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RE: Qualified Health Claim Petition – Vitamin D and Reduction of the Risk of Multiple Sclerosis (Docket No. FDA-2016-Q-2646)

Dear Dr. Matulka,

This letter responds to the health claim petition received on June 3, 2016, submitted to the Food and Drug Administration (FDA or the agency) on behalf of Bayer pursuant to Sections 403(r)(4) or 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §§ 343(r)(4) and 343(r)(5)(D)). The petition requested that the agency authorize a health claim characterizing the relationship between the consumption of vitamin D and a reduction in the risk of multiple sclerosis (MS). The petition proposed the following model health claim for use on the label or in the labeling of conventional foods and dietary supplements containing vitamin D:

“Vitamin D may reduce the risk of multiple sclerosis (MS).”

FDA evaluated the scientific evidence provided with the petition and other evidence related to your proposed claim. Based on this review, FDA determined that the scientific evidence supporting the proposed health claim did not meet the “significant scientific agreement” standard under § 403(r)(3)(B)(i) of the Act for conventional food or 21 CFR 101.14(c), which is applicable to dietary supplements. FDA notified you of this decision on September 6, 2016, and we received an email from you on September 7, 2016 stating that your client requests that the petition be changed to a qualified health claim petition on the said relationship. FDA considers this request as the petitioner choosing to seek FDA review of the petition as a qualified health claim petition. Thus, FDA filed the petition on September 9, 2016 as a qualified health claim petition and posted it on the Regulations.gov website for a 60-day comment period, consistent with the agency’s guidance for procedures on qualified health claims.¹ The agency received no comments in response to the petition.

This letter sets out the basis for FDA’s determination that there is no credible scientific evidence to support the proposed health claim and the reasons the agency is denying this claim.

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

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-

¹ See FDA “Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements” (July 10, 2003) [<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm053832.htm> (accessed December 5, 2017)].

related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease or health-related condition.² In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.³

FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.⁴ The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.⁵

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,⁶ review articles,⁷ and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements, such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications⁸ to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship.⁹ If additional studies are identified, the agency evaluates them individually.

² See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S. Ct. 310 (2004).

³ See FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final," January 2009.

[<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm> (accessed December 5, 2017)].

⁴ For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of this letter except when quoting or paraphrasing a regulation that uses the longer term.

⁵ In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See *supra*, note 3.

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

⁷ Review articles summarize the findings of individual studies.

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

⁹ Certain meta-analyses may be used as part of the health claim review process. See *supra*, note 3.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, which affect how humans respond to the consumption of foods and dietary substances (IOM, 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study (Spilker, 1991; Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality.¹⁰ This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics (other than relevance to the U.S. population, e.g., selection bias and whether important information about the study subjects such as age or smoking status was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.¹¹ The agency conducts this rating evaluation by

¹⁰ See *supra*, note 3.

¹¹ See *supra*, note 3.

considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of studies of each type and study sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,¹² and the overall consistency¹³ of the total body of evidence.¹⁴ Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship, and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food, regardless of whether the food is in conventional form or in the form of a dietary supplement (21 CFR 101.14(a)(2)).

The petition identified vitamin D as the substance that is the subject of the proposed claim. The petitioner noted that vitamin D, also known as calciferol, comprises a group of fat-soluble prohormones that are obtained through diet and endogenously synthesized in the skin on exposure to sunlight. The petitioner also noted that the two relevant vitamin D secosterols are vitamin D₃, which is obtained in the diet from consumption of animal-based foods (e.g. fatty fish, fish liver oil, egg yolks, beef liver) and synthesized from 7-dehydrocholesterol in sun-exposed skin, and vitamin D₂, which is naturally present in some plant-based foods (e.g., mushrooms), but at levels that are generally too low to be contributing significantly to the diet. Vitamin D₂ and D₃ are both manufactured for addition to fortified foods (e.g., milk, yogurt, and ready-to-eat breakfast cereals) and inclusion in dietary supplements. Finally, the petitioner noted that the FDA requires or allows addition of vitamin D₂, D₃, or a combination of the two forms, as a food additive, for several foods and as a nutrient supplement.

