U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY & APPLIED NUTRITION

February 1, 2023

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RE: Petition for a Qualified Health Claim – for Cocoa Flavanols and Reduced Risk of Cardiovascular Disease (Docket No. FDA-2019-Q-0806)

Dear Mr. Serio**:**

This letter responds to the qualified health claim petition you submitted to the Food and Drug Administration (FDA or we) on behalf of Barry Callebaut AG Switzerland on November 21, 2018. The petition was submitted pursuant to section 403(r)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(4)) and in accordance with FDA's guidance on the procedures for the submission of qualified health claim petitions ("qualified health claim procedures guidance").[1] The petition requested that the agency review the use of a qualified health claim regarding the relationship between the consumption of cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate and a reduced risk of cardiovascular disease (CVD). The petitioner also submitted four supplements with additional information to support the petition, dated August 30, 2019, March 3, 2021, June 24, 2021, and November 17, 2021.

The petition proposed the following language (with updated language provided in a supplement to the petition dated August 30, 2019) for a qualified health claim to be used on the labels or labeling of conventional foods:

"Supportive but inconclusive scientific evidence suggests that consuming at least 200 mg of cocoa flavanols daily, such as provided by high flavanol cocoa powder, or high flavanol semi-sweet or high flavanol dark chocolate, may reduce the risk of cardiovascular disease. This product contains at least 200 mg cocoa flavanols per serving. See nutrition information for _____ and other nutrients."

[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 January26, 2016)].

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"Diets containing at least 200 mg of cocoa flavanols per day, such as provided by high flavanol cocoa powder, or high flavanol semi-sweet or high flavanol dark chocolate, can reduce your risk of cardiovascular disease. There is credible scientific evidence supporting this claim, although the evidence is not conclusive. This product contains at least 200 mg cocoa flavanols per serving. See nutrition information for _____ and other nutrients."

"Although the evidence is not conclusive, daily intake of at least 200 mg of cocoa flavanols, such as provided by high flavanol cocoa powder, or high flavanol semi-sweet or high flavanol dark chocolate, may reduce the risk of cardiovascular disease. This product contains at least 200 mg cocoa flavanols per serving. See nutrition information for _____ and other nutrients."

"Daily consumption of at least 200mg of cocoa flavanols per serving may reduce the risk of cardiovascular disease. FDA has determined that the evidence is supportive, but not conclusive, for this claim."

FDA filed the petition for comprehensive review on February 22, 2019 (Docket number FDA-2019-Q-0806) and posted it on the Regulations.gov website with a 60-day comment period, consistent with FDA's guidance for procedures on qualified health claims. The supplements to the petition were also filed in the docket for the petition and considered in our evaluation.

FDA received 41 comments regarding the petition. Two of the 41 comments provided a substantial discussion of the body of evidence on the relationship between high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate and reduced risk of CVD, with one of the comments agreeing that the evidence was sufficient to support a claim and the other comment arguing that the existing body of evidence was not sufficient to support a claim. One of the 41 comments, which was opposed to a qualified health claim, opposed claims for chocolate products based on safety concerns. This comment is addressed in Section I.C Safety Review later in this letter. The remaining 38 comments (seven in support and 31 opposed) were brief and did not include additional information or further evidence that would either strengthen or weaken support for the petition. We considered these comments in our evaluation of the petition.

The initial deadline for FDA to respond to the petition was October 3, 2019; however, by mutual agreement, the deadline for our response was extended to January 12, 2023. This letter sets forth the results of FDA's scientific review of the evidence for the qualified health claim requested in the petition. As explained in this letter, FDA has determined that the current evidence supports a qualified health claim concerning the relationship between cocoa flavanols in high flavanol cocoa powder and reduced risk of CVD for conventional foods. This letter also discusses the factors that FDA intends to consider in the exercise of its enforcement discretion for a qualified health claim on conventional foods with respect to the consumption of cocoa flavanols in high flavanol cocoa powder and reduced risk of CVD.

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-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 publications[8] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease

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[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 [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims].

[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.

relationship.[9] If additional studies are identified, the agency evaluates them individually. 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 supplements.[10] 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). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.[11]

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.[12]

Next, FDA rates the remaining human intervention and observational studies for methodological quality. 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 – e.g., age, smoker vs. non-smoker – 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 from which FDA cannot draw scientific conclusions cannot be used to support the health claim relationship, and therefore are eliminated from further review.[13]

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[9] Certain meta-analyses may be used as part of the health claim review process. See *supra*, note 3.
[10] Institute of Medicine (2005). Dietary Supplements: A Framework for Evaluating Safety. Chapter 7, Categories of Scientific Evidence – In Vitro Data.
[11] See *supra*, note 3.
[12] *Id.*
[13] *Id.*

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.[14] 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 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,[15] and the overall consistency[16] of the total body of evidence.[17] 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 a food, regardless of whether the food is in conventional form or a dietary supplement that includes vitamins, mineral, herbs, or other similar nutritional substances (21 CFR 101.14(a)(2)). The petition and accompanying supplements identified cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate as the substance for the proposed qualified health claim.

Cocoa powder and semi-sweet/dark chocolate are food products made from cacao beans from the cacao tree (*Theobroma cacao*). [18] Chocolate products have a long history of use dating back thousands of years in the southern part of North America. Cocoa powder, semi-sweet/dark chocolate, and other cacao products have specific standardized requirements detailed in 21 CFR 163 ("Cacao Products").

Flavanols are a natural component of cacao beans and are found in cacao products traditionally consumed in the United States. While flavanols can be found naturally in numerous food sources, they are particularly abundant in the seeds of the cacao tree, cacao beans. Flavanol content of cacao products is dependent upon the cultivar, origin, agricultural practices, and postharvest practices and processing.

