negative health effects for some people.

The second type of restricted claims (the "health effects" claims) face separate restrictions from the "level of nutrient" claims. The NLEA bars all "health effects" claims (such as "This product is a good source of folate – a vitamin necessary for the prevention of neural tube defects") unless the FDA has issued a regulation specifically allowing for such claims and the product at issue does not contain a nutrient which the FDA, through regulation, has determined may be harmful to humans in certain specified circumstances. The NLEA allows the FDA to make such regulations on if it "determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence."[54] The NLEA then required the FDA to promulgate regulations which carry out the provisions of the new amendments to the Federal Food, Drug, and Cosmetic Act. Among other regulations required to be promulgated within 12 months, the NLEA required that the FDA examine the relationships between the following nutrients and diseases to determine whether claims regarding them may be made pursuant to the various subparts of the new (r) subsection: Calcium and osteoporosis, dietary fiber and cancer, lipids and cardiovascular disease, lipids and cancer, sodium and hypertension, dietary fiber and

[53]See 21 C.F.R. § 101.54 (2002).
[54]42 U.S.C. § 343(r)(3)(B)(i).

cardiovascular disease, folic acid and neural tube defects, antioxidant vitamins and cancer, zinc and immune function in the elderly, and omega-3 fatty acids and heart disease.

Thus, buried deep in the NLEA, laid the first impetus for the FDA to begin a course of action on the folic acid-neural tube defect relationship. Because of the NLEA, manufacturers of products containing sufficient quantities of folic acid could not claim consumption of their product would be helpful in the prevention of neural tube defects. This would have been one avenue by which women could learn about the importance of neural tube defects and identify those products containing sufficient quantities of the nutrient. The only way such claims could be placed on food labels was for the FDA to issue a regulation allowing for the claim to be made. However, pursuant to the NLEA, the FDA could not issue such a regulation unless there was sufficient scientific evidence and agreement among scientific experts as to the validity of the claim.

Initial Action under the NLEA

Pursuant to the NLEA, the FDA published in the November 27, 1991, edition of the *Federal Register* its proposed regulations regarding the "use of health claims that characterize the relationship of a food component to a disease or health-related condition on the labels and in the labeling of both conventional foods and dietary supplements."[55] The issuance of these proposed regulations marked the beginning of the FDA's transition to operating under the structure of the NLEA. Prior to the issuance of these proposed regulations, the FDA had actually begun its own process of authorizing the types of health claims at issue here. Originally, the FDA did not allow manufacturers to make claims on their food labels concerning the use of their product in relation to disease prevention. The FDA operated under the assumption that such claims classified the food as a drug under the Federal Food, Drug, and Cosmetic Act.[56] In 1987, however, the FDA "respond[ed] to the developing scientific data on the relationship between the nutrient content

[55]Labeling; General Requirements for Health Claims for Food, 56 Fed. Reg. 60537 (Nov. 27, 1991).
[56]*Id.*

of the diet and disease" by proposing to amend its regulations to allow truthful health claims which were supported in various specific ways by the scientific and medical communities, thus creating a safe harbor from FDA enforcement action.[57]

After manufacturers began to stretch the limits of the proposed regulations, prompting FDA enforcement action, the FDA in 1990 withdrew the 1987 proposal and reproposed the regulations in a more strict form. In the reproposal, the FDA suspended the safe harbor at least until final rules were adopted, which meant health claims would be examined by the FDA on a case by case basis. However, this line of proposed rules terminated after the President signed the NLEA, as the FDA then began to work to implement the NLEA's own general rules regarding health claims on labels. The NLEA directed the FDA to promulgate regulations authorizing health claims, and specifically directed the FDA to consider the appropriateness of 10 nutrient-disease relationships, of which folic acid-neural tube defects was one. Thus, beginning with the NLEA, if consumers were to be informed, through product labeling, of the beneficial effects of folic acid in preventing neural tube defects, the FDA would first have to authorize the use of such claims.

In the November 27, 1991, issue of the *Federal Register*, the FDA first proposed its regulations regarding health claims on food and dietary supplement packaging. The regulations cover such topics as making proposals to the FDA for new health claims, the issues the FDA will consider in deciding whether to approve the health claim (including safety and effects on the population), the requirements for validity (including the necessary level of scientific and medical community support), and specific requirements of the claim as proposed to be printed on food or dietary supplement labels. The regulations also prohibited any health

[57] *Id.* at 60538.

claims unless the claims had been approved by the FDA. Although most health claims would reach the FDA through a petition for consideration (a procedure outlined in these regulations), Congress placed the folic acid-neural tube defects relationship in front of the FDA in the NLEA, so no petition was necessary.

Since the NLEA required the FDA to act on 10 nutrient-disease relationships without waiting for petitions from the industry, the FDA followed its proposed regulations in the November 27, 1991, edition of the *Federal Register* with articles relating to each of the 10 relationships. Thus, the initial discussion of the folic acid-neural tube defects relationship also appears in the November 27, 1991, *Federal Register*.[58] There, the FDA proposed to decline authorizing the placement of health claims related to folic acid on labels for foods and dietary supplements. In this denial, the FDA used the standard established in the previously described *Federal Register* document in which it stated "such claims would only be justified for substances in dietary supplements as well as in conventional foods if the totality of the publicly available scientific evidence... supports a claim; and if there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims about such support."[59] Thus, following that standard, the FDA found that there was not sufficient agreement among scientific experts as to the effects and the necessary dosage of folic acid in the prevention of neural tube defects.

In reaching its decision to deny health claims regarding folic acid and neural tube defects, the FDA examined all of the scientific studies described in a previous section of this paper, with the exception of the Hungarian Study, which had not yet been released. It is therefore necessary to examine the FDA's analysis of the scientific evidence to determine why, when faced with the scientific evidence previously noted, it was unable to find sufficient scientific evidence and support for these health claims. Although the FDA did review other government and scientific literature in reaching its decision, it appears to have given very little weight to those pieces, making it unnecessary to review the FDA's commentary on those works here.

[58] Food Labeling: Health Claims and Label Statements; Folic Acid and Neural Tube Defects, 56 Fed. Reg. 60610 (Nov. 27, 1991).

[59] *Id.*

The FDA's reasons for not accepting the results of the scientific studies as conclusive enough to allow for the authorization of health claims appear to break down into four categories: (1) Location of the study participants, (2) Amount of folic acid used in the study, (3) Effects of other vitamins, (4) Flaws in the study, itself. First, the FDA discredited the results of many of the studies because of the location of the participants. The crux of the FDA's problem with the studies was that they were either studies of non-U.S. populations or were studies of subsets of populations within the U.S. which have higher than average rates of neural tube defects. For example, the FDA noted that the results of the Smithells study and the MRC study were difficult to project onto the general U.S. population because the U.S. is an area of relatively low risk for neural tube defects compared to the countries examined in those studies. Additionally, those studies, and others, examined only women who previously had a pregnancy affected by a neural tube defect, making those women at high risk for an additional affected pregnancy. Thus, the FDA expressed concern about generalizing the results obtained from these studies of "high-risk populations" to the larger population of "all women of child-bearing age."[60]

The FDA also expressed doubts about the generalizability of the studies, such as the Milunsky study and the Atlanta study, which took place in the U.S. It found the participants in the Milunsky study to not be representative of the general population because they were "receiving prenatal care and had a maternal α-fetoprotein screen or an amniocentesis."[61] The Atlanta study was problematic because the results were only statistically significant for white women, not for women of other races. Regarding both studies, the FDA noted that examined women who had taken vitamins and women "who take or are willing to take supplements may have other characteristics that by themselves decrease the risk of having an infant with a neural tube defect."[62] Thus, the FDA discounted the results of nearly all of the available studies because

[60] *Id.* at 60621.
[61] *Id.*
[62] *Id.*

for one reason or another, the studies did not have a population which had the necessary characteristics to make its results transferable to the general U.S. population.

The FDA also expressed concern over the differing amounts of folic acid used in the various studies. In general, the FDA seemed to regard the MRC study highly, calling it "carefully performed," and noting its significance.[63] However, despite this praise, the FDA was unwilling to find the necessary support from the study because it was conducted using supplements providing 4 mg of folic acid per day. This amount is higher than can be obtained from a diet high in folate-rich foods, and is higher than the amount legally allowed to be added to foods through supplementation.[64] The FDA classifies products which provide 4 mg of folic acid as drugs. Thus, the FDA considered the amounts used in the MRC study to be too high to authorize for consumption in the U.S., and therefore did not provide support for health claims regarding lower amounts of folic acid.

Although other studies used dosages of less than 4 mg of folic acid, the FDA discounted those studies because of the potential protective effects of other vitamins. The Smithells study used a lower amount of folic acid (0.36 mg), but, among other apparent problems, the FDA noted that the folic acid was part of a supplement which contained other nutrients, so the effect of the folic acid could not be isolated. The FDA found a similar problem with the Atlanta and Milunsky studies. In the Atlanta study the composition of the multivitamin could not be determined because women were interviewed between two and 16 years after having taken the multivitamin. In the Milunsky study the level of folic acid ingested by the participants varied from 0.1 mg to 1 mg. Additionally, the multivitamins used by the participants in that study also typically contained

[63] *Id.* at 60622.

[64] In 1991, the maximum amount of folic acid allowed to be added to food was governed by §172.345, which allowed folic acid to be added to food in an amount which would "not result in daily ingestion of the additive in excess of 0.4 mg."

vitamins A, C, D, or E, so the FDA questioned whether one or more of the other vitamins alone or together with folic acid may have provided the protective benefits. Thus, the FDA determined that "there is no scientific evidence that periconceptional supplementation of women of childbearing age with doses of folic acid lower than 4 mg per day will significantly reduce the risk of neural tube birth defects."[65]

Finally, the FDA was troubled by issues relating to the design of several of the studies. Regarding the Smithells study, for example, the FDA noted that "[n]o true control group was included," and that unsupplemented women were pregnant before entering the study, while supplemented women were recruited for the study prior to becoming pregnant.[66] The FDA also had problems with the fact that infants of fully-supplemented mothers were examined to determine whether the vitamins may have harmed the fetus, while only part of the results were published for this group, and no results were published for the unsupplemented mothers or partially-supplemented mothers, thus not allowing for comparison. Additionally, the FDA found bias weaknesses in several of the studies. Regarding the Atlanta study, the FDA noted the fact that participants had differing, and sometimes quite long recall periods. Also, it noted that there were differences between the case group and the control group in the areas of socioeconomic status and lifestyle characteristics. With the Mills study, the FDA noted a weakness resulting from the fact that the researchers were unable to identify and interview all cases. And, with the Milunsky study, the FDA noted issues related to nonresponsiveness of subjects. Thus, the FDA found the results of these studies to be somewhat problematic on structural grounds.

Based on the scientific evidence available as of 1991, the FDA thus concluded that it should not authorize health claims related to folic acid and the prevention of neural tube defects. The FDA concluded that, based

[65] Food Labeling, *supra* note 23, at 60622.
[66] *Id.* at 60620.

on the MRC study, women at high risk for neural tube defects need an amount of folic acid that is higher than can be obtained through natural sources and is at a level such that an adequate supplement would be considered a drug. While it found 4 mg may be advisable for high risk women after consultation with a physician, it found such an amount "inappropriate for a food."[67] Regarding amounts lower than 4 mg, the FDA determined there was "no scientific evidence that periconceptional supplementation... will significantly reduce the risk of neural tube defects."[68] Thus, the FDA was unwilling to find the requisite agreement of qualified scientific experts to allow manufacturers to use these health claims.

The CDC Recommendation

On September 11, 1992, the FDA's initial denial of health claims regarding the relationship between folic acid and neural tube defects was indirectly challenged by a completely contrary recommendation issued by the Public Health Service ("PHS") and the Centers for Disease Control ("CDC").[69] That day, the CDC published in its *Morbidity and Mortality Weekly Report* ("*MMWR*") a recommendation that "[a]ll women of childbearing age in the United States who are capable of becoming pregnant 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 defects]." Not only does this blanket recommendation of folic acid consumption for all women do exactly what the FDA was unwilling to do, it is based on the exact same scientific studies which, less than one year earlier, the FDA classified as inconclusive.