Therefore, the agency concludes that the substance identified in the petition, vitamin D, is a component of food and meets the definition of “substance” in the health claim regulation (21 CFR 101.14(a)(2)). Unless specified, we use the term “vitamin D” to mean D₂ (ergocalciferol), D₃ (cholecalciferol) or a combination of D₂ and D₃.

B. Disease or Health-Related Condition

¹² Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson, EB 1990).

¹³ Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill, AB 1965); See also Agency for Healthcare Research and Quality, “Systems to rate the scientific evidence” (March 2002) [<http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf>], defining “consistency” as “the extent to which similar findings are reported using similar and different study designs.”

¹⁴ See *supra*, note 3.

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified multiple sclerosis (MS) as the disease or health-related condition that is the subject of the proposed claim.

MS is a chronic, inflammatory and autoimmune disease that damages the central nervous system (CNS), which is made up of the brain, spinal cord and optic nerves in the eyes. MS affects myelin, the fatty substance that surrounds and protects the nerve fibers of CNS. MS also damages the nerve cell bodies, which are found in the brain's gray matter, as well as the axons themselves in the brain, spinal cord, and optic nerve (the nerve that transmits visual information from the eye to the brain).¹⁵ When any part of the myelin or nerve cell bodies is damaged, then the brain cannot send signals through the body correctly. A person with the disease initially may experience many symptoms such as muscle weakness or spasms, blurred or double vision, tingling or numbness. Gradually, the symptoms may persist and become disabling. Once the disease process begins, it continues, and as the disease continues brain injury accumulates. The agency concludes that MS is a disease, because in this state, systems of the body are not functioning properly. Therefore, FDA concludes that the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

C. Safety Review

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

It is not necessary for FDA to make any determination about the safety of vitamin D in this letter because the agency is denying the proposed claim for lack of credible evidence, as discussed in sections II and III.

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

To date, no surrogate endpoints have been recognized for evaluating the risk of MS. The petition considers the "**Clinically Isolated Syndrome**" (CIS), such as optic neuritis (sudden partial or complete blindness in one eye) as a surrogate endpoint of disease for MS. Based on our consult with the Center for Drug Evaluation and Research (CDER)'s Division of Neurology Products (FDA, 2016 memorandum to file), CIS is not considered to be a surrogate endpoint/biomarker of MS. Instead, those with a CIS diagnosis are considered to have MS (FDA, 2016 memorandum to file). After the initial symptoms of MS (e.g., optic neuritis, spinal cord syndromes), the stage of MS is designated as CIS, which can last for years, but eventually the majority of the patients with CIS will progress to the relapsing and remitting form of MS (RRMS) (FDA, 2016,

¹⁵ National Institutes of Health (NIH), National Institute of Neurological Disorder and Stroke (NINDS), Hope Through Research [https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Multiple-Sclerosis-Hope-Through-Research#3215_2 (accessed December 5, 2017)].

memorandum to file). A patient in the CIS stage of the disease may have further symptoms that make the diagnosis more certain. This may change the stage of the disease; however, the individual is still considered to have MS since the time of the initial symptoms (FDA, 2016 memorandum to file). The course of the MS is known to be erratic. At the onset of the disease, it is difficult to predict the progression of the disease (NIH, 2017). However, the majority of the individuals with MS will have short periods of symptoms followed by long stretches of relative relief (NIH, 2017). Therefore, for the purpose of this claim, for evaluating the relationship between the intake of vitamin D and risk of MS, we only considered studies that measured the onset of MS.