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[14] *Id.*

[15] Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson EB. 1990).

[16] 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 (accessed June 27, 2022)], defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."

[17] See *supra*, note 3.

[18] While both cocoa powder and chocolate are produced from cacao beans, the processes are separate, and differences include the removal of some parts of the bean (e.g., cocoa butter) or the addition of other ingredients (e.g., sugar). See Section IV.B.2, 'Manufacturing Process' in the petition for additional information.

A supplement to the petition, dated June 24, 2021, characterized "high flavanol cocoa powder" as having at least 4% of naturally conserved cocoa flavanols and "high flavanol semi-sweet/dark chocolate" having at least 0.70% to about 2.6% of naturally conserved cocoa flavanols, wherein the cocoa flavanols are the sum of DP 1 to DP 10 according to the AOAC method of analysis for cocoa flavanols (AOAC 2012). By way of example, 10 g of cocoa powder would need to have at least 400 mg of cocoa flavanols (4% of 10 g) to be "high flavanol cocoa powder," based on the petition.

FDA concludes that cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate, the substance identified in the petition, is a component of food and meets the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)). However, as discussed further in Section III, no credible studies were identified supporting a relationship between cocoa flavanols in high flavanol semi-sweet/dark chocolate and risk reduction of CVD, and therefore, the qualified health claims for which FDA intends to exercise enforcement discretion discuss only a relationship between cocoa flavanols in high flavanol cocoa powder and risk reduction of CVD.

B. Disease or Health-Related Condition

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 CVD as the disease or health-related condition that is the subject of the proposed claim.

CVD is broad term for diseases of the heart and blood vessels. Types of CVD include conditions such as coronary heart disease (CHD), stroke, and peripheral artery disease.[19] The agency concludes that CVD is a disease and therefore 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. Furthermore, the substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other physical or technical functional effect listed in 21 CFR 170.3(o) to the food, and must retain that attribute when consumed at levels that are necessary to justify a claim (21 CFR 101.14(b)(3)(i)).

[19] https://www.nhlbi.nih.gov/sites/default/files/media/docs/Fact_Sheet_Know_Diff_Design.508_pdf.pdf.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the substance, which is either a food or an ingredient that is the source of the substance, is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA (21 CFR 101.70(f)).

As discussed in Section I.A Substance, and in the petition, cocoa, chocolate, and other cacao products have a long history of human use. The petition discussed that fermented beverages made from chocolate date back to 1900 BC in Mesoamerica and by 2016, Americans consumed nearly 18% of the world's chocolate confectionery by value. Consequently, standards of identity have been established for cacao products in 21 CFR Part 163 ("Cacao Products"). Additionally, cacao (*Theobroma cacao L.*) is included in 21 CFR 182.20 as a GRAS substance.

One comment to the petition opposed the use of a qualified health claim for the consumption of cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate and reduced risk of CVD based on concerns about heavy metal contamination in chocolate products. The concerns in the comment were related to excess levels of lead and cadmium in chocolate products collected and evaluated in a survey conducted by the commenter. Individual cacao products that may be found to be contaminated or adulterated in violation of the Act are not permitted to be sold to consumers. However, as a general category, cacao products, including cocoa and semi-sweet/dark chocolate, are permitted for manufacture and sale in the U.S. and are GRAS substances.

FDA agrees that the petition demonstrated to FDA's satisfaction that cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate is safe and lawful for use in conventional foods. Therefore, FDA concludes that under the preliminary requirements of 21 CFR 101.14(b)(3)(ii), the use of cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate at the levels necessary to justify the claim is safe and lawful.

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

The petition considers the "Flow Mediated Dilation" (FMD) to be a surrogate marker for CVD. However, FMD is not considered to be a validated surrogate endpoint or biomarker for CVD.[20] For a biomarker to be considered a valid surrogate, it should explicitly serve as a replacement for the true clinical outcome(s). FMD does not reliably predict an effect on the corresponding clinical outcome(s), since literature suggests an association, but not surrogacy, between FMD and risk of CVD.[21] Therefore, for the purposes of this review, we considered only studies that measured surrogate endpoints and/or incidence of CVD, which are identified below.

FDA has identified the following disease endpoints to use in identifying CVD risk reduction for purposes of a health claim evaluation: the incidence of coronary events (myocardial infarction, ischemia), stroke, cardiovascular death, coronary artery disease, and atherosclerosis.

[20] See "FDA, 2020 Memorandum to File (Docket No. FDA-2019-Q-0806)".
[21] *Id.*

In addition, the following surrogate endpoints have been identified by FDA for evaluating CVD risk reduction for the purposes of a health claim: blood pressure reduction[22] and validated lipid biomarker concentrations (e.g., low-density lipoprotein cholesterol (LDL-C)). These surrogate endpoints and incidence of diseases were used to evaluate the potential effects of cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate on CVD risk.