The CDC first issued recommendations regarding folic acid use in the prevention of neural tube defects approximately one year earlier, in the August 2, 1991, edition of the *MMWR*.[70] There, the CDC examined the results of the MRC study and, based on the study's conclusions, issued a recommendation that women who previously had a pregnancy affected by a neural tube defect should consume 4.0 mg of folic acid for

[67] *Id.* at 60622.
[68] *Id.*
[69] CDC, *supra* note 43.
[70] *Id.*

the period beginning at least one month prior to becoming pregnant through the first three months of the pregnancy. Because this dosage was very high, but was the lowest amount used in a conclusive study, the CDC made this an interim recommendation, pending the outcome of future studies. The 1992 PHS recommendation, however, was made based on the same available data.

In its 1992 recommendations, the PHS briefly summarized the evidence, reached a conclusion based on the evidence, then made cautionary notes. The evidence the PHS used in making its recommendation is the same set of randomized controlled trials, nonrandomized intervention trials, and observational studies discussed above and examined by the FDA. The only exception is the PHS notes the preliminary results of the Hungarian study which, although not formally published until several months later, had been reported in a 1989 letter to the editor of the *Journal of the American Medical Association*.[71] In reviewing the scientific studies, with an emphasis on the MRC study, the PHS "inferred that folic acid alone at levels of 0.4 mg per day will reduce the risk of NTDs." Furthermore, the PHS estimated that use of folic acid at that level would reduce the occurrence of neural tube defects by 50% in the United States.

The PHS recommendation applied to all women of childbearing age who are capable of becoming pregnant because 50% of American pregnancies are unplanned and the protective effects require ingestion of folic acid before conception and in the first month of pregnancy. Thus, the PHS noted that folic acid needed to be delivered to the general population at the recommended levels. In order to achieve this, the PHS proposed three mechanisms: (1) improvement of dietary habits, (2) fortification of the food supply, and (3) use of dietary supplements. For implementation of its recommendation through one of these three avenues, the PHS turned specifically to the FDA, stating that the FDA would need to decide which of the suggested methods would best meet the PHS goal while ensuring that the population did not receive excessive amounts of folic acid. Thus, the PHS seems to have placed the ball directly in the FDA's court by making a strong, concrete

[71] A.E. Czeizel & G. Fritz, Letter to editor, 262 JAMA 1634 (1989).

recommendation based on the available scientific data, then specifically calling on the FDA to implement that recommendation.

The PHS recommendation was not, however, an unqualified recommendation. The PHS made clear, as it first mentioned in its 1991 recommendation, that high levels of folic acid may have unknown effects and may complicate the diagnosis of vitamin B_{12} deficiency. While noting that folic acid is water soluble, and thus excess is excreted through the urine, the PHS expressed concern that high levels may make it difficult to discover vitamin B_{12} deficiency in some people, delaying diagnosis and treatment and resulting in irreversible neurological damage. Therefore, the PHS's recommendation capped folic acid intake at 1 mg per day, which is why it noted that the FDA would need to exercise caution so as to provide the population with at least 0.4 mg of folic acid daily, while keeping total ingestion under 1 mg per day. Although it set 1 mg of folic acid as the safe upper limit, the PHS stated that women who previously had a pregnancy affected by a neural tube defect could still follow the 1991 recommendation of 4 mg per day, but should consult with their doctors regarding such a dosage.

FDA responds again

After being placed squarely in the spotlight by the 1992 PHS recommendation, the FDA responded in the January 6, 1993, *Federal Register*, where it again denied authorization of health claims touting the benefits of folic acid in reducing the prevalence of neural tube defects.[72] This second denial came over a year after the original denial was proposed in November, 1991. That initial proposal was followed by a comment period, which ended on February 25, 1992. Five months later, however, when faced with new scientific evidence, the FDA reopened the comment period, thus delaying this final action. After the FDA reopened the comment period, the PHS published its recommendation for daily folate consumption by women of childbearing age,

[72]Food Labeling: Health Claims and Label Statements; Folic Acid and Neural Tube Defects, 58 Fed. Reg. 2606 (Jan. 6, 1993).

which clearly stated that the FDA would need to act in order for the recommendation to be fulfilled.

The FDA's final denial of health claims in January 1993, therefore, addressed the PHS recommendation. Specifically, the FDA noted five issues raised by PHS which are the responsibility of the FDA under the Federal Food, Drug, and Cosmetic Act: "(1) Identifying the population at risk, (2) considerations of appropriate level of intake with respect to options for implementation, (3) magnitude of benefit, (4) safety considerations, and (5) implementing the recommendation."[73] These five issues, albeit in slightly altered form, are the basis for the FDA's ultimate decision to deny the health claims again. Therefore, these issues will be examined below in order to understand why, even when faced with the same scientific evidence with which the PHS dealt, the FDA was still unwilling to allow folic acid health claims to be included on product labeling.

The first issue the FDA examined was the estimation of the range of likely intakes of folic acid if a claim was authorized. The FDA anticipated that if such a claim were to be authorized, food manufacturers would add folic acid to their products in order to make use of the health claim, resulting in a situation where large portions of the population might consume more than 3 mg per day. Also, the FDA considered it possible that some groups within the general population, including heavy users of supplements, might consume more than 7 mg per day. This was a concern because the effects of consuming large quantities of folic acid for long periods of time were unknown. Thus, the FDA was uncertain of the amounts likely to be consumed if a health claim were to be authorized.

A second issue the FDA raised was the potential for safety concerns if people were to consume large quantities

[73] *Id.*

of folic acid. The first category of health issues relates to vitamin B_{12}. As the FDA noted, pernicious anemia of vitamin B_{12} results in readily apparent hematologic disturbances and more hidden neurologic disturbances. However, certain levels of folic acid can improve the hematologic symptoms while apparently allowing the neurologic damage to continue. Thus, because the hematologic disturbances are more apparent, and thus are a symptom used to diagnose vitamin B_{12} deficiency, if they are masked by folic acid the neurologic damage may continue unchecked. Because the FDA was uncertain as to what levels of folic acid will allow the masking of symptoms of pernicious anemia while neurologic damage continues, it feared that levels of folic acid people were likely to ingest if a health claim were to be authorized might be high enough to cause this problem.

A second potential safety issue was that it was uncertain how pregnant women would respond to large doses of folic acid. Besides masking pernicious anemia, the FDA noted that high levels of folic acid may inhibit nutrient absorption or cause damage to the fetus's neural tube development. A third potential safety issue was the unknown effects of folic acid on persons taking antifolate drugs to treat such conditions as psoriasis, rheumatoid arthritis, bronchial asthma, malaria, hypertension, Crohn's disease, gout, epilepsy, and AIDS. As part of the treatment of these conditions, patients take drugs which interfere with folate metabolism, and the FDA was concerned that if such individuals were to ingest high levels of folic acid, the folic acid could interfere with the effectiveness of their medications or be potentially toxic. A fourth, but somewhat related health risk is that it is unknown whether high levels of folic acid might interfere with the effectiveness of anticonvulsant medications taken by epileptics. Thus, these four categories of potential health uncertainties were more reasons the FDA was unwilling to authorize health claims for folic acid. It is interesting to note, however, that despite the importance the FDA gives to the uncertainties regarding these health areas in this publication, it made very little mention of them in its proposed regulation denying the health claims, instead

focusing mostly on the fact that folic acid may not be effective at doses lower than 4 mg.

The FDA's third issue related to its denial of health claims is the difficulty in reaching the target population. The FDA notes that there are approximately 70 million women of reproductive age in the U.S., of whom 4 million become pregnant each year, and 2,500 will have a pregnancy affected by a neural tube defect. Therefore, the FDA was uncertain how best to determine its target population, and then reach that entire target population (while not excluding portions of it, such as economically disadvantaged members of the group) while not harming the entire American population of 250 million. Complicating this decision, according to the FDA, is the fact that the magnitude of the preventive effects of different levels of folic acid is unknown. This leads to the FDA's fourth issue regarding health claims: that an effective minimum level of folic acid is simply unknown. This concern stemmed from the fact that the effects of folic acid in the diet were unknown in most of the scientific studies, so dietary folate may have played some role in producing the results. Therefore, it was difficult for the FDA to determine what the minimum effective amount of folic acid would be. This is problematic because in order to ensure all women are protected before and during early pregnancy, all women (and therefore, the entire population) would need to consume adequate levels of folic acid during their entire childbearing period (which can be 30 years). This would result in the *entire population* ingesting folic acid, and the FDA wanted to minimize lifetime exposure to prevent other potential problems. Thus without a minimum effective dose, the FDA seemed unwilling to allow widespread consumption of folic acid at higher than necessary levels. A related concern was the FDA's final issue, and that is that the PHS presented three potential options (improved diets, fortification of food, and dietary supplements) for ensuring the target population receives adequate folic acid, so the FDA needed to determine which of the methods best serves its goals.

As evidenced by these issues, the FDA seemed reluctant to authorize health claims relating to folic acid's preventative effect regarding neural tube defects largely because of potential unknown risks related to ingestion of levels of folic acid at levels higher than presently consumed. This concern is certainly valid, as any step taken by the FDA which would increase the amount of folic acid consumed by the general population would be severely criticized and could be devastating if high doses of folic acid turn out to be harmful in some way. If the health concerns were as serious as the FDA described them as being, however, it is suspicious that they were only used as a justification for inaction after the FDA's original justification (that there was not sufficient expert agreement as to the preventative effects of folic acid at levels below 4 mg) was tarnished by the PHS's opposite finding.

FDA reverses its course

In the October 14, 1993, *Federal Register*, only nine months after again declining to authorize health claims regarding the benefits of folic acid in reducing neural tube defects, the FDA completely reversed course and offered what might be considered a three part folic acid package of proposed regulations.[74] The FDA first proposed a series of regulations authorizing the folic acid-neural tube defect health claims and proposing regulations which would govern the use of such claims. Second, the FDA proposed regulations to alter the standards of identity for certain enriched foods so as to require the addition of folic acid to those products. Finally, the FDA also proposed amendments to the food additive regulations so as to place limitations on the amount of folic acid which could be added to foods. This section will describe the new regulations and summarize the FDA's reasoning for proposing them in the given form. It will also attempt to illuminate the reasoning behind the FDA's sudden reversal from the position articulated nine months earlier, which was that the potential uncertain health risks were too great for folic acid to be used on a wide-spread basis. A later section detailing the final regulations will continue the discussion of the substance of the regulations,

[74]Food Labeling: Health claims and Label Statements; Folate and Neural Tube Defects, 58 Fed. Reg. 53254 (Oct. 14, 1993).

highlighting those areas in which the final regulations differ from the proposed regulations.

In order to understand the health claims authorized by the FDA in 1993, it is first necessary to understand what took place during the previous nine months that caused the FDA to reverse the final regulations which did not allow for such health claims to be made. The first item to note is that the timing of the January, 1993, final rules declining to authorize the health claims was impacted by two factors. First, it was delayed by the continuous release of new data. As was previously discussed, the comment period for the proposed version of the rules was reopened in July, 1992, after it had been closed for five months, in order for the FDA to take into consideration new data which was being released. This likely delayed the release of the final rules to at least the extent of the reopened comment period.

Despite the delay, the final regulations were also impacted by the language of the NLEA. That act required the FDA to issue proposed regulations on the ten nutrient-disease relationships (of which folic acid-neural tube defects was one) within one year, which the FDA did when it denied the use of folic acid health claims. It also required the FDA to issue final regulations within two years. The end of the two year period was drawing near when the FDA reopened the comment period in July, 1993, which likely placed the FDA in a bind. If it did not act, the proposed regulations would have become final, pursuant to the NLEA's hammer provision. So, while the FDA may have been nearly ready to authorize these health claims, the fast approaching deadline may have offered inadequate time to properly draft and propose new authorizing regulations. This timing issue, combined with the fact that 1992 saw the release of both the results of the Hungarian study and the PHS folic acid intake recommendation, probably contributed to the situation where the FDA issued one set of final regulations in January, only to completely reverse itself with new proposed regulations in October of the same year.