The petition cited 85 publications as evidence to substantiate the relationship for the proposed claims (see Docket No. FDA-2016-Q-2646). These publications consisted of 27 review articles^{16 17}; two reports on the vitamin D dietary reference intakes (IOM, 2011a; 2011b); two studies on intake of vitamin D in the US (Bailey et al., 2010; Burgaz et al., 2007); three studies on the safety of vitamin D supplementation in MS patients (Kimball et al., 2007; Marcus et al., 2012; Smolders et al., 2010); one longitudinal study of lesions on magnetic resonance imaging (MRI) and its relation to long-term disability in MS patients (Brex et al., 2002); four studies on association of vitamin D intake and serum D (Gallagher et al., 2014; Heaney et al., 2003; Logan et al., 2013; Nelson et al., 2009); one study on the existing global prevalence of MS (Wade, 2014); one report of intake of vitamins and minerals in the US (WWEIA, 2014); one study on Epstein-Barr virus antibodies and serum vitamin D in the MS population (Salzer et al., 2013); one study on individuals with genetically lowered serum vitamin D levels and MS (Mokry et al., 2015); one report on the chemical structure of vitamin D (ChemSpider, 2015); a description of the clinical trial BENEFIT on clinicaltrials.gov website (clinicaltrials.gov); four publications on diagnostic criteria of MS (Dalton et al., 2002; McDonald et al., 2001; Polman et al., 2005, 2011); three reports on estimation and prevalence of MS globally (Multiple Sclerosis International Foundation, 2013; National MS Society, 2015; Noonan et al., 2010); one letter on statistical errors in the estimation of the recommended dietary allowance for vitamin D (Veugelers and Ekwaru, 2014); one systematic review on vitamin D intake and serum D levels (Whiting et al., 2015); and, two meta-analyses on vitamin D intake and MS risk (Duan et al., 2014; James et al., 2013). We also assessed all the publications excluded by the petition (see petition appendixes I, VI, VIII), and did not find any studies that could be evaluated as relevant credible evidence for a relationship between vitamin D and **risk of MS**.

¹⁶ Alroughani et al., 2012; Ascherio et al., 2007a, 2007b; Brownlee and Miller, 2014; Dwyer et al., 2003; Fisniku et al., 2008; Freedman, 2014; Hathcock et al., 2007; Heaney et al., 2015; Heaney and Holick, 2011; Holick, 2012; Jones, 2008; Kamm et al., 2014; Kantarci et al., 2016; Katsavos and Anagnostouli 2014; Miller, 2012; Miller et al., 2012; Morrow et al., 2010; NIH, 2011; Papadopoulos and Verkman, 2012; Pierrot-Deseilligny et al., 2012; Prietl et al., 2013; Simon et al., 2011; Smyk et al., 2013; Thacher and Clarke, 2011; Wacker and Holick, 2013; Wolpowitz and Gilcrest, 2006.

¹⁷ These reviews included various topics such as an overview of MS, CIS, and vitamin D; the role of vitamin D on MS; environmental factors such as sunlight exposure and vitamin D on MS; the role of infection on MS; drug therapy for MS; estimation of usual intakes of nutrients; safety and toxicity of vitamin D intake; general health benefits of vitamin D; overview of biomarkers of MS (the process of considering a biomarker and a list of the biomarkers' diagnostic potential); vitamin D and immune function; vitamin D and liver disease; and the association between serum vitamin D levels and MS.

In addition, the petition provided seven human intervention studies¹⁸ and 22 observational studies¹⁹ that evaluated the relationship between vitamin D and MS. We did not identify any additional studies through a literature search from which scientific conclusions could be drawn about the relationship between vitamin D intake and risk reduction of MS.

A. Assessment of Review Articles and Meta-analysis **FDA ignores Meta-analyses**

Although useful for background information, review articles and meta-analysis do not contain sufficient information on the individual studies that they reviewed and, therefore, FDA cannot draw any scientific conclusions from this information. FDA cannot determine factors such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement) from the review articles and meta-analyses. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies were flawed in critical elements such as design, conduct, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, review articles and meta-analyses supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance/disease relationships claimed by the petitioner.

B. Assessment of Intervention Studies

FDA reviewed seven interventions studies that evaluated the relationship between vitamin D intake and MS (Burton et al., 2010; Derakhshandi et al., 2013; Kampmen et al., 2012; Kimball et al., 2011; Soilu-Hanninen et al., 2012; Sotirchos et al., 2016; Stein et al., 2011).²⁰ These seven studies included individuals previously diagnosed with MS, ranging from early to late stages of the disease. Burton et al. (2010) was an open label²¹ randomized controlled vitamin D supplementation study of patients with MS. The Kimball et al. (2011) study was performed on the same subjects as Burton et al. (2010). A randomized, double blind pilot vitamin D supplementation study by Derakhshandi et al. (2013) was conducted on patients with optic neuritis. The study by Soilu-Hanninen et al. (2012) was conducted on MS patients receiving vitamin D supplements as an add-on therapy to the drug Interferon β -1b (used for treatment of MS patients). Kampman et al. (2012) and Sotirchos et al. (2016) also performed studies in MS patients receiving vitamin D supplements. A study by Stein et al. (2011) was conducted in 23 MS patients receiving high-dose vitamin D and calcium daily. Nineteen of these patients also received drugs (such as Interferon or Copaxone) for treatment of MS (Stein et al., 2011).