The petition cited 241 publications in the initial letter and accompanying supplements as evidence to substantiate the relationship for the proposed claim (see Docket number FDA-2019-Q-0806). Conclusions could not be drawn for 207 of these studies.[23] 34 publications evaluated the relationship between cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate and risk reduction of CVD. The 34 publications described 21 intervention studies[24] (discussed in Section II.C) and 13 individual observational studies[25] (discussed in Section II.D). The comments to the petition cited 50 additional publications and websites that were not already included in the petition or accompanying supplements or found by FDA.[26] Through a literature search, FDA also identified a total of 31 intervention studies[27] that evaluated the relationship between cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate and risk of CVD.[28]

A. Assessment of Review Articles, Systematic Reviews/Meta-Analysis, Government Reports and Other Background Materials

Although useful for background information, review articles, systematic reviews/meta-analyses, reports and guidelines from federal and international agencies and professional associations do not contain sufficient information on the individual studies reviewed and, therefore, FDA could

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[22] FDA-NIH have identified diastolic blood pressure (DBP) and systolic blood pressure (SBP) as surrogate endpoints for measuring blood pressure (FDA-N1H Biomarker Working Group- BEST. 2016) [https://www.nebi.nlimnih.gov/books/NRK453484/] (accessed June 5, 2020). Because either elevated SBP (≥ 130mm Hg) or DBP (≥ 80 mm Hg) can be used to diagnose hypertension, the reduction of either can be considered beneficial in reducing the risk of hypertension. FDA has also identified Mean Arterial Pressure (MAP) as a surrogate endpoint for predicting risk of hypertension (See "FDA, 2021 Memorandum to the File (Docket No. FDA-2016-Q-3770)"). MAP is the average arterial pressure throughout one cardiac cycle, systole, and diastole. For the purposes of this review, the agency evaluated only studies that measured SBP, DBP, or MAP.

[23] For reasons these 207 studies were excluded, see "FDA, 2022 Memorandum to the File (Docket No FDA-2019-Q-0806)".

[24] Balzer et al., 2008; Davison et al., 2008; Engler et al., 2004; Esser et al., 2004; Farouque et al., 2006; Fisher et al., 2006; Flammer et al., 2012; Grassi et al., 2005a, 2005b, 2008, 2015; Heiss et al., 2007, 2010; Mogollon et al., 2013; Monagas et al., 2009, Muniyappa et al., 2008; Njike et al., 2011; Sansone et al., 2015, 2017; Taubert et al., 2003; Wang-Polagruto et al., 2006.

[25] Buijsse et al., 2006, 2010; Djoussé et al., 2011a, 2011b; Duarte et al., 2019; Greenberg et al., 2018; Hertog et al., 1993; Ho et al., 2018; Janzsky et al., 2009; Larsson et al., 2018; Lewis et al., 2010; Mink et al., 2007; Mostofsky et al., 2000.

[26] See "FDA, 2022 Memorandum to the File (Docket No.FDA-2019-Q-0806)."

[27] Almoosawi et al., 2012; Bogaard et al., 2010; Crews et al., 2008; Davison et al., 2010; De Palma et al., 2016; Deideri et al., 2012; Desch et al., 2010; Fraga et al., 2005; Carcia Yu et al., 2020; Heiss et al., 2015; Koli et al., 2015; Leyva-Soto et al., 2016; Martinez-Lopez et al., 2014; Masrioiacovo et al., 2015; Massee et al., 2015; Neufingerl et al., 2013; Nickols-Richardson et al., 2014; Pereira et al., 2014; Rassaf et al., 2016; Ried et al., 2009; Rodriguez-Mateo et al., 2018; Rostami et al., 2015; Rull et al., 2015; Sesse et al., 2022; Shiiina et al., 2007, 2019; Sorond et al., 2013; Sudarma et al., 2011; Tabuert et al., 2007; Tzounis et al., 2011; West et al., 2014.

[28] FDA literature review was expanded to include studies on cocoa flavanols and all validated surrogate endpoints (SBP, DBP, MAP, validated lipid biomarkers) and incidence of CVD.

not draw any scientific conclusions from these sources. FDA could not determine factors such as the study population characteristics or nutrient composition of experimental diets. Similarly, the lack of detailed information on studies summarized in review articles, meta-analyses, letters, and reports prevents the agency 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. As a result, the background materials supplied by the petition and in the public comments did not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship claimed by the petitioner.

B. Assessment of Animal Studies

FDA uses animal studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease, and they can also be used to generate hypotheses or to explore a mechanism of action. However, they cannot adequately support a relationship between the substance and the disease in humans. FDA did not consider the animal studies cited with the petition as providing any supportive information about the substance-disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of CVD, nor can the studies mimic the human body's response to the consumption of cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate. Therefore, FDA could not draw any scientific conclusions regarding cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate and the reduction of risk of CVD from the animal studies cited in the petition.

C. Assessment of Intervention Studies

FDA evaluated 52 intervention studies that investigated the relationship between consumption of cocoa flavanols and risk of CVD. Seven of these intervention studies (Davison et al., 2008; Engler et al., 2004; Grassi et al., 2005a, 2005b, 2008, 2015; Sansone et al., 2015) were specifically mentioned by the petition as being the most pertinent for substantiation of a relationship between cocoa flavanols and FMD (as the petition's stated biomarker of CVD). Although as mentioned above, FMD is not an acceptable validated surrogate endpoint, all seven of these studies also reported other validated surrogate endpoints (e.g., blood pressure and/or lipid biomarkers), and therefore, we evaluated these studies as well.

Of the 52 studies, scientific conclusions could not be drawn from 50 of them, including six of the seven studies identified as pertinent studies by the petition.[29] Twenty-four studies[30,31] either did

[29] This section contains a general discussion of major flaws in the reports of intervention studies from which scientific conclusions could not be drawn. Such studies may have other flaws in addition to those specifically mentioned.

[30] Almoosawi et al., 2012; Crews et al., 2008; Engler et al., 2004; Fraga et al., 2005; Farouque et al., 2006; Flammer et al., 2012; Carcia Yu et al., 2020; Grassi et al., 2005a, 2005b, 2008; Leyva-Soto et al., 2016; Martinez-Lopez et al., 2014; Monagas et al., 2009; Nickols-Richardson et al., 2014; Njike et al., 2011; Pereira et al., 2014; Ried et al., 2009; Rostami et al., 2015; Shiiina et al., 2007; Sorond et al., 2013; Sudarma et al., 2011; Taubert et al., 2003, 2007; West et al., 2014.