While the timing requirements of the NLEA and the timing of the Hungarian study results and the PHS recommendation may explain the FDA's seemingly contradictory actions during 1993, the fact that the two sets of regulations are contradictory seems on its surface to be somewhat troubling. This is troubling because in January, 1993, the FDA refused to permit folic acid health claims on products because it thought the risks of increased folic acid intake might be harmful to certain groups within the U.S. population. Why, then was the FDA willing to reverse course nine months later? The answer seems to be the general progression of available information and, perhaps, external pressure placed on the agency. As was previously discussed, the FDA first refused to allow folic acid health claims because it declared that there was no consensus among the scientific community as to the benefits of folic acid at levels permissible under then-current regulations.[75] Then, when the PHS reached the opposite conclusion based on the same scientific evidence, the FDA based the final rules declining authorization of health claims on the premise that the potential risks of increased folic acid intake were unclear.[76] Finally, in the proposed regulations authorizing folic acid health claims, the FDA downplayed the problem of unknown risks by establishing a "safe upper limit of intake of 1 mg of folate/day for all population groups."[77] By setting this upper limit, the FDA argued that it had "tentatively concluded that [the] safety problems can be resolved."[78] By finding an upper limit to be helpful in mitigating the potential safety issues, the FDA thus issued, with the proposed regulations currently at issue, proposed food additive regulations relating to folic acid, which will be discussed in the following section.

Perhaps sensing that observers may be uneasy with the FDA's complete reversal of course on an issue where it previously found there to be potential health risks, the agency described each of the potential health risks it noted in its January, 1993, release and explained why they were no longer a problem when coupled with additional regulations which ensure the general population will ingest no more than 1 mg of folic acid per

[75] Food Labeling, *supra* note 56.
[76] Food Labeling, *supra* note 70.
[77] Food Labeling, *supra* note 72, at 53266.
[78] *Id.*

day. The FDA first addressed what seemed to be its most serious concern regarding folic acid's risks – the potential for folic acid to mask a vitamin B_{12} deficiency's symptoms, complicating diagnosis while neurologic damage continues. In the new proposed rules, the FDA clarified its previous concern, noting that many of the studies showing the potential masking effect used doses of folic acid of 5 mg per day and higher. The evidence of the masking effect at levels of folic acid under 1 mg per day is much less convincing. Thus, the FDA seemed more comfortable, although still not certain, that by keeping daily folic acid intakes below 1 mg per day the potential for masking of vitamin B_{12} deficiency should be limited.

The second concern the FDA previously raised was the unknown effects of high levels of folic acid on pregnant women and unborn fetuses. In the new proposed rules, the FDA still seemed concerned about this issue, as the uncertainty remained. However, the FDA seemed to think the 1 mg per day cap on folic acid intake was low enough to be safe. The third category of concern in the January, 1993, final rules centered around potential harms from high folic acid intake by people with epilepsy. While the FDA previously expressed concern that folic acid may reduce the effectiveness of anticonvulsant medications and exacerbate seizures, it noted here that such studies used very high does of folic acid (5 mg to 75 mg per day). It also noted that in a study using 3 to 5 mg of folic acid per day, there appeared to be no harmful effect of folic acid in epileptics. Thus, it again cited the 1 mg per day upper limit as the reason this concern is no longer prohibitive of health claims.

The fourth health concern the FDA previously cited was that high levels of folic acid may be damaging to people taking anti-folate medications for a wide variety of diseases. On this issue, the FDA noted several studies which suggested that 1 mg per day of folic acid does not interfere with anti-folate medications, but the FDA did request additional information on this area, as it seemed to remain unsatisfied by the data available at that time. Thus, the FDA's willingness to allow folic acid health claims, despite having serious

safety concerns only nine months earlier, seems to be a product of two issues. First, the FDA's fears may not have been as extreme as the earlier rules portrayed, as a more revealing description of the data showed that often the safety concerns arise only with very high levels of folic acid. Second, the FDA seems to have satisfied itself that if the general population consumes less than 1 mg per day, it will not be ingesting enough folic acid for the potential harms to be realized. Therefore, while certainly not erasing the safety issues, the FDA seems to have at least convinced itself (either from outside pressure or from more review of the data) that these issues can be avoided with appropriate restrictions in place.

The Requirements

The FDA's proposed rules authorizing the use of health claims regarding folic acid and neural tube defects were titled "Health claims: folate and neural tube defects."[79] The first noteworthy point about the proposed rule is the use of "folate" rather than "folic acid." The FDA decided that folate was the more appropriate word to use in the regulation, since it wanted to include both the natural food forms and the vitamin forms under this rule.[80] Because of this purposeful change in terminology used in the regulation, the term folate will also be used here, when appropriate.

The requirements of the rules are classified into two categories: the more basic general requirements[81] and the more detailed specific requirements.[82] The general requirements are mostly an inclusion by reference of the general health claim requirements applicable to all health claims, as the rule requires that "[t]he health claim for a food or supplement meets all of the general requirements of §101.14 for health claims, except that a food or dietary supplement may qualify to bear the health claim if it meets the definition of the term 'good source."' The requirements of §101.14 are indeed general and will only be discussed here to the extent

[79] 21 C.F.R. § 101.79.
[80] Food Labeling, *supra* note 72, at 53280.
[81] 21 C.F.R. § 101.79(c)(1).
[82] 21 C.F.R. § 101.79(c)(2).

necessary. The more interesting part of the general requirement is that foods may carry a folic acid health claim if they meet the definition of "good source." The standard requirement for health claims, specified in §101.14(d)(2)(vii), is that foods must be "high" in the particular substance at issue. The term "high" in this case is defined, along with the terms "rich in" and "excellent source of," to be permissibly used on food labels containing at least 20% of the RDI of a particular substance.[83] "Good source," on the other hand, is part of the less stringent terms, including "contains" and "provides," which are permissible if the product contains 10% to 19% of the RDI of a particular substance.[84] The FDA proposed to allow health claims regarding folate when a food contains as little as 10% of the RDI of folate because "folate is ubiquitously distributed among many foods in the U.S. food supply."[85] The FDA noted that although many vegetables, including okra, broccoli, spinach, turnip greens, Brussels sprouts, and others, do contain enough folate per serving (more than 20% of the RDI) to qualify for "high" status, the "great majority of foods contain folate at lower levels."[86] For example, the FDA notes that oranges, grapefruit, many berries, cabbage, lettuce, corn, cauliflower, peas, many vegetable juices, beets, and parsnips contain enough folate per serving (10% to 19% of the RDI) to qualify as a "good source" but not enough to qualify as "high." Because so many foods contain small, but not inconsequential, levels of folate, and eating a diet in accordance with the current dietary guidelines would provide enough of those foods to provide, in total, the RDI of folate, the FDA proposed allowing folate health claims on products with lower levels of folate.

Beyond the above general requirements, the FDA's proposed rules under §101.79 also contain several specific requirements, which form the crux of the guidelines for the proposed health claims. First, and most importantly, the proposed rules allow the use of "[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

[83] 21 C.F.R. § 101.54(b).
[84] 21 C.F.R. § 101.54(c).
[85] Food Labeling, *supra* note 72, at 53281.
[86] *Id.*

their risk of having a pregnancy affected by spina bifida or other neural tube defects." In making such a claim, the FDA requires manufacturers to specify several items, including the nutrient at issue. The FDA allows manufactures to use the following terms in describing the nutrient: "folate," "folic acid," "folacin," "folate, a B vitamin," "folic acid, a B vitamin," or "folacin, a B vitamin" in meeting this requirement. Both "folate" and "folacin" were allowable terms and synonyms under the current regulatory structure, and "folic acid" was added here because of its use in the PHS recommendation.

The FDA also requires manufacturers making the health claim to specify the health condition, allowing them to use any of the following descriptions: "neural tube defects," "birth defects, spina bifida, or anencephaly," "birth defects of the brain or spinal cord, anencephaly or spina bifida," or "spina bifida or anencephaly, birth defects of the brain or spinal cord" in so doing. The FDA chose these specific variants because they allow manufacturers to provide terms with which the public may be familiar (since neural tube defects may not be a phrase known to many people), but also are specific enough so as not to lead women to believe that folate may prevent all birth defects. Exactly which phrases the FDA meant to propose is somewhat unclear, as in the explanatory test accompanying the proposed rules, the FDA states that the proposed rule contains "the birth defect spina bifida," although the text of §101.79(c)(2)(i)(C) does not include this language. Also, the explanatory text includes the phrase "the birth defects spina bifida and anencephaly," while the text of the rule instead states "birth defects, spina bifida, or anencephaly." These oversights, although troublesome in that they occur in such a specific, text-based section of the rule, appear corrected in the final rule, discussed below.

The proposed rules also place several other specific requirements on potential health claims. First, the FDA

proposed to require the health claims state that neural tube defects have many potential causes, while also not implying that folate intake is the only factor in determining risk.[87] Also, the rules require that health claims state that neural tube defects are not widespread but are very serious, so as not to mislead women into thinking they are common.[88] Furthermore, health claims may not make reference to "any specific degree of reduction in risk of neural tube defects" which may be attributed to folate.[89] Health claims may not, therefore, make reference to the PHS estimate that folate intake could reduce by 50% the prevalence of neural tube defects.

Dietary supplements and fortified foods must also carry an additional statement if they contain more than 25% of the RDI of folate. If they include a health claim related to folate, they must also state that 1 mg per day is the safe upper limit of folate intake.[90] The FDA proposed to require this extra warning in these cases so people can monitor their intake of these foods. The FDA did not believe that monitoring was necessary in foods with less folate. Under the proposed rules, however, no foods are permitted to state that a certain amount of folate is more effective in preventing neural tube defects than a lower amount.[91] This, the FDA stated, is consistent with the research showing that general dietary improvement yields a reduction of risk. Finally, all foods with folate health claims must also identify diets adequate in folate through the use of such phrases as "Adequate amounts of folate, a B vitamin, can be obtained from diets rich in fruits, including citrus fruits and juices, vegetables, including dark green leafy vegetables and legumes, enriched grain products, including breads, rice, and pasta, fortified cereals, or a dietary supplement."[92] These long, wordy statements are designed to ensure women learn ways to improve their overall diet so as to include

[87] 21 C.F.R. § 101.79(c)(2)(i)(D).
[88] 21 C.F.R. § 101.79(c)(2)(i)(E).
[89] 21 C.F.R. § 101.79(c)(2)(i)(F).
[90] 21 C.F.R. § 101.79(c)(2)(i)(G).
[91] 21 C.F.R. § 101.79(c)(2)(i)(H).
[92] 21 C.F.R. § 101.79(c)(2)(ii)(B).

adequate folate.

The FDA also included in the proposed rules several rules of a more technical variety. First, the health claims may only be used on dietary supplements which meet the United States Pharmacopoeia standards for disintegration and dissolution. This will ensure the folate contained in a dietary supplement will be absorbed into the body.[93] Second, no foods containing more than 100% of the RDI for vitamin A as retinol or preformed vitamin A or vitamin D may bear a folic acid health claim.[94] The reasoning behind this rule is the fear that women may attempt to increase their folic acid intake by consuming more products containing folate, and if those products contain high levels of certain forms of vitamin A or D, they could ingest excessive levels of those vitamins. Excessive vitamin A has been associated with birth defects, and excessive vitamin D is potentially toxic, so the FDA included this rule in an attempt to ensure women do not receive excessive amounts of those vitamins. Third, any product bearing a folic acid health claim must include the amount of folate per serving in the nutrition label.[95] And, finally, products may not bear a folate health claim if they contain certain high levels of fat, saturated fat, cholesterol, or sodium.[96] However, in addition to these technical requirements, the FDA does provide for certain optional information to be included in the claim, such as the relationship between folate and neural tube defects, a recommendation that women with a history of neural tube defects should consult their doctor, and a statement showing the recommended daily value of folate is 400μg[97] (0.4 mg).[98]

These many restrictions and requirements seem extremely cumbersome, to the point that a health claim

[93] 21 C.F.R. § 101.79(c)(2)(ii)(C).
[94] 21 C.F.R. § 101.79(c)(2)(iii).
[95] 21 C.F.R. § 101.79(c)(2)(iv).
[96] 21 C.F.R. § 101.14(a)(4).
[97] Throughout the paper, I use the units of measure specified by the specific cited authority. For conversion purposes, 1 mg is equal to 1,000 μg.
[98] 21 C.F.R. § 101.79(c)(3)(i), (ii), (iii).

must be very long in order to meet the requirements. The FDA provided several examples of model health claims, and they illustrate this problem. The following is one of those, and is the shortest of the examples provided by the FDA:

> Women who consume adequate amounts of folate, a B vitamin, daily throughout their childbearing years may reduce their risk of having a child with a neural tube defect. Such birth defects, while not widespread, are very serious. They can have many causes. Adequate amounts of folate can be obtained from diets rich in fruits, dark green leafy vegetables and legumes, enriched grain products, fortified cereals, or a supplement. Folate consumption should be limited to 100μg per day from all sources.[99]

This example shows how long a health claim likely needs to be in order to satisfy the requirements of §101.14 and §101.79. Whether this is prohibitively long will be discussed later.