¹⁸ Burton et al., 2010; Derakhshandi et al., 2013; Kampman et al., 2012; Kimball et al., 2011; Soilu-Hanninen et al., 2012; Sotirchos et al., 2016; Stein et al., 2011.

¹⁹ Ascherio et al., 2014; Banwell et al., 2011; Cortese et al., 2015; Etemadifar et al., 2012; Horakova et al., 2013; Kuhle et al., 2015; Loken-Amsrud et al., 2012; Lucas et al., 2011; Mandia et al., 2014; Martinelli et al., 2013; Mirzaei et al., 2011; Mowry et al., 2010, 2012, 2015; **Munger et al., 2004**, 2006, 2011, 2014, 2016; Pierrot-Deseillingny and Souberbielle, 2013; Pihl-Jensen and Frederiksen, 2015; Ueda et al., 2014.

²⁰ In this section, significant flaws in the reports of these studies from which scientific conclusions could not be drawn are generally discussed. Such studies may have other flaws in addition to those specifically mentioned.

²¹ An open-label trial is a type of clinical trial in which both the researchers and participants know which treatment is being administered.

These seven studies evaluated the treatment effect of vitamin D intake rather than its effect on reducing the risk of MS. Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.²² These claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim. In evaluating health claim petitions for risk reduction, FDA considers evidence from studies in individuals already diagnosed with the disease only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people.²³ Given that such evidence was not available, the agency cannot draw any scientific conclusions from these studies. Therefore, scientific conclusions could not be drawn from the seven studies described above about the relationship between vitamin D intake and MS.

C. Assessment of Observational Studies

FDA evaluated a total of 22 observational studies that were submitted in the petition and investigated the association between vitamin D and MS risk. Scientific conclusions could not be drawn from these 22 observational studies for one or more of the reasons discussed below.²⁴

Fifteen of the 22 studies included individuals previously diagnosed with MS, ranging from early to late stages of the disease.²⁵ In addition, 13 of these 15 studies²⁶ and three additional observational studies (Munger et al., 2006, 2016; Ueda et al., 2014) used serum vitamin D levels as a marker of vitamin D intake evaluating its relationship with MS risk. Furthermore, we identified two observational studies that evaluated the association between serum vitamin D levels and MS risk (Munger et al., 2017; Nielsen et al., 2017).

As previously noted, this claim involves reducing the risk of a disease in people who do not already have the disease that is the subject of the claim. In evaluating health claim petitions for risk reduction, FDA considers evidence from studies in individuals already diagnosed with the disease only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. As we explained above, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people.

²² See *supra*, note 3.

²³ See *supra*, note 3.

²⁴ See *supra*, note 19.

²⁵ Ascherio et al., 2014; Banwell et al., 2011; Etemadifar et al., 2012; Horakova et al., 2013; Kuhle et al., 2015; Loken-Amsrud et al., 2012; Lucas et al., 2011; Madnia et al., 2014; Martinelli et al., 2013; Mowry et al., 2010, 2012, 2015; Munger et al., 2014; Pierrot-Deseillingny and Souberbielle, 2013; Pihl-Jensen and Frederiksen, 2015.

²⁶ Ascherio et al., 2014; Banwell et al., 2011; Etemadifar et al., 2012; Horakova et al., 2013; Kuhle et al., 2015; Loken-Amsrud 2012; Lucas et al., 2011; Madnia et al., 2014; Martinelli et al., 2013; Mowry et al., 2010, 2012, 2015; Pihl-Jensen and Frederiksen, 2015.

Given that such evidence was not available in these observational studies, the agency cannot draw any scientific conclusions from these studies.