[31] Three studies (Engler et al., 2004; Grassi et al., 2005b, 2008) in this group were part of the seven studies submitted by petition as most relevant for substantiation of their qualified health claim. Engler et al., 2004 reported

not provide the exact amount of flavanols in the dark chocolate and/or cocoa powder studied or did not report the cocoa flavanols (DP 1 -10) and only reported total polyphenols, which is not the substance of the qualified health claim petition. Seventeen studies[32,33] used cocoa flavanols extracts as the substance. However, the substance identified in the petition and accompanying supplements is cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate, and cocoa flavanols extracts are therefore not acceptable as a substance. In two other studies (Davison et al., 2008;[34] Wang-Polagruto et al., 2006), it was not clear whether the substance provided to participants was an extract or actual cocoa powder. Regardless, the substance in these two studies did not meet the criteria set by the petition for high flavanol cocoa powder (containing at least 4% of naturally conserved cocoa flavanols). For the reasons cited above, scientific conclusions could not be drawn from these 46 studies.

Five studies (De Palma et al., 2016; Desch et al., 2010; Esser et al., 2014;[35] Mogollon et al, 2013; Rull et al., 2015) used inappropriate controls, such as chocolate with flavanols in it. Without an appropriate control group, it cannot be determined whether changes in the endpoints of interest are due to substance intake or due to unrelated and uncontrolled extraneous factors (Spilker, 1991).[36] Thus, scientific conclusions could not be drawn from these studies.

In one randomized, cross-over study (Koli et al., 2015), the body weight of participants was decreased significantly in the control group (reduced snack without any added chocolate) compared to treatment group (reduced snack with 49 grams (g) of dark chocolate (1230 mg flavanols, degree of polymerization 1-10/100 g)) after eight weeks of intervention. We cannot determine if the reported result of the study, which was no statistically significant difference in blood pressure or other lipid parameters between groups, was due to intake of cocoa flavanols from dark chocolate or due a significant reduction in body weight in the control group ($p < 0.027$). Reduction of body weight has a lowering effect on blood pressure and lipid

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that 213 mg procyanidins and 46 mg of epicatechin was in 46 g of Dove® dark chocolate. Per the petition, the definition of high flavanol chocolate should have at least 0.7% to about 2.6% of naturally conserved cocoa flavanols (see Section I.A 'Substance"). Thus, in 46 g of Dove® dark chocolate, the flavanols (DP1 -DP10) should have been at least 322 mg (46 g x 7 =322 mg). A supplement provided by the petition on June 24, 2021, reported that Barry Callebaut performed an analysis of Dove® dark chocolate and revealed total cocoa flavanols of 230 mg. Both this amount (230 mg) analyzed by Barry Callebaut and what is reported in the article (213 mg of procyanidins) do not meet the definition of high flavanol dark chocolate for this petition. Both Grassi et al., studies (2005b and 2008) reported total polyphenols and did not report the actual flavanols (defined as DP1-DP10) content in 100 g of dark chocolate. To meet the definition of high flavanol dark chocolate (per the petition definition of the substance), the 100 g of chocolate should have provided at least 700 mg of flavanols. Per the June 24, 2021 petition supplement, the 66 mg (Grassi et al., 2005b) and 111 mg (Grassi et al., 2008) of epicatechin does not meet the definition of substance for this qualified health claim.

[32] Balzer et al., 2008; Davison et al., 2010; Deideri et al., 2012; Fisher et al., 2006; Heiss et al., 2007, 2010, 2015; Masrioiacovo et al., 2015; Massee et al., 2015; Muniyappa et al., 2008; Rassaf et al., 2016; Rodriguez-Mateo et al., 2018; Sansone et al., 2015, 2017; Sesso et al., 2022; Shiiina et al., 2019; Tzounis et al., 2011.

[33] Sansone et al., 2015 is one of the seven studies submitted as most pertinent for substantiation of this claim. The substance of this study was flavanol extract.

[34] This study was also one of the seven studies submitted by petition as most relevant for substantiation of this claim. The article did not report the actual gram amount of cocoa beverage or powder. Therefore, we could not determine if the cocoa beverage meets the definition of the substance provided by petition or not. In addition, it appears that the substance is an extract.

[35] One of the seven studies submitted by petition as most pertinent for validation of this health claim.

[36] See *supra*, note 3.

parameters.[37] Thus, no scientific conclusion can be drawn from this study.

In a randomized, double blind, parallel study of 142 healthy male and female consuming either 6 g/day of cocoa powder (containing 325 mg flavanols) or milk without any flavanols (control group) for period of four weeks (Neufingerl et al., 2013), no statistical analysis was conducted to ensure an accurate comparison of results between the control and treatment group. Statistical analysis is a critical factor in evaluating evidence for the substance-disease relationship because it provides the comparison between subjects consuming cocoa flavanols from cocoa powder and those not consuming the substance (i.e., control) to determine whether there is reduction in in CVD risk.[38] Hence, no scientific conclusion could be drawn from this study.

Consequently, scientific conclusions could not be drawn from a total of 52 studies about the relationship between intake of cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate and risk of CVD. Scientific conclusions could be drawn from two publications that evaluated the relationship between cocoa flavanols in high flavanol cocoa powder and risk of CVD. There were no studies that evaluated the relationship between cocoa flavanols in high flavanol semi-sweet/dark chocolate and risk of CVD from which scientific conclusions could be drawn.