Fortification

By proposing to authorize folate health claims, the FDA created the possibility that food manufacturers might add folic acid to their products in order to place the health claim on the products. This could have resulted in the U.S. population ingesting high, and perhaps dangerous, levels of folate. However, if the FDA restricted the addition of folate to foods, women of childbearing age might not receive enough, thus limiting the protective benefits. Therefore, at the same time as it proposed rules related to the folate health claims, the FDA also proposed a fortification policy to add folate to certain foods and proposed changes in the food additive rules to restrict the foods to which folate could be added. A discussion of the fortification program follows, with a discussion of the amendments to the food additive regulations commencing following that discussion.

Since neural tube defects occur very early in pregnancy, before many women know they are pregnant, the FDA decided that fortification of the food supply would increase the likelihood that women of childbearing age would receive adequate folate. However, the goal of ensuring that women of childbearing age receive adequate folate must be balanced with a goal of preventing excess folate intake in any segment of the popula-

tion. In order to achieve both of these goals, the FDA had to consider many issues, including which products to fortify, what levels of fortification to require, what safe upper limit of folate intake to adopt, what level of bioavailability of folate and folic acid in foods to require, and what estimates of likely daily folate ingestion would be accurate. Only after consideration these issues was the FDA able to propose a plan for folic acid fortification.

The first issue the FDA needed to consider was which foods to fortify with folic acid. The fortification of the U.S. food supply began in the 1940s, when the FDA created a standard of identity for several enriched cereal-grain products.[100] To qualify to bear the label "enriched," the products had to contain certain levels of thiamin, riboflavin, niacin, and iron. The FDA deemed the addition of these nutrients necessary in order to both replace nutrients lost during milling and to ensure adequate dietary intake. Cereal-grain products were selected for fortification because they met certain criteria for carriers of nutritional fortification and were consumed by a "significant portion of the population in an amount adequate to meaningfully increase intakes of [the] nutrient."[101] In determining foods to consider for folate fortification, the FDA again looked for foods which were a staple consumed by a significant portion of the target population. The FDA considered cereal-grain products, fruit juices, dairy products, and breakfast cereals as candidates for fortification. Specifically within the cereal-grain category, the FDA considered foods with established standards of identity, including the following "enriched" products: bread, rolls, and buns; wheat, corn, and rice flours; corn grits; corn meals; farinas; rice; macaroni products; and noodle products. Among the non-cereal-grain products with standards of identity which the FDA considered were milk, yogurt, fruit juices, and canned fruit nectars. None of the standards of identity for these foods allowed, at that time, the addition of folate.

Once the FDA had its selection of potential fortification candidates, it then needed to determine the appropriate level of fortification before choosing one of the candidates. This was a complicated procedure,

[100] Food Labeling, *supra* note 72, at 53271.
[101] *Id.*

requiring the FDA to consider how much folate in foods would be absorbed into the body (bioavailability), how much folate people were likely to ingest, and how much folate could be ingested safely over the long term. As has previously been mentioned, the FDA determined that 1 mg should be considered the safe upper limit of daily folate intake so as to minimize the potential for unknown complications to arise related to high folate intake. However, determining the 1 mg limit also required the FDA to examine whether the 1 mg should include all folate or just added folic acid (from fortification or dietary supplements), and whether the 1 mg limit was too low to allow women of childbearing age to consume enough folate to receive the protective benefits. The FDA concluded that the 1 mg limit was high enough that, given the proper fortification program, most target women would regularly consume the RDA of folate through their diets. The FDA determined that the limit would be for all folates, not just added folic acid. The FDA also determined that in using the 1 mg upper limit, it would not consider the bioavailability of various forms of folate, even though it had been presented with evidence that folic acid added to foods and supplements is more easily absorbed by the body than natural folates found in foods. The FDA had also been given evidence that folate is absorbed differently when consumed with certain foods and beverages. However, due to the complicated nature of these issues, the FDA decided not to include these issues in its determination of levels of folate consumed as part of the 1 mg per day maximum.

In determining the amount of folate to include in fortified foods and dietary supplements, the FDA used the Department of Agriculture's Nationwide Food Consumption Survey ("NFCS") on individual intake during 1987-1988.[102] The NFCS was a survey in which respondents provided data on their diets over a three day period. From that, the researchers estimated the daily food and nutrient intake of the U.S. population and its various subgroups. The FDA used this data to determine the level of folate intake per day for various groups in the population. It then used various scenarios of fortification (for example, the FDA considered a scenario

[102]United States Department of Agriculture, *Nationwide Food Consumption Survey/Individual Intake 1987-1988*, accession number PB90-504044, National Technical Information Service, Springfield, VA, 1990.

in which grain products contained 70 μg of folic acid per 100 g, or one in which certain juices contained 140 μg of folic acid per 100g) and recalculated folate intakes using the hypothetical levels of fortification. The FDA noted, however, that using this method could present two different errors: it could underestimate the amount of food typically eaten, and it could underestimate the folate content of the foods eaten.

According to the FDA, the amounts of food typically reported by volunteers in the NFCS survey only provided 70% of the amount of calories necessary for these people to maintain their present weight, indicating that people underreported the food they ate. Therefore, the FDA took into account this potential 30% underreporting by using the 95th percentile of calorie intake to estimate folate intake for "high" consumers and used the 25th percentile to estimate the folate intake for "low" consumers. The second potential for error is that methods for determining folate levels in foods often produce inaccurate results, and manufacturers who report nutrient levels on nutrition labels often add extra of the nutrient in order to ensure the product contains at least the amount on the label. These issues complicate the determination of actual folate intake, probably producing an actual folate intake higher than the estimated intake. Despite these issues, the FDA decided only to use the upward adjustment in calorie intake described above to correct for these potential problems.

After considering the potential for error, the FDA tested folate intakes in 12 different fortification scenarios. It determined that fortification of cereal-grain products, fruit juices, and dairy products was not a viable alternative, as it resulted in high consumers in most population groups consuming over 1,000 μg per day without supplements. In fact, children 1 to 10 years old who were high consumers were estimated to ingest over 4,000 μg per day. Therefore, the FDA concluded that fortification of dairy and juice products should not

be permitted. In focusing on fortifying cereal-grain products, the FDA considered three levels of fortification: 70, 140, and 350 μg of folic acid per 100 g. Running the estimates with these numbers showed that while 350 μg pushed some high users beyond the 1 mg per day maximum, the lower two amounts kept all high user groups below the maximum.

The FDA also calculated the likely folate intake for consumers following the USDA Food Guide Pyramid, determining that whether low or high consumers reached the RDA or exceeded the 1 mg maximum depended on whether they included as part of their diet a breakfast cereal fortified with either 25% or 100% of the RDA of folate. When the diet included a breakfast cereal with 100% of the RDA, some consumers, especially high consumers age 51 and up and males age 19 to 50, would exceed the 1 mg per day maximum with a fortification of cereal-grain products at the 140 and 350 μg per day level. However, 70 μg per day fortification would not provide enough folate for many women of childbearing age. Therefore, the FDA proposed to require fortification of enriched foods at 140 μg per 100 g and to limit breakfast cereals to 100 μg per serving, while allowing dietary supplements to contain up to 400 μg per serving. At this level, no consumer groups would be likely to exceed the daily maximum, and even women in the low categories could ingest at least 230 μg per day. Although this is not the RDA, the FDA noted that there is evidence that even that level could reduce the risk of a neural tube defect. Thus, the FDA settled on this scheme for fortification, even though all of the target population would not likely receive the RDA, because a higher level might put some groups in danger.

Food Additives

By proposing a fortification program to ensure women of childbearing age receive adequate folate from food sources at the same time as it proposed authorization of health claims regarding folic acid and neural tube

defects, the FDA created a situation in which the U.S. population might receive very high quantities of folic acid. Since the fortification program was designed to provide adequate folate from cereal-grain products and breakfast cereals, if manufacturers began adding folic acid to their products in order to utilize the new health claims, there was a possibility that a large percentage of foods might contain folic acid. Therefore, as the final piece to its three part plan, the FDA simultaneously proposed amendments to the food additive regulations which would prevent folic acid from being added to foods other than breakfast cereals and those foods with standards of identity requiring the addition of folic acid.[103] Additionally, the amendments were to limit the amount of folic acid added to breakfast cereals.

Until 1993, when the folic acid plan was proposed, folic acid had been treated in the regulations under a plan dating back to 1973.[104] The regulation allowed folic acid to be added to foods so long as the maximum intake of the food (or dietary supplement) typically consumed during a one day period would not provide consumers with more than 0.4 mg of folic acid per day.[105] Additionally, that number was 0.1 mg for infant foods, 0.3 mg for foods for children under 4, and 0.8 mg for pregnant or lactating women. Under that rule, however, manufacturers would be free to add 0.4 mg of folic acid to each serving of their products, potentially resulting in a situation where many foods each contained the RDA for folic acid. This would far surpass the FDA's 1.0 mg per day target maximum.

Therefore, the FDA proposed a new food additive amendment for folic acid containing several basic provisions.[106] First, the new regulation would allow dietary supplements to continue to contain 0.4 mg of folic acid, as the FDA considered that amount to be safe. Second, the new regulation would allow foods with new standards of identity requiring folic acid fortification to be fortified with the proper amount of folic acid.

[103]Food Additives Permitted for Direct Addition to Food for Human Consumption; Folic Acid (Folacin), 58 Fed. Reg. 53312 (Oct. 14, 1993).
[104]38 FR 20725.
[105]Previous §172.345. See also 58 FR 53312 at 53313.
[106]Proposed §172.345. See also 58 FR 53312 at 53317.

Third, infant formulas would continue to be permitted to contain added folic acid in a manner consistent with the Federal Food, Drug, and Cosmetic Act. Foods used under medical supervision would also be exempted from the new regulations. Finally, folic acid would be permitted to be added to breakfast cereals at a rate of no more than 0.1 mg per serving. Thus, breakfast cereals were really the only food without a standard of identity to which folic acid could be added. The 0.1 mg per serving maximum was somewhat controversial in that it would require the reformulation of several cereals which contained the full RDA of folic acid at the time the regulation was proposed. However, breakfast cereals containing more than 0.1 mg of folic acid were not singled out, as any food which did not fall into one of the above categories and contained added folic acid would need to be reformulated under the proposed regulation. This was necessary, according to the FDA, to ensure that the amount of folate consumed by the population was adequately controlled.

Thus, three years after the passage of the NLEA, and one year after the PHS made its folic acid recommendation, the FDA had proposed regulations which completely overhauled its treatment of folic acid. Instead of allowing manufacturers of non-standardized foods to include a full day's worth of folic acid in their products, the FDA created a comprehensive system to deliver adequate folate to women of childbearing age while not delivering excessive folate to any segment of the population. Through fortification of standardized foods and breakfast cereals, authorization of health claims regarding folic acid and neural tube defects, and the prevention of folic acid addition to other foods, the FDA hoped to provide for an adequate, but controlled, supply of folate to passively reach thousands of people. As will be seen, however, even though the FDA proposed this program in October, 1993, and provided for a short two-month comment period, it would be years before rules were finalized and implemented.

The Final Rules

Despite the fact that the FDA proposed the folate package of regulations in late 1993, it was not until March

of 1996 that it issued the final regulations.[107] During the nearly two and a half year period between the issuance of the proposed and final regulations, the FDA received nearly 100 comments regarding its proposals. The comments came from a wide variety of sources, including government agencies, a foreign government, state governments, consumer advocacy groups, and manufacturers of foods and dietary supplements, among others. Thus, this section presents an overview of the most important comments, including those which prompted the FDA to alter the proposed regulations, in an attempt to highlight the differences between the proposed and final rules. It should be noted, however, that these final rules apply to both conventional foods and to dietary supplements. Dietary supplements did receive certain differing treatment prior to the enactment of these regulations, but that will be addressed in a later section.