Furthermore, although vitamin D consumption through intake of foods and supplements has an impact on the circulating level of 25OHD²⁷ (hereafter “serum vitamin D”), there are other factors that affect this serum level. The major source of vitamin D in the body is formed from activation of 7-dehydrocholesterol via exposure of the skin to ultraviolet B (Holick, 2007; IOM, 2011b). This endogenous production contributes greatly to the concentration of serum vitamin D (IOM, 2011b). Factors, such as aging, season of the year, latitude, use of sunscreen, and melanin pigmentation are reported to affect the circulating vitamin D levels (IOM, 2011b). There are other factors, such as adiposity (lower serum vitamin D levels with increased adiposity) and African American ancestry as well as other dark-skinned groups, as a result of their greater skin pigmentation (reported to have lower serum vitamin D levels) that may impact circulating vitamin D levels as well (IOM, 2011b). Therefore, serum vitamin D concentration is considered a good indicator of vitamin D status; however, it is not a valid biomarker of vitamin D intake because serum levels reflect the cumulative contributions of both exposure to sunlight and dietary intake (IOM, 2011b; FDA, 2007 (72 FR 497; January 5, 2007 proposed rule)). For this reason, scientific conclusions cannot be drawn from studies that used serum vitamin D levels as a biomarker of vitamin D intake and risk reduction of MS.

Four observational studies, explained briefly below, investigated dietary intake of vitamin D, from conventional foods and/or multi-nutrient supplements, and risk reduction of MS. There are several limitations on drawing conclusions from observational studies that estimate nutrient intake from conventional foods and/or multi-nutrient supplements, which are described below.

In observational studies that estimate nutrient intake from conventional foods, measures of vitamin D intake are based on recorded dietary intake methods, such as food frequency questionnaires (FFQ), diet recalls, or diet records, in which the type and amount of foods consumed are estimated. The vitamin D concentration values in each food consumed are then estimated from nutrient composition tables, such as the U.S Department of Agriculture (USDA) National Nutrient Database (NND) for Standard Reference (SR). The vitamin D data from nutrient composition databases are limited in number of foods with analytical data. Beginning in 2006, the USDA nutrient data laboratory started to assess and improve the vitamin D analytical methods and to better analyze samples from major food sources of vitamin D (Holden et al., 2008; USDA, 2009). Since the release of SR 22,²⁸ vitamin D concentrations, either analytical or imputed, are included for about 2,800 food items in the USDA/NND (Holden et al., 2008; USDA, 2009). However, these food composition databases still do not consider the naturally occurring 25-hydroxyvitamin D content of animal based food products (Taylor et al., 2014).

Another common weakness of observational studies is the limited ability to ascertain the actual food or nutrient intake for the population studied as a result of poor memory, over- or

²⁷ Both vitamin D from food intake and through sunlight exposure can be stored and released from fat cells. Vitamin D is transported to the liver which is then converted to 25 hydroxyvitamin D (25(OH)D). Serum 25(OH)D is the major circulating form of vitamin D and therefore is often used by clinicians to assess vitamin D status (Holick, 2007).

²⁸ The USDA has published a vitamin D addendum to their NND since the release of SR 22 in 2009 (USDA, 2009).

underestimation of portion sizes, and recall bias²⁹ (Flegal, 1999). Accurate information on amounts used in food processing is often not asked in interviews nor known by most study respondents. Also, the dietary questionnaires are not capable of measuring vitamin D intake because of the highly variable contents of food (IOM, 2011b). Factors such as variations in sunlight, seasons and climatic conditions, practices of vitamin D supplementation of animals, and animal breeds can make the vitamin D content of the food vary widely (Calvo et al., 2004; Taylor et al., 2014). Furthermore, the vitamin D content of foods may vary (e.g., due to food processing/ cooking procedures, or storage conditions (e.g., exposure to light, duration, and temperature)) (Jakobsen and Knuthsen, 2014; Schmid and Walther, 2013). Thus, it is difficult to estimate with reasonable accuracy the amount of the nutrient consumed based on reports of dietary intake from conventional foods. To accurately estimate the intake of vitamin D requires direct chemical analysis of the diet consumed, which is not done when assessing vitamin D intake in observational studies.