Grassi et al. (2015) was a moderate quality randomized, double blind, controlled cross-over study in 20 Italian adults (n=11 men and n=9 women) with a mean age of 53.8 $\pm$ 8.9 years. The baseline BMI of the study subjects was 25.4 ± 2.4 Kg/m^2, and SBP and DBP were 122.9 ± 8.7 and 74.9 ± 5.6, respectively.[39] The subjects received 10 g/day of cocoa powder containing total flavanols of 0 (control group), 80, 200, 500, and 800 mg for a period of 1 week each,[40] with a 1-week washout[41] between each period. Based on the characterization of "high flavanol cocoa powder" in the petition (discussed in Section I.A Substance), levels of ≥ 400 mg of cocoa flavanols per 10 g/day of cocoa powder were eligible for our evaluation. Therefore, we only compared the results of subjects that received cocoa powder containing 500 mg and 800 mg of cocoa flavanols to subjects that received cocoa powder containing 0 mg of cocoa flavanols (control group). During the study, office, and 24-hour ambulatory blood pressure were measured at the end of each week of treatments. Office SBP and DBP significantly decreased in each 500 mg and 800 mg cocoa flavanol dosage compared to the control group ($p < 0.05$). Although 24-hour[42] SBP and DBP were measured, statistical analysis between the 500 mg or 800 mg levels and control group was not performed. Therefore, we cannot determine the impact of either 500 mg or 800 mg of cocoa flavanols versus 0 g of cocoa flavanols on 24-hour ambulatory blood

[37] DHHS, NIH/NHLBI (2013) Evidence Report- Managing overweight and obesity in adults- systematic evidence review from the Obesity Expert Panel. https://www.nhlbi.nih.gov/sites/default/files/media/docs/obesity-evidence-review.pdf.
[38] See *supra*, note 3.
[39] All reported data are mean ± standard deviation.
[40] Although the study period was one week for each intervention period plus one week of washout, the study was stopped for a period of about 13 months due to an earthquake in the area. The study was continued after 13 months with no further explanation by authors and was accepted for publication by a peer reviewed journal. Hence, we accepted this study (Section III).
[41] Wash out period is the time within a cross-over design study during which subjects do not receive an intervention. See *supra*, note 3.
[42] 24-hour blood pressure measurements provide an added advantage of allowing measurements of central tendency and variability analysis (see FDA, 2020 Memorandum to the File).

pressure.

Bogaard et al. (2010) was a moderate quality, randomized, double blind, controlled cross-over study in 42 adults (n=32 men, n=10 postmenopausal women) from the Netherlands (Amsterdam) with a mean age of 62 ± 4.5 years. The baseline BMI of the study subjects was 25.9 ± 2.4 and office SBP and DBP were 142 ± 14 and 84 ± 7.9, respectively.[43] These subjects were considered to have "high normal" blood pressure or stage 1 hypertension. Participants were assigned to receive a milk based flavanol-rich (i.e., 305 mg of flavanol) cocoa powder[44] (3.6 g/day) drink (treatment group) or milk with 0 mg of flavanols (control group) for a duration of 3 weeks each, with a two-week washout between intervention periods. The 24-hour ambulatory, day, and night SBP and DBP were measured for each group after three weeks of treatment. Comparing the treatment and control groups, the mean difference in blood pressure was not statistically significant for 24-hour, day, or night SBP and DBP.

D. Assessment of Observational Studies

FDA evaluated a total of 13 individual observational studies. Seven of these studies were submitted by the petitioner in their initial letter (Buijsse et al., 2006, 2010; Djoussé et al., 2011a, 2011b; Duarte et al., 2019; Hertog et al., 1993; Mostofsky et al., 2000). Six additional studies[45] were submitted in supplements to their petition (Greenberg et al., 2018, Ho et al., 2018,[46] Larsson et al., 2018, Lewis et al., 2010, Janzsky et al., 2009, and Mink et al., 2007). For the reasons discussed below, no scientific conclusions about the relationship between cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate and risk reduction of CVD could be drawn from any of these 13 individual studies.

Eleven[47] studies reported an estimation of habitual consumption of various forms and types of dietary chocolate and/or other cocoa containing products, rather than an exact amount of high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate consumed, while two studies (Hertog et al., 1993; Mink et al., 2007) reported total intake of polyphenols or flavonoids from other sources (e.g., vegetables, fruits, and beverages) in addition to various types of chocolate. None of these studies met the criteria of the substance set forth in the petition and accompanying supplements. Consequently, conclusions could not be drawn from these observational studies to evaluate the relationship between cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate and risk reduction of CVD.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency

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[43] See *supra*, note 37.
[44] Acticoa™ Cocoa powder (Barry Callebaut, Belgium).
[45] These six studies were submitted by petition as part of one systematic review/meta-analysis (Krittanawong et al., 2020) on March 3, 2021.
[46] The petitioner submitted this as an abstract (Ho, Y. et al. 2018 -Abstract 15879: Chocolate Consumption and Risk of Coronary Artery Disease, The Million Veteran Program. *Lifestyle and Behavioral Medicine,*). FDA obtained the published article for review.
[47] Buijsse et al., 2006, 2010; Djoussé et al., 2011a, 2011b; Duarte et al., 2019; Greenberg et al., 2018; Ho et al., 2018; Janzsky et al., 2009; Larsson et al., 2018; Lewis et al., 2010; Mostofsky et al., 2000.