Although the FDA received comments favoring and criticizing nearly every aspect of the proposed health claims regulations, it decided not to alter most of the provisions. However, the FDA did alter certain aspects of the regulations in response to the comments it received, and the vast majority of the alterations were designed to simplify the required parts of the authorized health claims in some way. For example, one change the FDA made throughout the regulations was to require that all references to an amount of folate be expressed in a percentage of the RDI, with an option for the microgram equivalent to be used in parentheses. This was designed to limit confusion that may result from using different measures to express the relevant amounts of folate. Similarly, the FDA also decided to permit, as part of the required identification of the health-related condition, manufacturers to use "birth defects of the brain or spinal cord" or "brain or spinal cord birth defects" to eliminate confusion in women who are not familiar with the more technical terms like neural tube defects, spina bifida, or anencephaly.[108]

Many other of the FDA's alterations were the product of a desire to allow the claims to be as simple

[107] Food Labeling, *supra* note 4 at 8752.
[108] 21 C.F.R. § 101.79(c)(2)(i)(C).

and succinct as possible. The FDA noted that the use of health claims was not as widespread as it had anticipated, and it attributed that at least partly to the fact that the required health claims may be too long. Therefore, it made several changes designed to decrease the required elements for health claims. As part of this effort, the FDA removed the requirement that health claims needed to contain examples of foods which could be included in a diet to increase folate intake. Instead, the claims need only state that folate should be consumed as part of a healthy diet.[109] Also, the FDA altered the requirement that dietary supplements or foods containing more than 25% of the RDI of folate carry a cautionary statement regarding excessive folate intake. Instead, the FDA decided to require the statement only on foods and supplements containing more than 100% of the RDI of folate.[110] The FDA and some commentators worried, in addition to the length problem, that such a low threshold might result in too many caution statements, possibly resulting in an effort by women to avoid foods with folate. The FDA also eliminated the requirement that health claims state that neural tube defects have many causes, as it decided that the requirement that health claims not imply that folate is the only risk factor in neural tube defects should achieve the necessary educational purpose. Finally, the FDA also eliminated the required statement that the prevalence of neural tube defects is low.

Thus, when the health claims authorization went into effect on April 19, 1996, the FDA had streamlined the initial requirements to make the health claims both potentially easier for consumers to understand and easier for manufacturers to implement. As was noted in the previous section, under the proposed rules, even the shortest example of a health claim including all of the required statements was prohibitively long. Under the final rules, a health claim could be as short as "Adequate folate in healthful diets may reduce a woman's risk of having a child with a brain or spinal cord birth defect."[111] This claim, being much shorter than was previously required, was thought to be more appealing to both consumer and manufacturers, thus increasing

[109] 21 C.F.R. § 101.79(c)(2)(i)(H).
[110] 21 C.F.R. § 101.79(c)(2)(i)(F).
[111] 21 C.F.R. § 101.79(d)(1)(ii).

the likelihood that women of childbearing age would be able to more easily identify foods high in folate.

In the same issue of the *Federal Register*, the FDA also issued its final rules regarding the folate fortification program.[112] Like the final health claims rules, the final fortification rules were accompanied by a discussion of the 170 letters the FDA received regarding the proposed rules. However, the final fortification rules only differ in one way from the proposed rules: the final rules were to become effective two years after issuance, as opposed to one year under the proposed rules. The FDA made this change to allow manufacturers adequate time to exhaust their inventory of packaging before making the necessary folate-related changes to the post-fortification packaging. Also, the two year delay would give manufacturers time to properly reformulate their products to include folate. However, it is worth noting that this delay pushed the effective date for the fortification program back to January 1, 1998, which is over seven years after the agency was first required to act on the folate-neural tube defects situation by the NLEA.

The other noteworthy aspect of the text accompanying the final fortification rules is the FDA's analysis of the economic costs of the program relative to the vitamin B_{12}/pernicious anemia situation, which was the FDA's main reason for not implementing the folate program in the first place. Using data released after the proposed regulations had been issued in 1993, the FDA determined that each case of neurologic disability resulting from low levels of folate masking pernicious anemia would result in a utility loss of, on average, $537,948. Including medical bills, the average cost per case was estimated at $570,000. The FDA calculated the annual benefits to society of folate fortification at between $220 and $700 million. This results in a break-even number of neurologic disability cases of between 386 and 1,228 annually, which are the number of neurologic disability cases resulting from the folic acid changes that can occur before the new policy becomes more expensive and harmful than the previous one. This seems to compare favorably to the potential for 500 cases of folate-caused neurologic disabilities estimated to occur based on the one study the FDA cited. This

[112]Food Standards: Amendment of Standards of Identity for Enriched Grain Products to Require Addition of Folic Acid, 61 Fed. Reg. 8781 (March 5, 1996).

is interesting in that while it shows the potential for a net gain by society from the folate fortification, the gain is by no means guaranteed since the societal losses, in the form of neurologic disabilities, may outweigh the societal benefits from the prevention of a percentage of neural tube defects.

The amendments to the food additive regulations are the third piece of the folate package and were also published in final form in March of 1996.[113] Like the fortification rules, the food additive amendments differed little from those proposed over two and a half years earlier. Although it seems that many of the 59 letters the FDA received on the topic argued for a safe upper limit of either more or less than the proposed 400 μg per day, the FDA determined that adequate evidence for changing that limit did not exist, so the limit remained unchanged. The FDA did, however, make two changes of note to the proposals. The first change allowed manufacturers to add folate to meal-replacement products.[114] The rationale for this was that meal-replacement products are typically intended to serve as an entire meal, and since they are consumed in place of other foods, they should be allowed to contain folate. Thus, the FDA added a rule allowing meal-replacements which are consumed once per day to contain 400 μg of folate, while those intended to be consumed more than once per day may contain 200 μg. The FDA noted that the safe upper limit of folate was not a serious worry with meal-replacements because their volume and caloric nature make their use self-limiting.

This self-limiting quality also played a part in the FDA's other change to the proposals: allowing breakfast cereals to contain 400 μg folate, rather than being restricted to 100 μg. The FDA's original goal in proposing the limitation was to avoid excessive folate intakes in groups consuming multiple bowls of breakfast cereal per day. However, the comments received persuaded the FDA that breakfast cereals, like meal replacements, are self-limiting. This therefore seemed inconsistent with the plan's allowance of dietary supplements, which are not self-limiting, to contain 400 μg. Additionally, the FDA noted that only three to six percent of breakfast

[113]Food Additives Permitted for Direct Addition to Food for Human Consumption; Folic Acid (Folacin), 61 Fed. Reg. 8797 (March 5, 1996).
[114]21 C.F.R. § 172.345(h).

cereals actually contained 400 μg of folate, and the remainder will not have an incentive to add folate above 100 μg because 100 μg allows them to qualify for use of folate health claims. Thus, these assumptions persuaded the FDA to remove the lower limitation on folic acid addition to breakfast cereals and allow them to contain the full RDI per serving.[115]

Dietary Supplements

Once the final regulations went into effect, that may have seemed like the end of the FDA's nearly decade-long struggle to develop a policy regarding folate. The struggle was not over, however, in the area of dietary supplements. Although the discussion to this point has treated the folate situation for food and dietary supplements as being the same, there were actually some slight differences in the treatment of foods and dietary supplements which led to several years of litigation following the enactment of the final regulations. In the NLEA, Congress directed the FDA to authorize health claims for foods only when the FDA determines, "based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence."[116] Thus, Congress gave the FDA the standard with which it was to evaluate health claims regarding foods. But with dietary supplements, though, Congress was more lenient, stating only that such health claims made regarding dietary supplements were to "be subject to a procedure and standard, respecting the validity of such a claim, established by regulation of the Secretary."[117] So for health claims regarding dietary supplements, Congress delegated determination of a standard of review to the FDA. As explained by the House Floor Manager:

[115]Three months later, FDA revoked the standard of identity for corn grits, enriched corn grits, quick grits and yellow grits ("grits") and added grits to the list of non-standardized foods to which folic acid may be added. See 61 Fed. Reg. 27771 and § 172.345(d).
[116]42 U.S.C. § 343(r)(3)(B)(i).
[117]42 U.S.C. § 343(r)(5)(D).

> The FDA is given the discretion to define both the procedure and the standard because the principals in the Senate could not agree on the appropriate procedure or the appropriate standard. It is obvious from the language that the agency could adopt the same procedure and standard that Congress has adopted for disease claims on food other than vitamins; it is also obvious that it could adopt a stronger standard for vitamins, minerals herbs, and other similar nutritional substances.[118]

Thus, the FDA was left to determine the standard for dietary supplements.

Before the FDA could act, Congress in 1992 passed the Dietary Supplement Act of 1992 ("DS Act").[119] The DS Act prohibited the FDA from implementing the NLEA with respect to dietary supplements prior to December 15, 1993. Also, it required the FDA to issue proposed regulations to implement the NLEA regarding dietary supplements by June 15, 1993, and the proposed regulations were to become final if final regulations were not established by December 15, 1993. Therefore, when the FDA proposed its final rules regarding health claims, generally, on January 6, 1993, they applied only to foods. The FDA then made dietary supplements subject to the same rules in a June 18, 1993 proposal.[120] Then, as discussed previously, on October 14, 1993, the FDA proposed rules authorizing a folate-neural tube defect health claim which, because of the June 18, 1993, proposal, would apply in the same manner to both foods and dietary supplements. Because of the hammer provision of the DS Act, though, the proposed rules became final by operation of law on December 31, 1993, insofar as they applied to dietary supplements, since the FDA had not yet published final rules.[121] When the FDA enacted the final rules regarding folate health claims on March 5, 1996, it therefore had to revoke the proposed rule which had become final for dietary supplements and replace it with the final rules.[122]

[119]Dietary Supplement Act of 1992, Pub. L. No. 102-571 (1992).
[120]58 Fed. Reg. 33700 (June 18, 1993).
[121]Food Labeling: Health Claims and Label Statements; Folate and Neural tube Defects, 59 Fed. Reg. 433 (Jan. 4, 1994).
[122]Food Labeling, *supra* note 4, at 8753.

By 1996, therefore, the FDA had enacted regulations which treated dietary supplements and conventional foods the same regarding the folate health claims. In fact, the FDA seemed convinced at that point that 0.4 mg of folate daily in any form was satisfactory. It had received comments criticizing the section of the proposed rules which banned claims stating "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."[123] These critical comments came from dietary supplement marketers Durk Pearson and Sandy Shaw, joined by the American Preventive Medical Association, which is a health care advocacy organization composed of health care practitioners ("Pearson Plaintiffs").[124] The Pearson Plaintiffs had asked the FDA to authorize a claim stating ".8 mg of folic acid in a dietary supplement is more effective in reducing the risk of neural tube defects than a lower amount in foods in common form"[125] ("0.8 claim"). The FDA denied the claim stating first that "the scientific literature does not support the superiority of any one source over others" and second that the scientific literature and the comments submitted did not provide "a basis for stating that a specific amount of folate is more effective than another amount."[126]

The Pearson Plaintiffs filed suit against the FDA in the United States District Court for the District of Columbia.[127] In the suit, the plaintiffs challenged the FDA's denial of not only the folic acid claim, but also the denial of claims regarding dietary fiber and cancer, antioxidant vitamins and cancer, and omega-3 fatty acids and coronary heart disease. Although the Pearson Plaintiffs based their claim on a number of grounds, the case ultimately came down to two. First, they claimed that by not allowing them to make the 0.8 claim accompanied by some sort of disclaimer, the FDA had violated their First Amendment rights. Second, they claimed that by not giving the "significant scientific agreement" requirement a definition, but using that phrase as the reason for denial of their claims, the FDA violated the Administrative Procedure

[123] 21 C.F.R. § 101.79(c)(2)(i)(H) in proposed rules, redesignated as §101.79(c)(2)(i)(G) in final rules.
[124] *Pearson et al. v. Shalala, et al.* 164 F.3d 650, 651 (D.C. Cir. 1999).
[125] *Pearson et al. v. Shalala, et al.* 130 F. Supp. 2d 105, 108 (D.D.C. 2001).
[126] Food Labeling, *supra* note 4, at 8760.
[127] *Pearson et al. v. Shalala, et al.* 14 F. Supp. 2d 10 (D.D.C. 1998).