Conventional foods and multi-nutrient supplements contain not only vitamin D, but have additional nutrients that may be associated with the metabolism of vitamin D or the pathogenesis of the MS. Because foods and multi-nutrient supplements can consist of many nutrients and other food components, it is difficult to study the nutrient or food components in isolation (Sempos et al., 1999). See Sempos et al. (1999) and Willett (1990; 1998) regarding the complexity of identifying the relationship between a specific nutrient within a food and a disease. For studies based on recorded dietary intake of such foods or multi-nutrient supplements, it is not possible to accurately determine whether any observed effects of vitamin D on MS risk were due to: 1) vitamin D alone; 2) interactions between vitamin D and other nutrients or substances; 3) other nutrients acting alone or together; or, 4) decreased consumption of other nutrients or substances contained in foods displaced from the diet by the increased intake of vitamin D-rich foods.

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

²⁹ In case-control studies, a participant who has been diagnosed with a disease (case) may recall the foods consumed differently than a healthy individual (control).

dietary intake of conventional foods as the sole source for concluding that a relationship exists between a specific nutrient and disease risk; the effect could actually be harmful.³⁰

Therefore, observational studies conducted in conventional foods and multi-nutrient supplements do not provide credible evidence for a claim for risk reduction for a single nutrient because, in fact, the nutrient in supplement form may decrease, has no effect, or actually increase risk of the disease or health-related condition. Furthermore, no scientific conclusions about vitamin D and risk of MS may be drawn from observational studies on multi-nutrient supplements unless the multi-nutrient supplement contains no known confounders that may affect the metabolism of vitamin D or affect the pathogenesis of the disease.

The study by Cortese et al. (2015) is a Norwegian component of the multi-national case-control study,³¹ Environmental Factors In Multiple Sclerosis (EnvIMS), that evaluated the association between vitamin D supplementation through cod liver oil at different postnatal ages and risk of MS. A total of 953 MS patients with maximum disease duration of 10 years and 1,717 controls self-reported their cod liver oil use from childhood to adulthood (at ages 0-6, 7-12, 13-15, 16-18, 19-24 and 25-30 years and recent years). A significant inverse association between cod liver oil use during adolescence (ages 13-18 years) and MS risk was reported. However, no significant association of cod liver oil use and MS risk during childhood or adult life was observed. This study evaluated cod liver oil supplements that contained other nutrients, such as vitamin A and vitamin E and omega-3 fatty acids. As mentioned above, we cannot rely on observational studies that estimated vitamin D intake from multi-supplements (in this case cod liver oil) that contain other nutrients that may affect the risk of MS. The authors of this study mentioned that their findings might be due to the protective effect of other cod liver oil ingredients. Vitamins A and E, as well as omega-3 fatty acids, have become of interest as possible disease-modifying candidates of MS and a U-shaped pattern of association between serum vitamin A levels and MS

³⁰ In *Pearson v. Shalala*, the D.C. Circuit noted that FDA had “logically determined” that the consumption of a dietary supplement containing antioxidants could not be scientifically proven to reduce the risk of cancer where the existing research had examined only foods containing antioxidants as the effect of those foods on reducing the risk of cancer may have resulted from other substances in those foods (164 F.3d 650, 658 (D.C. Cir 1999)). The D.C. Circuit, however, concluded that FDA’s concern with granting antioxidant vitamins a qualified health claim could be accommodated by simply adding a prominent disclaimer noting that the evidence for such a claim was inconclusive given that the studies supporting the claim were based on foods containing other substances that might actually be responsible for reducing the risk of cancer. *Id.* The court noted that FDA did not assert that the dietary supplements at issue would “threaten consumer’s health and safety.” *Id.* at 656. There is, however, a more fundamental problem with allowing qualified health claims for nutrients in dietary supplements based solely on studies of foods containing those nutrients than the problem the D.C. Circuit held could be cured with a disclaimer. As noted above, even if the effect of the specific component of the food constituting the dietary supplement could be determined with certainty, recent scientific studies have shown that nutrients in food do not necessarily have the same beneficial effect when taken in the form of a dietary supplement. See Lichtenstein and Russell (2005). Indeed, not only have studies on single nutrient supplements established that the benefits associated with the dietary intake of certain nutrients do not materialize when the nutrients are taken as a supplement, but some of these studies have actually indicated an *increased* risk for the very disease the nutrients were predicted to prevent. *Id.* Thus, an observational study based on food provides no information from which scientific conclusions may be drawn for the single nutrient supplement.