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 number of studies and number of subjects per group, whether the body of scientific evidence supports a health claim relationship for the U.S. population or a target subgroup, whether study results supporting the proposed claim have been replicated,[48] and the overall consistency[49] of the total body of evidence.[50] 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, the totality of the scientific evidence for a relationship between cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate and CVD risk reduction includes two publications describing three analyses of intervention trials. Both studies included small samples sizes (20 in one study and 42 in the other) and very short duration (one week and three weeks). Furthermore, both studies were of moderate methodological quality. Neither of the studies was conducted in the U.S., with one taking place in Italy and the other in the Netherlands. One study was conducted in individuals with normal blood pressure, and one was conducted in those with "high normal" blood pressure or with stage 1 hypertension. The Grassi et al. (2015) study, which was conducted in subjects with normal blood pressure, showed a significant lowering effect of office SBP and DBP after seven-day consumption of high flavanol cocoa powder (10 g/day) containing either 500 mg or 800 mg of cocoa flavanols compared to the control group. In the Bogaard et al. (2010) study, which was conducted in subjects with "high normal" blood pressure or stage 1 hypertension, no significant lowering effect of blood pressure (either 24-hour, day, and night SBP and DBP) was observed after three weeks intake of 305 mg of cocoa flavanols (from 3.6 g/day high flavanol cocoa powder) compared to the control group. The Grassi et al. study only reported statistical analysis for office blood pressure measurement between each treatment group receiving cocoa flavanols and the control group, but not for 24-hour measurements. However, Bogaard et al. reported 24-hour, day, and night blood pressure measurements for all groups. Furthermore, the Grassi et al. study was stopped for a period of about 13 months due to earthquake in the area, but it continued with no further explanation by authors. Because the study was accepted for publication in a peer-reviewed journal, we considered the study to be credible. However, it is not clear whether this long lag in the study might have caused any disturbances in diet composition, lifestyle changes, or baseline blood pressure of the subjects between the period before the earthquake and the period after the earthquake (13 months later). The consistency and replications of the findings among similar and different study designs is important for evaluating the strength of the evidence.[51] Lack of consistency among studies evaluating the same substance-disease relationship weakens the strength of the evidence.

Due to a very small number of credible studies with a moderate methodological quality, the small number of subjects and short duration of the studies, the location of the studies outside of

[48] See *supra*, note 15.
[49] See *supra*, note 16.
[50] See *supra*, note 3.
[51] See *supra*, notes 3, 15, 16.

the U.S., and most importantly, the lack of replication and inconsistency in the results of these two studies, FDA determines that there is very limited credible evidence for a relationship between the consumption of cocoa flavanols in high flavanol cocoa powder and risk reduction of CVD.

Although the petition requested claims that included cocoa flavanols in high flavanol semi-sweet/dark chocolate, the two credible studies only evaluated cocoa flavanols in high flavanol cocoa powder. A determination about cocoa flavanols in high flavanol semi-sweet/dark chocolate cannot be made based on the information from these studies. Credible studies that specifically evaluate the relationship between the consumption of cocoa flavanols in high flavanol semi-sweet/dark chocolate and risk reduction of CVD are necessary to draw conclusions. This data is especially important because semi-sweet/dark chocolate has much higher levels of calories, total fat, and saturated fat than cocoa powder, which could influence the effects on CVD risk.

The claims in the petition discuss a relationship between consumption of 200 mg of cocoa flavanols daily and reduced risk of CVD. The credible scientific evidence for this relationship, which is very limited, does not support the establishment of a daily intake of 200 mg of cocoa flavanols or any other daily dietary intake recommendation levels for the general U.S. population (see Section IV.A).

Based on FDA's review of the strength of the total body of scientific evidence for the proposed claims, the agency has determined that qualifying language should be included to convey the limits on the strength of the scientific evidence supporting the relationship. FDA thus intends to consider the exercise of its enforcement discretion for a qualified health claim, about cocoa flavanols in high flavanol cocoa powder and risk reduction of CVD, on the label or in the labeling of qualified products that includes a truthful and non-misleading description of the strength of the body of scientific evidence, i.e., "very limited." Such a description is truthful and not misleading because, while the evidence provides support for the claimed relationship, the evidence is very limited.

Based on the above, FDA concludes that there is very limited credible evidence for a relationship between cocoa flavanols in high flavanol cocoa powder and risk reduction of CVD.

IV. Other Enforcement Discretion Factors

A qualified health claim on the label or in the labeling of conventional foods about consumption of cocoa flavanols in high flavanol cocoa powder and reduced risk of CVD, for which FDA intends to consider the exercise of its enforcement discretion, is required to meet all applicable statutory and regulatory requirements under the Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard, and the requirement that the claim be made in accordance with an authorizing regulation.

Other exceptions to the general requirements for qualified health claims are discussed below, as well as enforcement discretion factors specific to qualified health claims about consumption of cocoa flavanols in high flavanol cocoa powder and reduced risk of CVD. High flavanol cocoa

powder can also be used as an ingredient in foods. The petition identified foods that could have high flavanol cocoa powder as an ingredient, including beverages, cereals, cereal bars and bakery products, such as biscuits, bread, and cake. Factors in the exercise of enforcement discretion for use of the qualified health claims in foods containing high flavanol cocoa powder are also described in the following sections.

A. Qualifying Level of High Flavanol Cocoa Powder to Achieve the Claimed Effect

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for "high" has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (21 CFR 101.14(d)(2)(vii)). The agency finds that this provision cannot be applied to qualified health claims about consumption of cocoa flavanols in high flavanol cocoa powder and reduced risk of CVD. As discussed in Section III, the scientific evidence for this relationship, which is very limited, does not support the establishment of a recommended daily dietary intake level for the general U.S. population. However, limiting our consideration of enforcement discretion to products that contain cocoa flavanols in high flavanol cocoa powder in amounts that have been observed to reduce the risk of CVD in at least some well-conducted scientific studies will help ensure that consumers do not see the claim on products that contain so little of the substance that such products would be very unlikely to provide any health benefit.