Act ("APA"). Although the District Court granted the FDA's motion to dismiss and held for the FDA on all claims, the Circuit Court reversed and held against the FDA on both of the aforementioned grounds.[128] Regarding the FDA's refusal to allow the 0.8 claim accompanied by a qualifying disclaimer, the Circuit Court placed emphasis on whether the claim was inherently misleading or only potentially misleading. It said that if the claim was inherently misleading, it may be prohibited. But, if the claim was only potentially misleading, the FDA would need to meet the standards of the *Central Hudson*[129] test for evaluating governmental regulation of potentially misleading commercial speech.[130] Under this test, although the court found that the FDA's interest in the regulation was substantial (protecting public health and preventing consumer fraud), and that the prohibition was directly advancing the FDA's interest, the court found that the FDA's prohibition was potentially not reasonably related to achieving its goals.[131] The court noted that there is generally a preference for more disclosure rather than suppression of speech, which would lean in favor of allowing the 0.8 claim accompanied by a disclaimer rather than banning the claim completely. The court therefore remanded the issue to the FDA to provide evidence that a disclaimer could not cure the health claim.

Regarding the APA claim, the court noted that the APA prohibits agencies from engaging in "arbitrary and capricious action."[132] The court held that under this principle, "it must be possible for the regulated class to perceive the principles which are guiding agency action."[133] By not giving any clarifying explanation of "significant scientific agreement," but still using it as a basis for rejecting the claims, the FDA was not complying with the APA. Thus, the court remanded this issue to the FDA to "explain what it means by significant scientific agreement or, at minimum, what it does not mean."[134] Because of this issue, and

[128] 164 F.3d 650 (D.C. Cir. 1999).
[129] *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of N.Y.*, 447 U.S. 557 (1980).
[130] *Id.* at 656.
[131] *Id.* at 657.
[132] *Id.* at 660.
[133] *Id.* at 661.
[134] *Id.*

the First Amendment disclaimer issue, the court invalidated §101.79(c)(2)(i)(G), which, as discussed above, prohibited claims that one type of folate was superior to another type at a different level, as well as those regulations relating to the other nutrient-disease relationships challenged by the Pearson Plaintiffs.

The FDA's reaction to the *Pearson* decision was somewhat slow in coming. Nine months after the decision, the FDA published a request for scientific data related to the nutrient-disease relationships at hand in the case as part of an effort to reevaluate the scientific evidence at issue.[135] Then, on December 1, 1999, over 10 months after the *Pearson* decision, the FDA outlined its plan for implementation of the decision.[136] The multi-part plan included, in addition to reevaluating the scientific data regarding the nutrient-disease claims at issue, issuing a clarification of the "significant scientific agreement" standard and conducting rulemaking regarding dietary supplements in general and rulemaking regarding the *Pearson* claims. The clarification of the "significant scientific agreement" standard came in the FDA's "Guidance for the Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements," which the FDA made available in December of 1999. Then, 18 months after the *Pearson* decision, the FDA finally revoked the regulations which denied authorization of claims regarding the substance-disease relationships which had been struck down by the court.[137] Although the regulations had been struck down and were revoked, manufacturers were still not able to make claims such as the 0.8 claim because the FDA still refused to authorize the claims.

One week after revoking the invalidated regulations, the FDA on October 10, 2000, issued a letter decision in which it again denied authorization of the 0.8 claim, even with qualifying disclaimers. In so doing, the FDA broke the 0.8 claim down into three parts. First, it evaluated whether 0.8 mg of folic acid is more effective

[135]Food Labeling: Health Claims and Label Statements; Request for Scientific Data and Information, 64 Fed. Reg. 48841 (Sept. 8, 1999).

[136]Food Labeling: Health Claims and Label Statements for Dietary Supplements; Strategy for Implementation of Pearson Court Decision, 64 Fed. Reg. 67289 (Dec. 1, 1999).

[137]Food Labeling: Health Claims and Labeling Statements;... Folate and Neural Tube Defects; Revocation, 65 Fed. Reg. 58917 (Oct. 3, 2000).

than a lower amount, and found that the scientific evidence was unclear and did not support the conclusion. Second, it evaluated the compositional component of claiming that dietary supplements are more effective than foods in common form. The FDA found that since the same chemical form of folic acid is added to both dietary supplements and to fortified foods, it would be misleading to say that dietary supplements are more effective than foods. And third, regarding the physiological effectiveness of folic acid versus natural food folate, the FDA noted that although folic acid may have a higher bioavailability, the two are both used by the body and offer the same protective effects. Thus, the FDA concluded that the scientific data did not support the claim. The FDA also considered the claim to be inherently misleading and incurable through the use of a disclaimer.

The Pearson Plaintiffs responded to the FDA's letter decision by filing another lawsuit on November 13, 2000.[138] In the suit they sought a "preliminary injunction enjoining the FDA from taking any action which would prevent Plaintiffs from using their desired folic acid health claim."[139] The Pearson Plaintiffs again used the First Amendment as the basis for their suit, claiming that the FDA "fundamentally misread and misapplied" the Court of Appeals' decision, to which the FDA responded that the 0.8 claim was not protected speech because it was "inherently misleading" and incurable through a disclaimer.[140] Although the case was again before Judge Gladys Kessler, the district court judge who had ruled in favor of the FDA in the previous lawsuit, the Judge this time had harsh words for the FDA. She wrote that "the FDA simply failed to comply with the constitutional guidelines outlined in *Pearson*. Indeed, the agency appears to have at best, misunderstood, and at worst, deliberately ignored, highly relevant portions of the Court of Appeals Opinion."[141] She noted that the Court of Appeals had "strongly suggested" that the 0.8 claim was potentially, not inherently, misleading, and was probably curable with a disclaimer.

[138] 130 F. Supp. 2d 105 (D.D.C. 2001).
[139] *Id.* at 107.
[140] *Id.* at 112.
[141] *Id.*

After examining the FDA's reasoning in its letter opinion, the court found the FDA's determination that the claim was inherently misleading and unable to be cured with disclaimers to be arbitrary and capricious. She therefore found the FDA to be in violation of the Court of Appeals' decision, and remanded the case to the FDA with instructions ordering it to "draft one or more appropriately short, succinct, and accurate disclaimers."[142] The FDA responded with a letter dated April 3, 2001, in which it approved the use of the claim if accompanied by the disclaimer "FDA does not endorse this claim. Public health authorities recommend that women consume 0.4 mg folic acid daily from fortified foods or dietary supplements or both to reduce the risk of neural tube defects." This, the FDA claimed, was preferable to the disclaimers proposed by the courts in that it fully explains why the FDA found the claim misleading and inaccurate. The FDA wrote that it would exercise its enforcement discretion regarding supplements bearing the 0.8 claim so long as the disclaimer "is placed immediately adjacent to and directly beneath [it], with no intervening material, in the same size, typeface, and contrast as the claim itself." The letter also noted, however, that the FDA still believed the 0.8 claim to be misleading and incurable through a disclaimer, so it had filed with the court a motion for reconsideration.

Judge Kessler denied this motion on May 7, 2001, with more harsh words for the FDA, finding that it still had not satisfied the "heavy burden" required to suppress the health claim.[143] She wrote, "[i]n moving for reconsideration, Defendants again seem to ignore the thrust of *Pearson I*," and "[i]n its motion for reconsideration, the FDA has again refused to accept the reality and finality of" the Court of Appeals' decision finding the claims not inherently misleading should be treated with disclaimers, not suppression.[144] After this rebuke the FDA and the Pearson Plaintiffs reached an agreement under which the FDA allowed the use of the 0.8 claim when accompanied by the FDA's proposed disclaimer, and the case was finally

[142] *Id* at 120.
[143] *Pearson, et al. v. Thompson, et al.* 141 F. Supp. 2d 105 (D.D.C. 2001).
[144] *Id.* at 112.

dismissed on June 4, 2001.[145]

Impact of FDA's Actions

Although the court battles concerning health claims and dietary supplements continues on today, the FDA's three-part action on the folate issue during the mid-1990s has remained largely unchanged since the fortification program became mandatory in January of 1998. Therefore, it is possible now to examine early studies analyzing the potential effects of the program. Although it does not appear that there has been extensive research in this area, there are studies and data available regarding the rate of neural tube defects both before and after fortification and regarding the levels of folate present in the U.S. population's blood.

One study, published in the June 20, 2001, issue of the *Journal of the American Medical Association*, looked at the occurrence of neural tube defects in the U.S. before and after the fortification of the food supply ("Honein study").[146] The study examined birth certificates from 45 states during the period from January, 1990, to December, 1999.[147] Birth certificates, since 1989, have included check boxes for certain birth defects, including both anencephaly and spina bifida. Although the authors note that birth certificate data may not be of the highest quality, they attempted to control for its abnormalities through statistical techniques. The authors used data from three times periods to create the comparison. They used births from October, 1998, through December, 1999, as the post-fortification period, since the fortification program had been completely implemented prior to when those pregnancies would have begun. Then, for the two pre-fortification periods they examined data from October, 1995, through December, 1996, and from 1990 through 1996. Additionally, the authors looked at data from all women and also separately at data from women who received no

[145]It is interesting to note that FDA is still litigating certain other health claims for dietary supplements. Judge Kessler recently issued decisions regarding claims for antioxidant vitamins and saw palmetto extract.

[146]Margaret A. Honein, *Impact of Folic Acid Fortification of the U.S. Food Supply on the Occurrence of Neural Tube Defects*, 285 JAMA 2981 (2001).

[147]The study did not include birth certificates from New Mexico, New York, and Oklahoma because birth certificates there did not include birth defect information for a part of the survey period, and it did not include Connecticut or Maryland because birth defect status was not stated on more than 25% of birth certificates for various periods during the study.

prenatal care until at least the third trimester, since those women would have been unlikely to abort a neural tube defect-affected fetus because of strict anti-late term abortion laws.

The authors compare the various categories of data in numerous ways, and most yield a decline in neural tube defects from the earlier periods to the post-fortification period. For example, the rate of spina bifida in all births declined 23% from the 1995-96 period to the 1998-99 period, and the rate of anencephaly declined 11% between the same periods. Overall, the total rate of neural tube defects declined 19%, from a rate of 37.8 to 30.5 cases in every 100,000 live births. The authors observed similar percentage declines in comparing the data from 1990-96 with the post-fortification period, and in the various comparisons of data from mothers receiving only late or no prenatal care. Comparing quarterly data from 1990 through 1999, the authors noted fairly constant rates of both spina bifida and anencephaly during the pre-fortification period, but found statistically significant declines for both during three of the five post-fortification quarters examined. In analyzing these results, the authors note several weaknesses, mostly related to problems with birth certificate reporting of birth defects. The authors make few conclusions about the results, but the 19% decline in neural tube defects after fortification, with no similar decline in overall birth defects, does seem to be evidence that the FDA's fortification program was achieving valuable results. The 19% decline, though, is smaller than was predicted by many of the studies, leaving readers to speculate whether folate is less important than predicted, whether the fortification program was not adding enough folate to women's diets, or some other factor was at play.