³¹ In a case-control study, a group of cases are identified as the individuals in whom the disease of interest was diagnosed during a given year and controls are selected from individuals who do not have the disease in the same time period (*Epidemiology Beyond the Basics*, page 29 Aspen Publishers, 2000).

risk was reported in a registry-based smaller Cohort study (Cortese et al., 2015). Cortese et al. (2015) mentioned that they cannot exclude the possibility that vitamin A in cod liver oil contributed to their findings. The dose-response relationship observed between cod liver oil use during adolescence might be attributed, in part, to a protective effect of vitamin A, which increases along with vitamin D in higher doses of cod liver oil (Cortese et al., 2015). Furthermore, case control studies are often subject to methodological issues such as recall bias, which can potentially affect the validity of findings in these types of studies.³² For these reasons, we cannot draw scientific conclusions from this study.

Mirzaei et al. (2011), in a retrospective analysis of Nurses' Health Study (NHSII), investigated the association between in utero vitamin D exposures and risk of MS in the offspring during adulthood. This was measured by mothers' milk intake and other dietary vitamin D intake (food plus supplements) using FFQ, and predicted serum vitamin D during pregnancy and their daughters' risk of developing MS later in adulthood. The MS cases were identified from 35,372 nurses in NHSII, that their mothers participated in the study in 2001 (Nurses' Mothers' study). 199 MS cases were confirmed. The Nurses' Mothers' questionnaire in 2001 asked about diet and typical serving sizes for 24 food items during their entire pregnancy. Since serum vitamin D was not measured for the Nurses' Mothers, the investigators developed a prediction model, using the mothers' characteristics including factors known to influencing circulating vitamin D, as predictors of serum vitamin D levels. For the reasons discussed above, we do not consider studies that evaluate the association between estimated intakes of vitamin D from dietary sources and risk of MS as credible evidence. In addition, we do not consider the use of serum vitamin D levels as an acceptable biomarker of vitamin D intake. Based on these reasons, we cannot draw scientific conclusions from this study.

Munger et al. (2004) examined the association between dietary vitamin D intakes and risk of MS in two large cohorts of women in NHS and NHSII. There were reports of 76 cases of MS in the NHS and 97 cases in the NHSII with onset of symptoms after initiation of the study. Participants in NHS completed a FFQ in 1980, 1984, 1986, 1990 and 1994, while those in NHSII cohort completed the FFQ in 1991 and 1995. In addition, current use of dietary supplements that contained vitamin D was collected every two years; however, the dose of vitamin D supplement was not specified in the questionnaire and was assumed to be 400 IU. Supplemental vitamin D intake in this study was primarily from multi-supplements (containing other nutrients such as vitamins A, C, E, B₁, B₂, B₆, B₁₂, folate, zinc and calcium) and only a small percentage of women reported using supplements that only contained vitamin D (Munger et al., 2004). As mentioned above, studies that measure vitamin D intake from conventional food (with methods such as FFQ), and multi-nutrient supplements are not considered as credible evidence for determining a relationship between vitamin D intake and risk of MS. Furthermore, the authors of this study stated that because vitamin D intake from supplements was primarily from multivitamins, vitamin D intake was correlated with intakes of other components of the supplement. Based on these reasons, we cannot draw scientific conclusions from this study.

Munger et al. (2011) also investigated the relationship between vitamin D intake and MS risk in women that participated in NHS and NHS II during adolescence. Typical dietary intake during

³² See supra, notes 3.

adolescence (aged 13-18 years) was assessed in the NHS cohort in 1986 with a 24-item high school FFQ (HS-FFQ) and in NHSII cohort in 1998 with a supplemental 134 HS-FFQ. Women were also asked about their multivitamin use (no single supplement) as “yes/no” response and frequency of use during adolescence. For the reasons discussed above, we do not consider studies that measure vitamin D intake from conventional foods and/or multivitamin supplements appropriate for assessing a relationship between vitamin D intake and risk of MS. Based on these reasons, we cannot draw scientific conclusions from this study.

For the above reasons, FDA concludes that no scientific conclusions about the relationship between the vitamin D intake and risk of MS can be drawn from the observational studies.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of various types of studies and sample sizes), whether the body of evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,³³ and the overall consistency³⁴ of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship, and if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

As discussed in Section II, there were no intervention or observational studies from which scientific conclusions could be drawn about the relationship between the vitamin D intake and MS risk. Based on its review of the totality of publicly available scientific evidence, FDA concludes that there is no credible evidence for a relationship between intake of the vitamin D intake and reduced risk of MS.