As discussed in Section I.A Substance, the petition and accompanying supplements characterized high flavanol cocoa powder as having at least 4% of naturally conserved cocoa flavanols. The RACC for cocoa powder is one tablespoon, which is approximately 5 to 6 g of cocoa powder.[52] Therefore, according to the petition, the amount of cocoa flavanols that would be present in high flavanol cocoa powder is at least 4% of 5g cocoa powder, which would equal 200 mg per RACC. The credible study with positive results supporting the relationship between high flavanol cocoa powder and risk reduction of CVD, Grassi et al., (2015), evaluated levels of cocoa flavanols in cocoa powder at the 4% level. The study evaluated cocoa flavanol levels of 500 mg and 800 mg per 10 g cocoa powder.

Based on the petition and the credible study with positive results supporting the relationship between high flavanol cocoa powder and risk reduction of CVD, high flavanol cocoa powder that bears the claim must have at least 4% of naturally conserved cocoa flavanols and contain at least 200 mg cocoa flavanols per RACC.

Because the petition characterized the substance of this qualified health claim as cocoa flavanols in high flavanol cocoa powder or high flavanol semi-sweet/dark chocolate, and no credible studies were identified supporting a relationship between cocoa flavanols in high flavanol semi-sweet/dark chocolate and risk reduction of CVD, the qualified health claims for which FDA intends to exercise enforcement discretion only discuss a relationship between high flavanol cocoa powder and risk reduction of CVD. To be eligible for the claim, foods containing high

[52] See, for example, USDA, Food Data Central, "Cocoa, dry powder, unsweetened" (https://fdc.nal.usda.gov/fdc-app.html#/food-details/169593/nutrients).

flavanol cocoa powder as an ingredient would similarly need to include at least one tablespoon (5-6 g) of high flavanol cocoa powder, which includes 200 mg of cocoa flavanols per RACC. For example, a brownie, which has a RACC of 40g, would need to contain at least one tablespoon (5-6 g) of high flavanol cocoa powder per RACC as an ingredient, as well as meeting all other health claim requirements, such as not exceeding the disqualifying nutrient levels and containing the required minimum nutrient content amount, in order to bear the claim.

B. Total Fat, Saturated Fat, and Cholesterol Criteria for CVD-Related Health Claims

In regulations authorizing CVD-related health claims, FDA has generally required, with a few exceptions, that foods bearing the claims be low in fat as defined by 21 CFR 101.62(b)(2), low in saturated fat as defined by 21 CFR 101.62(c)(2), and low in cholesterol as defined by 21 CFR 101.62(d)(2) (see authorized claims in 21 CFR §§ 101.75, 101.77, 101.81, 101.82, and 101.83). In addition, most currently authorized CVD-related health claims require that the food meet the definition of a "low fat" food (21 CFR 101.62(b)(2) (see authorized claims in 21 CFR sections 101.77, 101.81, 101.82, and 101.83). With a RACC of one tablespoon (5 to 6 g), cocoa powder meets the definition of "low fat," "low saturated fat," and "low cholesterol." Therefore, FDA intends to consider the exercise of enforcement discretion for cocoa powder bearing the claim if it meets the "low fat," "low saturated fat," and "low cholesterol" definitions.

Similarly, foods containing high flavanol cocoa powder will be expected to meet the "low fat," "low saturated fat," and the "low cholesterol" definitions. Certain types of foods that may include high flavanol cocoa powder, especially bakery products, often have levels of total fat, saturated fat, and cholesterol that disqualify them from being low fat, low saturated fat, and low cholesterol foods. The credible study with positive results (Grassi et al., 2015) supporting the relationship between high flavanol cocoa powder and risk reduction of CVD did not evaluate high flavanol cocoa powder in different types of foods, with the exception of mixing the high flavanol cocoa powder in water to make a beverage. We are therefore unable to determine whether the cocoa flavanols in high flavanol cocoa powder would have the same effects on risk of CVD when consumed as an ingredient in various food products where the levels of total fat, saturated fat, and cholesterol exceed "low" levels. Therefore, FDA intends to consider the exercise of enforcement discretion for foods containing high flavanol cocoa powder that meet the "low fat," "low saturated fat," and "low cholesterol" definitions.

C. Disqualifying Nutrient Levels

Under the general requirements for health claims, a food may not bear a health claim if the food exceeds any of the qualifying levels for total fat, saturated fat, cholesterol, or sodium content (21 CFR 101.14(e)(3)). For individual foods, the disqualifying nutrient levels are 13 g of total fat, 4 g of saturated fat, 60 mg of cholesterol and 480 mg of sodium per RACC, per label serving size, and per 50 g if the RACC is 30 g or less or 2 tablespoons or less (21 CFR 101.14(a)(4)). Cocoa powder does not exceed the disqualifying nutrient levels for total fat, saturated fat, cholesterol, and sodium per RACC, per label serving size, and per 50 g. Therefore, FDA intends to consider the exercise of enforcement discretion for high flavanol cocoa powder bearing the claim that does not exceed the disqualifying nutrient levels. FDA also intends to consider the exercise of enforcement discretion for foods containing high flavanol cocoa powder that do not

exceed the disqualifying nutrient levels.

D. 10 Percent Minimum Nutrient Content Requirement

Under the general requirements for health claims, a conventional food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10 percent of the Daily Value (DV) for vitamin A, vitamin C, iron, calcium, protein, or dietary fiber per RACC (see 21 CFR 101.14(e)(6)). The purpose of this provision is to prevent the use of health claims on foods with minimal nutritional value.