Evidence of a decline in the number of neural tube defects is also evident in the data available from the CDC. According to the CDC, there were 24.88 cases of spina bifida per 100,000 live births in 1991, as compared with 20.7 cases in 2000.[148] This decline is more pronounced considering the fact that from 1990 through 1995 the rate rose to 27.98 before declining to the 2000 levels. The decline in cases of anencephaly is less

[148]Statistics available on-line at www.cdc.gov/nchs/fastats/pdf/nvsr50_05t49.pdf, www.cdc.gov/nchs/products/pubs/pubd/hestats/folic/folic.htm

pronounced, though, as the rate went from 12.79 in 1992 to 10.7 in 2000 (the rate in 1991 was 18.38 – far higher than the rate in any of the following years). These declines of 16.8% and 16.3%, respectively, are somewhat more modest than may have been predicted, but do translate into over 250 less cases of neural tube defects each year.[149]

Other studies examined the effects of fortification on the level of folate in the blood. One such study was published in *The New England Journal of Medicine* on May 13, 1999 ("Jacques study").[150] That study examined the results of tests performed on the offspring of people who participated in a heart disease study in Framingham, Massachusetts, conducted during the late 1940s. The offspring were examined several times, including once in the early 1990s and once in the late 1990s. The authors of the Jacques study determined that most products subject to fortification were fortified by July, 1997, so they used those participants examined after that date as the test group, and the data from the early 1990s as the control. Specifically, the authors examined the plasma folate and total homocysteine concentrations[151] from those participants' blood work. They found that in participants who did not use supplements, the plasma folate concentrations increased by 117% after fortification, while the number of participants with low folate concentrations decreased by 92%. Also, homocysteine levels decreased by 50% among those who did not use supplements. Folate levels were higher and homocysteine levels were lower among those who did use supplements. This data led the authors to conclude that fortification has had a substantial effect on these folate indicators. Although the study participants were largely middle-aged and older adults, the authors note that there is no reason to believe there are not similar changes in the folate levels of women of child-bearing age.

The findings of the Jacques study were similar to those of a study published in the September 11, 1999,

[149]Based on approximately 4,031,591 live births per year (which is the number of live births, excluding New Mexico, reported by CDC in 2000). See www.cdc.gov/nchs/fastats/pdf/nvsr50_05t49.pdf.

[150]Paul F. Jacques, et al., *The Effect of Folic Acid Fortification on Plasma Folate and Total Homocysteine Concentrations*, 340 New Eng. J. Med. 1449 (1999).

[151]The authors state that homocysteine concentration is a marker for folate status.

edition of *The Lancet* ("Lawrence study").[152] The authors of the Lawrence study evaluated data on serum folate concentrations in samples of blood submitted to Kaiser Permanente in Southern California from 1994 through 1998. The 98,351 samples were from persons of all ages, with half coming from those age 40 to 69 years old, and 53% from women. The authors found that the percentage of participants with high serum folate levels (defined as greater than or equal to 20 μg/L) increased from 25.6% in 1994 to 45.3% in 1998, while the percentage with low serum folate levels (less than 2.7 μg/L) decreased from 1.3% to 0.3% during the same period. Over that period, the medium level increased from 12.6 μg/L to 18.7μg/L. In evaluating this data, the authors determined that the increase in folate levels was likely due to fortification, and that the results may be similar to those of the population at large. Thus, the Lawrence study and the Jacques study both found levels of folate in the blood to have increased sharply after the implementation of the folic acid fortification program. There appear to be no studies showing contrary results.

Commentary

In the early part of 2003, we can now step back and review a largely finished process regarding folic acid. The link between folic acid and neural tube defects seems to have become solidified into common medical knowledge among practitioners, foods and dietary supplements are allowed to carry a health claim regarding use of the product and the protective benefits of folic acid, and our food supply has been fortified with folic acid so that, even if we have never heard of it, we are sure to ingest at least some quantity of it most days. Aside from a few commentators who think the level of fortification is still not high enough, the action surrounding folic acid has largely died down, and mostly come to an end. So we can now ask three important questions. First, was the process worth the trouble and expense? Second, did the process go as well as it should have? And third, what, if any, role should the FDA have had in the process?

[152] Jean M. Lawrence, et al., *Trends in serum folate after food fortification*, 354 The Lancet 915 (1999).

Costs versus benefits

Regarding the first question, now that the folic acid controversy has wound down, we can attempt to examine whether the process was actually worthwhile. This is a multi-part inquiry, the first part of which calls into question the number of lives saved. As has been discussed previously, prior to the FDA's action on folic acid approximately 2,500 babies each year were born with neural tube defects, and an unknown number of additional fetuses were affected by neural tube defects but were aborted through planned terminations after diagnosis or through spontaneous abortions. Because of the deadly or crippling nature of neural tube defects, having over 2,500 births affected by them is tragic. However, the number is tiny considering the fact that there are over 4 million births in the United States each year.

So, was all of the work by scientists, the FDA, and others really necessary? Although the number of neural tube defects is small in comparison to the overall number of births, the struggle becomes much more valuable when one considers what a high percentage of the cases could be prevented with folic acid. As previously stated, simply obtaining adequate folic acid, women could prevent anywhere from 40% to 70% of neural tube defects. This translates into anywhere from 1000 to 1750 less cases each year, and that does not even count the number of fetuses which would not be aborted as a result of a defect. The fact that such a huge portion of the defects can be prevented with folic acid certainly helps balance the fact that the actual number of prevented cases is a small fraction of the total number of births. Does this justify the money and time devoted to folic acid? Perhaps, but perhaps not. It does, however, at least make it much more justifiable.

Beyond just the sheer number of cases of neural tube defects involved from the beginning, asking whether or not the campaign was worth while also requires looking at the actual results. Here, two pieces of data are

important: the actual decline in the incidence of neural tube defects and consumer awareness of the necessity of folic acid in preventing birth defects. Regarding the former, it has already been noted that the incidence of neural tube defects has declined over the past 10+ years. Studies of most states have shown declines in spina bifida and anencephaly prevalence of 25% and 21%, respectively, from 1996 to 2001, although the 1999-2001 rates were fairly constant.[153] Taking into account data going back even further, the total rates for both disorders appear to be down over 30% from the early 1990s.[154] These numbers do show significant progress, but certainly not the progress which was predicted during the early days of the campaign. Does this mean the campaign was not worth while, since only 500 to 750 cases were probably prevented? Probably not. Indeed, it was especially worthwhile to the 500 to 750 children who are healthy today but may have otherwise been born with a neural tube defect. It may, however, indicate that the FDA's conservative levels of fortification may need to be increased before the population receives the maximum protective effects of folic acid.

The numbers, though, only tell a part of the story. The folic acid campaign had two prongs: fortification and health claims. The issue originally arose out of Congress's demand that the FDA consider a health claim regarding the relationship between neural tube defects and folic acid, and the fortification issue arose along the way. So, originally, the issue arose as part of Congress's desire to see consumers receive more information regarding the health effects of foods. This approach seems to be a more person-centered approach, as it requires women to take responsibility for their own nutrition and ensure they receive adequate folic acid at all times. The FDA eventually also pursued the more passive method of fortification as it probably, wisely, knew that many women would not take responsibility for increasing their folic acid intake, so some sort of passive delivery method was necessary. This two-pronged approach should, in theory, provide women with information regarding which products contain high levels of folic acid, and why that is important, as well as

[153] T.J. Mathews, et al., *Spina Bifida and Anencephaly Prevalence – United States, 1991-2001*, 51 MMWR 9, (Sept. 13, 2002).
[154] *Id.*

providing them, passively, with folic acid in case they do not actively seek it.

However, the results on the consumer awareness front are, at best, disappointing. Just a quick survey of grocery store shelves is all that is necessary to show that producers have not embraced the FDA's blessing of a folic acid health message. Few products, if any, bear any type of folic acid claim. Also, few women seem to know about folic acid or its helpful benefits. The 1998 March of Dimes and Gallup Organization phone survey of over 2000 women age 18-45, mentioned previously, revealed that while 32% of women were taking a multivitamin daily and 68% of women had heard of folic acid, only 13% knew it helped prevent birth defects, and only 7% knew it needed to be taken before pregnancy.[155] Although the response rate was low (51%), and the numbers did show an increase from the levels of awareness in 1995, they show that even after the FDA had allowed health claims to appear on products and required fortification, the vast majority of women still had no idea why folic acid is important and how it needs to be used. This is even more surprising considering that the folic acid campaign was covered by all major newspapers, including the *New York Times* and the *Washington Post*, and the health benefits of folic acid have been written about repeatedly in both newspapers.

What, if anything, does this evidence show? While it may indicate a lack of responsibility on the part of American women or a failure of the FDA's attempts to educate the public through health claims on product labels, it perhaps shows that the FDA was correct in proposing, along with the health claim authorization, the fortification program now in place. The FDA's error on this front was that it far overestimated the number of women who would seek out folic acid, thus causing it to overestimate the amount of folic acid women would receive. This evidence also shows that, in hindsight, the FDA spent too much time pondering the health claim issue. In its defense, the FDA seems to have sincerely thought companies would race to

[155]CDC, *Knowledge and Use of Folic Acid by Women of Childbearing Age – United States, 1995-1998*, 48 MMWR 325 (April 30, 1999).

place a folic acid health claim on their products, thus flooding the market with these health claims, causing consumers to buy up folate-rich foods in large quantities. This is all evidenced from its continual hand-wringing in the *Federal Register* during the mid-1990s. However, the health claims it proposed seem too long and clumsy to be workably included in most food packaging. Although the FDA realized that and authorized much shorter claims than it originally proposed, the authorized claims were still probably too wordy and "boring" to appeal to manufacturers. As a result, few foods carry a folic acid claim, and few consumers know what folic acid is. So, baring some sort of intensive informational campaign, the fortification program seems to be the main vehicle of folic acid intake for most women. Thus, in hindsight, the FDA could have devoted more time to rapidly instituting the fortification program, and potentially authorizing higher levels of fortification, and, as will be discussed below, spent less time debating the merits of the various health claims.

Evaluating the process

Returning now to the second of the originally-posed questions, it is necessary to examine whether the process the FDA actually undertook was as well-run as possible. One thing is exceedingly clear – the FDA moves very slowly. It took no action on folic acid, despite the mounting evidence of its health benefits, until the issue was thrust into its lap in the NLEA. Then, it took three years before it even issued proposed regulations. Another three years passed before the final regulations were issued, and two more years before fortification became mandatory. Thus, the entire process took nearly eight years, from start to finish. To be fair, the FDA needs to be cautious with any process of this nature. Allowing health claims which later turn out to be incorrect or dangerous, or requiring fortification with a nutrient which could later prove fatal, would be, at best, damaging, and at worst, deadly, to the FDA's credibility and trustworthiness. As Dr. David Kessler, Commissioner of the FDA during the folic acid period, explained in a *New York Times* article, "a decision

to add a pharmacologically active nutrient to the food supply is very weighty. You have to get it right, and you have to get it right the first time. There is no simple answer and no simple solution is readily apparent. We want to make major inroads on this disease, but we don't want to harm anyone."[156] The FDA is rightly justified in moving slowly. However, eight years is an exceedingly long time for a process such as this. In the interim, preventable cases of neural tube defects killed or paralyzed hundreds of children who might otherwise have been healthy.

In arguing in favor of reform of the FDA in advance of the 1997 FDA Modernization Act ("1997 Act"), Senators Barbara Mikulski and Nancy Kassembaum stated, "Rarely, however, is a word spoken about the cases of spina bifida that could have been averted had the FDA not delayed for years in permitting health claims to be made about the benefits of folic acid in preventing such neural tube disorders."[157] The slow speed at which the FDA moved, even if reasonable in most cases, becomes somewhat less so considering that the only harmful effect even mentioned of large quantities of folic acid was a potential rare masking of a vitamin B_{12} deficiency in elderly people. Thus, the FDA was forced to balance the potential beneficial effects of folic acid for a small percentage of babies with the potential harmful effects for a small percentage of the elderly – not an easy tradeoff. Were this folic acid process to occur today, it may not have taken quite the same amount of time and energy, at least on the health claims issue, because Congress, through the 1997 Act, made it easier for manufacturers to bypass the FDA in placing health claims on their products. The Act allows manufacturers to place a health claim on their food products, unless the FDA has banned such a claim through regulations, if the manufacturer gives the FDA 120 days notice and the following requirement is met:

[156]Marian Burros, *Eating Well*, N.Y. Times, Jan 5 1994, at C4.
[157]Barbara Mikulski & Nancy Kassebaum, *The FDA Can Work Better*, Wash. Post, July 26, 1996, at A27.

> [A] scientific body of the United States Government with official responsibility for public health protection or research directly relating to human nutrition (such as the National Institutes of Health or the Centers for Disease Control and Prevention) or the National Academy of Sciences or any of its subdivisions has published an authoritative statement, which is currently in effect, about the relationship between a nutrient and a disease or health-related condition to which the claim refers.[158]

This change therefore may avert the lengthy delay which occurred with the folic acid health claims. Since the CDC, though the PHS, issued its folic acid recommendation in 1992, had this change been in effect then, it would presumably have allowed manufacturers to make folic acid claims without FDA approval.