IV. Agency’s Consideration of Disclaimers or Qualifying Language

FDA considered but rejected use of a disclaimer or qualifying language to accompany the proposed claim for consumption of Vitamin D and a reduction in the risk of multiple sclerosis. The agency concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances, where there is no credible evidence to support the claim. Adding a disclaimer or incorporating qualifying language that effectively characterizes the claim as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the message conveyed by the unsubstantiated claim. *See, e.g., In re Warner-Lambert Co.*, 86 F.T.C. 1398, 1414 (1975), *aff’d*, 562 F.2d 749 (D.C. Cir. 1977) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); *Novartis Consumer Health, Inc. v.*

³³ See *supra*, note 12.

³⁴ See *supra*, note 13.

Johnson & Johnson-Merck Consumer Pharms. Co., 290 F.3d 578, 598 (3d Cir. 2002) (“We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer.”); *Pearson v. Shalala*, 164 F.3d 650, 659 (D.C. Cir 1999) (where the weight of evidence was against the claim, FDA could rationally conclude that the disclaimer “The FDA has determined that no evidence supports this claim” would not cure the misleadingness of a claim). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim. *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir.) (per curiam) (upholding FTC order to excise “Dollar a Day” trade name as deceptive because “by its nature [it] has a decisive connotation for which any qualifying language would result in contradiction in terms.”), *cert denied*, 423 U.S. 827 (1975); *Continental Wax Corp. v. FTC*, 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States*, 169 F.2d 375 (9th Cir. 1948) (discussing “self-contradictory labels”). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g., United States v. Millpax, Inc.*, 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (disclaimer stating that “no claim is made that the product cures anything, either by the writer or the manufacturer” was ineffective where testimonials in a magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.*, 855 F. Supp. 534, 543 (D.R.I.) (“The intent and effect of the FDCA in protecting consumers from... claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing.”), *judgment amended on other grounds*, 862 F. Supp. 717 (1994).

Further, under the *Central Hudson* analytical framework, misleading commercial speech is not protected under the First Amendment.³⁵ Here, because the petitioner’s proposed claim is not supported by credible evidence, it is inherently misleading and thus not protected under the First Amendment. *See Alliance for Natural Health v. Sebelius*, 786 F. Supp. 2d 1, 17 (D.D.C. 2011) (“Claims which are not supported by credible evidence are misleading commercial speech and may be prohibited under the threshold step of the *Central Hudson* test.”).³⁶

V. Conclusions

Based on FDA’s consideration of the scientific evidence and other information submitted with your petition, FDA concludes that there is no credible evidence to support a qualified health claim for vitamin D intake and reduced risk of multiple sclerosis. Thus, FDA is denying your petition for a qualified health claim.

³⁵ Under the *Central Hudson* framework, the threshold question is whether the speech is false or inherently or actually misleading or concerns unlawful activity – such speech may be prohibited. *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 563-66 (1980). If the speech is truthful and not inherently or actually misleading, the government must establish that the regulation directly advances a substantial governmental interest and the regulation is no more extensive than necessary to serve that interest. *Id.*

³⁶ Even if the remaining prongs of the *Central Hudson* test applied, the Government clearly has a substantial interest in ensuring that consumers are not misled by false or misleading health claims that are not supported by credible evidence, and that requiring specific health claims on labels to be adequately substantiated by scientific or medical evidence directly advances the asserted governmental interest, and is no more extensive than necessary to serve that interest. *See POM Wonderful, LCC v. FTC*, 777 F.3d 478, 502 (DC Cir. 2015), *cert. denied*, 136 S. Ct. 1839 (2016) (“the injunctive order’s requirement of *some* [randomized and controlled human clinical trial] substantiation for disease claims directly advances, and is not more extensive than necessary to serve, the interest in preventing misleading commercial speech.”).

Please note that scientific information is subject to change, as are consumer consumption patterns. In the event that new information is submitted to the agency, FDA intends to evaluate it to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support the use of a qualified health claim or that will support significant scientific agreement.

Sincerely,

Douglas A. Balentine
Director
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Center for Food Safety
and Applied Nutrition

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