FDA has previously exempted certain foods from the 10 percent minimum nutrient content requirement when it has determined that such exemptions could assist consumers in maintaining healthy dietary practices. For example, we considered a qualified health claim for walnuts and a reduced risk of CHD even though walnuts did not meet the 10 percent minimum nutrient content requirement.[53] We also allowed authorized health claims for dietary noncariogenic carbohydrate sweeteners and dental caries (21 CFR 101.80) and for plant sterol/stanol esters and risk of coronary heart disease (21 CFR 101.83) for certain foods that did not meet the 10 percent minimum nutrient content requirement of 21 CFR 101.14(e)(6).

While cocoa powder is comprised proportionately of a high percentage of protein and fiber, the small RACC size makes it difficult for cocoa powder to meet the 10 percent minimum nutrient content requirement. However, we have determined that there is credible evidence to support qualified health claims for reduced risk of CVD, and the use of the claims may provide consumers with information about the potential health benefits of consumption of cocoa flavanols in high flavanol cocoa powder. If FDA did impose the 10 percent minimum nutrient content requirement, it would prevent cocoa powder from bearing the qualified health claims. Therefore, for the purposes of these qualified health claims, the agency intends to consider the exercise of its enforcement discretion with respect to 21 CFR 101.14(e)(6) for qualified health claims in the labeling of high flavanol cocoa powders that do not meet the 10 percent minimum content requirement.

In contrast, the RACC sizes for foods containing high flavanol cocoa powder (e.g., cereals, bakery products, etc.) are much larger than the RACC for cocoa powder, which may allow for the specific nutrients in 21 CFR 101.14(e)(6) to meet the 10 percent minimum content requirement. Additionally, the credible study with positive results supporting the relationship between high flavanol cocoa powder and risk reduction of CVD did not evaluate high flavanol cocoa powder in different types of foods. Therefore, we do not have information to determine that foods containing high flavanol cocoa powder should be able to bear the claim when the minimum nutrient requirement is not met. We conclude that it is appropriate for foods containing high flavanol cocoa powder to meet the 10 percent minimum nutrient content requirement. Therefore, FDA intends to consider the exercise of enforcement discretion for foods containing high flavanol cocoa powder bearing the claim that contain at least 10 percent of the Daily Value for vitamin A, vitamin C, iron, calcium, protein, or dietary fiber per RACC.

[53] http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072910.htm.

V. Conclusions

Based on FDA's consideration of the scientific evidence submitted with the petition and other pertinent scientific evidence, FDA concludes that there is very limited credible scientific evidence for a qualified health claim for cocoa flavanols in high flavanol cocoa powder and risk reduction of CVD, provided that the qualified claim is appropriately worded so as not to mislead consumers.

All of the claims proposed by the petition describe the level of evidence supporting them as "supportive but not conclusive" or "not conclusive." Qualifying language will inform consumers about the level of science supporting the claim and prevent them from being misled about the strength of the supporting evidence. However, describing the level of evidence supporting the claim that consumption of cocoa flavanols in high flavanol cocoa powder reduces risk of CVD as "supportive but not conclusive" or "not conclusive" is not accurate. These terms overstate and therefore mischaracterize the strength of the evidence of a relationship between cocoa flavanols in high flavanol cocoa powder and reduced risk of CVD. As discussed in Section III of this letter, the evidence suggesting that consumption of cocoa flavanols in high flavanol cocoa powder may reduce the risk of CVD is very limited due to a very small number of credible studies with a moderate methodological quality, the small number of subjects and short duration of the studies, the location of the studies outside of the U.S., and most importantly, the lack of replication and inconsistency in the results of these two studies.

All of the proposed claims discuss a relationship between consumption of 200 mg of cocoa flavanols daily and reduced risk of CVD. However, as discussed in Section IV.A, the credible scientific evidence for this relationship, which is very limited, does not support the establishment of a recommended daily dietary intake level for the general U.S. population.

Most of the petition's proposed claims discuss a relationship between cocoa flavanols in high flavanol semi-sweet/dark chocolate and reduced risk of CVD. However, there were no credible studies from which we could draw any conclusions on a relationship between cocoa flavanols in high flavanol semi-sweet/dark chocolate and risk reduction of CVD (see Sections II and III). The two studies from which conclusions could be drawn only evaluated the relationship between cocoa flavanols in high flavanol cocoa powder and reduced risk of CVD (see Section III). Credible studies that specifically evaluate the relationship between the consumption of cocoa flavanols in high flavanol semi-sweet/dark chocolate and risk reduction of CVD are necessary to draw conclusions. This data is especially important because semi-sweet/dark chocolate has much higher levels of calories, total fat, and saturated fat than cocoa powder, which could influence the effects on CVD risk.

Thus, FDA intends to consider exercising its enforcement discretion for the following qualified health claims:

"Cocoa flavanols in high flavanol cocoa powder may reduce the risk of cardiovascular disease, although FDA has concluded that there is very limited scientific evidence for this claim."

"Cocoa flavanols in high flavanol cocoa powder may reduce the risk of cardiovascular disease. FDA has concluded that there is very limited scientific evidence for this claim."

"Very limited scientific evidence suggests that consuming cocoa flavanols in high flavanol cocoa powder, which contains at least 4% of naturally conserved cocoa flavanols, may reduce the risk of cardiovascular disease."

"Very limited scientific evidence suggests that consuming cocoa flavanols in high flavanol cocoa powder, which contains at least 4% of naturally conserved cocoa flavanols, may reduce the risk of cardiovascular disease. This product contains at least 4% of naturally conserved cocoa flavanols. See nutrition information for_____ and other nutrients."

FDA intends to consider exercising its enforcement discretion for the above qualified health claims when all factors for enforcement discretion identified in Section IV of this letter are met.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement, that will no longer support the use of the above qualified health claims, or that may raise safety concerns about the substances that are the subject of the claims.

Sincerely,

Claudine J. Kavanaugh -S

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