The proper role for the FDA

Finally, it is now possible to review the FDA's role in the folic acid process to critically examine whether the current system is appropriate, or whether the FDA might better play a more active or passive role during similar undertakings in the future. As has been mentioned, the FDA's role in the folic acid process was centered around the fortification and food additives issue and around the health claims issue. As has been discussed, the FDA moved slowly in dealing with each of these issues, but did act on both fronts. Its actions regarding the fortification and food additives portion of the folic acid process, although slow, seem to be actions which are appropriately within the FDA's jurisdiction, especially since they led to a successfully-implemented fortification system. However, the FDA's actions regarding health claims seem more problematic. Although the resulting folic acid health claims regulations were a product of the same process as fortification, they led to a major lawsuit and have not produced a situation where folic acid health claims are widely used.

There are numerous problems with the current FDA approach to health claims regulations. First, the regulations often require health claims to be prohibitively long and complicated. As the folic acid example shows, the FDA seems concerned with providing consumers with full, non-misleading health claims. In attempting to achieve this goal, the FDA takes a paternalistic approach by requiring manufacturers to provide large amounts of information so as to prevent all possible misinterpretations. This paternalism results in regula-

tions requiring the health claims to be so long that they likely become unattractive to manufacturers and too long to quickly catch a consumer's eye.

A second problem with the health claims requirements is that they often prevent manufacturers from making true statements about their products. Because of the many elements required by the regulations to appear in a health claim, a manufacturer desiring to use a shorter, but still entirely true, health claim would be unable to do so. The problem was even more relevant prior to the passage of the 1997 Act, which allows manufacturers to bypass the FDA if certain other governmental bodies have made nutrient-disease relationship statements. As Noah and Noah note in their pre-1997 Act article, manufacturers would then have been barred from placing the following claim on product labels: "The U.S. Centers for Disease Control (CDC) have encouraged all women of childbearing age to consume 0.4 milligrams of folic acid each day to reduce their risk of having a pregnancy which results in a neural tube birth defect such as spina bifida."[159] Even after the passage of the 1997 Act, manufacturers may still be prevented from making a true statement such as this, even though it is accurately based on the PHS recommendation, because the FDA has required that certain additional elements must appear in folic acid health claims.

A third problem with the FDA's health claim authorization process is that manufacturers can circumvent the regulations. In her article discussing numerous ways manufacturers avoid the FDA's health claims regulations, Heller notes that the largest loophole in the regulations is that while health claims must be pre-approved by the FDA, structure/function claims need no such pre-approval.[160] Manufacturers have, therefore, made use of statements they claim to be structure/function claims, even though the same statements would be barred if classified as health claims. A structure/function claim "describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, [and] characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or

[159]Lars Noah & Barbara A. Noah, *Liberating Commercial Speech: Product Labeling Controls and the First Amendment*, 47 Fla. L. Rev. 63, 68 (1995).

[160]Irene Ringel Heller, *Functional Foods: Regulatory and Marketing Developments*, 56 Food and Drug L.J. 197, 199 (2001).

function..."[161] whereas a health claim "characterizes the relationship of any nutrient to a disease or health related-condition."[162] The line between these two types of claims is fine, but as Heller reports, after the FDA denied authorization of a health claim relating folic acid, vitamin B_6, and vitamin B_{12} to a reduced risk of heart disease, the Kellogg Company began placing the claim "adequate intakes of folic acid, vitamin B_6, and B_{12} may promote a healthy vascular system" on certain of its products, calling it a structure/function claim.[163] Similarly, although the Campbell Soup Company's V8 vegetable juice contains too much sodium to qualify for an FDA-approved health claim, Heller notes that Campbell placed the statement "Research... suggests that antioxidants [in V8 juice] may play an important role in slowing changes that occur with normal aging" on V8, justifying the move by calling the statement a structure/function claim.[164] Both the Kellogg and Campbell claims seem very much like the health claims the FDA regulates, and both claims are specifically barred from product labels if they are classified as health claims. Both, however, were used by manufacturers under the guise of structure/function claims. If manufacturers are allowed to use such claims on their products without the FDA's approval, it seems almost pointless for any manufacturer to bother following the FDA's cumbersome health claims restrictions.

Thus these problems, and certainly there are others, paint the FDA's health claims regulatory scheme as cumbersome, restrictive, and easy to circumvent. What, then, are the potential options for improvement? One option would be to remove regulation of health claims from the FDA's jurisdiction and create an unregulated, market-driven environment. Manufacturers in an unregulated environment would then be allowed to place claims on their products as they see fit. Under this type of system, keeping labels accurate and truthful would be left to the market, and it would likely force consumers to take a more active role in learning about nutrition in order to determine which claims are accurate and which are less accurate or even misleading.

[161] 21 U.S.C. § 403(r)(6)(A).
[162] 21 U.S.C. § 343(r)(1)(B).
[163] Heller, *supra* note 160, at 209.
[164] Heller, *supra* note 160, at 210.

Because the basic nutrition labeling panel would still appear on food products, consumers would need to take a more proactive role in examining the panel to ensure they select foods which form a complete, healthy diet. This system is fairly risky, however, because as the FDA found when it loosened its health claim standards prior to the enactment of the NLEA, manufacturers in an unregulated environment are willing to stretch the limits of truthfulness.[165] Because, as has been discussed, consumers may be unwilling or unable to take a more active role in seeking out information about nutrition, they may be unable to discern truthful from misleading health claims.

More likely, if regulation of health claims is removed from the FDA's jurisdiction it would move into the Federal Trade Commission's ("FTC") jurisdiction. Through the Fair Packaging and Labeling Act,[166] the FTC already regulates the labeling of all consumer commodities (except those under the FDA's jurisdiction) to ensure proper disclosure and prevent deception of consumers. Because the FTC already has experience in regulating product labels, it might be better equipped to deal with the issue of health claims. In fact, the FTC submits comments on FDA proposals regarding health claims, as it did recently in the matter of labeling requirement for trans fatty acids.[167] Additionally, the "FTC considers the prevention of deceptive health-related advertising claims to be one of its highest priorities, and has taken action in numerous cases involving deceptive health-related claims about food products and dietary supplements."[168] Thus, there is clearly overlap between the two agencies' jurisdictions, so it seems possible that the FTC, with its broad experience in consumer products labeling, might be better equipped to regulate the health claims area.

A third alternative approach would involve combining the two agencies' expertise so as to make the health

[165] See *supra* note 57.
[166] 15 U.S.C. §§ 1451-1461.
[167] Staff of the Bureau of Economics, the Bureau of Consumer Protection, and the Office of Policy Planning of the Federal Trade Commission, *In the Matter of Food Labeling: Trans Fatty Acids in Nutrition Labeling, Nutrient Content Claims and Health Claims*, December 16, 2002. Available on-line at http://www.ftc.gov/be/v030003.htm#N_4_.
[168] *Id.*

claims regulatory scheme work more efficiently. Such a move might actually be underway at the time of this writing. On December 18, 2003, the FTC, citing the fact that the current system has led to a number of false health claims on dietary supplements and a decreased number of total health claims on conventional foods, announced that it would be coordinating with the FDA on a new consumer health information initiative to eliminate false health claims while making it easier for manufacturers to use health claims in labeling.[169] Although it is too early to determine exactly how this new initiative will operate, if it works as described, by both eliminating false claims and making health claims easier to use, perhaps it will be a solution to the flaws in the current regulatory scheme.

Finally, although it appears that the FDA is moving to change the current health claims regulation system, there are certain positive aspects of the current system which provide support for its retention. Despite being cumbersome, overly restrictive, and easy to circumvent, the current system protects consumers from certain misleading information. The FDA must strike a balance between providing consumers with enough information for them to make informed choices and keeping required information limited enough so as not to overwhelm consumers or prevent manufacturers from providing any information. Just as the FDA moved slowly and cautiously on the entire folic acid regulatory package in order to ensure it made no mistakes, the FDA's cumbersome, restrictive system for approving health claims potentially keeps a large portion of false or misleading information away from consumers. Closing the structure/function loophole would further reduce the flow of misleading information, which seems to be the only dangerous aspect of the current system. As noted, each of these potential courses for handling future regulation of the health claims area has both positive and negative aspects. Although deregulating health claims and allowing market forces to govern is the simplest approach, manufacturer abuse of health claims during the regulatory thaw preceding the NLEA's passage likely eliminated any possibility of this course being taken. Maintaining the current system

[169]FTC, *FTC and FDA Coordinate for New Consumer Health Information Initiative*, December 18, 2002. Available on-line at http://www.ftc.gov/opa/2002/12/ftcfda.htm.

is also unlikely because the FDA has shown that, while very diligent in its pursuit of safe and effective health claims, it is simply not able to efficiently control this area. Because it is too small, too inexperienced in this area, or simply too cautious, if the FDA continues to control the regulation of health claims it is unlikely that consumers will soon see health claims in the quantity necessary for the claims to be of true assistance. It might therefore be prudent to attempt to pursue either a joint system of control between the FDA and the FTC, or to have the FTC take total control of health claims. While evaluating the FTC's ability to do the monitoring and regulatory work effectively is outside the scope of this paper, it seems at first blush that the FTC's vast experience in monitoring labeling of all non-food and drug projects might make it better able to create an efficient regulatory system. So, while the proper course of future action is perhaps unclear, it is apparent that the FDA's current cumbersome, circumventable system is in need of a change before properly-monitored health claims can effectively inform and educate the consuming public. Hopefully the current cooperative effort between the FDA and the FTC will create the changes necessary for a more effective regulatory system.

Conclusion

Thus today, 13 years after the passage of the NLEA, the folic acid controversy seems to have passed. Manufacturers can use folic acid health claims on their products, and enriched foods now include one more nutrient. More people know about folic acid and its benefits, although those understanding its benefits are still woefully in the minority. Folate levels in the blood are up, and the prevalence of neural tube defects is down. So, where should we go from here? It seems obvious from the evidence presented that progress has been made, but more is certainly possible. Two solutions seem to exist: more fortification and more education. The first is the passive track, simply adding more folic acid to fortified foods. Many researchers have pushed for higher levels of fortification, and the FDA did consider it during the mid-1990s. However,

with increased fortification comes increased risks. Folic acid has recently been shown to have potential benefits in other health areas, such as the prevention of cardiovascular disease and Alzheimer's disease, so increased fortification may be an option.[170] However, the risks which concerned the FDA originally seem still to be present.

On the other hand, we might also try an increased level of consumer education. It seems somewhat ludicrous that in order to get American women of childbearing age to consume adequate folic acid, the government has to fortify the food supply, thus affecting the entire population. An education plan would place more responsibility on individual women to be sure they eat a healthy diet and perhaps take a vitamin supplement. It is a sad day when the government needs to force people to do something beneficial for their health, as otherwise they would not do it. Nonetheless, such a plan has had success in South Carolina, for example, where the state spends $1 million per year on a folic acid informational campaign including billboards, television commercials, and informational materials and programs at bridal registries, colleges, and health care providers.[171] From 1992 to 1998 South Carolina's rate of neural tube defects, originally twice the national average, was cut in half. Nationally, therefore, an informative campaign may be helpful in increasing awareness. Perhaps the newly announced partnership between the FDA and the FTC in the area of health claims will produce an environment more conducive to the use of health claims by manufacturers, thereby increasing the use of product labeling in as part of what could be a broader educational campaign.

Whatever the future may hold, it is evident from the foregoing that the process involved to reach the present situation regarding folic acid has been long and complicated. However, it has also been safe. Perhaps in this situation the FDA could have moved more quickly, but hindsight is 20/20. Although, sadly, many children may have been born with neural tube defects as a result of the slow speed of the process, this must be

[170] Marian Burros, *Eating Well; One More Reason to Eat Your Greens*, N.Y. Times, May 16, 2001, at F5.
[171] Eric Nagourney, *Campaign Touts the Benefits of Folic Acid*, N.Y. Times, Dec 12, 2000, at F8.

balanced with the unknown risks which worried the FDA every step of the way. As with any such process, although there are certain things which probably should have been done differently, there were also valuable lessons learned and, perhaps most importantly, things are better as a result of it. As more evidence is released, changes will probably need to be made in the current rules and regulations, but hopefully those, too, will continue to make the food supply safer and healthier.