July 21, 2020

Ms. Sarah Roller
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Washington, DC 20007

RE: Health Claim Petition – Consumption of Cranberry Products and Reduced Risk of Recurrent Urinary Tract Infection in Healthy Women
(Docket No. FDA-2018-Q-0739)

Dear Ms. Roller:

This letter responds to the health claim petition dated September 8, 2017, submitted to the Food and Drug Administration (FDA or the agency) on behalf of Ocean Spray Cranberries, Inc. pursuant to section 403(r)(4) and section 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 regarding the relationship between the consumption of cranberry products and the reduced risk of recurrent urinary tract infection in healthy women.

The petition proposed the following language for an authorized health claim for conventional food and dietary supplement cranberry products:

"By consuming one serving of cranberry products each day, like [X amount of this identified cranberry product], healthy women who have had a urinary tract infection (UTI) may reduce their risk of recurrent UTI."

"Consuming one serving of cranberry products each day, like an [X amount of this identified cranberry product], may help prevent recurrent urinary tract infection (UTI) in healthy women."

"Consuming one serving of a food containing cranberries or cranberry juice each day, like an [X amount serving of this identified cranberry product] may help prevent recurrent urinary tract infection (UTI) in healthy women."

FDA sent you a letter dated September 22, 2017, in which we requested confirmation that all nonclinical laboratory trials relied upon in your petition, as well as all clinical or other human investigations relied upon, were conducted in accordance with our current regulations with respect to either good laboratory practice regulations or to requirements for institutional review boards (21 CFR 101.70(c) and (d)). You responded in a letter dated October 4, 2017 by

providing a supplement to your petition in which you confirmed that all relevant regulations had been followed.

FDA then contacted you by telephone on December 12, 2017 to discuss the status of your petition, at which time you agreed to a 60-day extension for FDA to file your petition.

FDA evaluated the scientific evidence provided with the petition and other evidence related to your claim. Based on our review, FDA determined that the scientific evidence supporting the proposed health claim did not meet the "significant scientific agreement" standard necessary to bear a health claim. FDA notified you of this decision in a telephone conversation held on February 13, 2018, at which time you agreed to have your petition evaluated as a qualified health claim petition rather than as an authorized health claim petition. As a follow-up to this conversation, you sent us an email message dated February 16, 2018 confirming your intention to have FDA review your petition as a qualified health claim petition.

FDA filed the petition on February 20, 2018 for comprehensive review 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 eleven comments on this petition: four of the comments expressed support for the petition's qualified health claim, six comments were opposed to the petition, and one comment was neutral. FDA considered all eleven comments, as well as the references that were submitted as attachments to some of the comments, in its evaluation of the petition.

Comments in support of the petition cited evidence from clinical trials that showed beneficial effects of cranberry products (i.e., juice and dietary supplements) on reducing the risk of UTIs. Some of the comments supporting the petition emphasized the advantage of using a natural, non-pharmacological approach such as cranberry consumption, rather than a drug, for reducing the risk of UTIs. A comment opposed to the petition suggested that the proposed qualified health claim could be "dangerous" because it might discourage patients from otherwise seeking timely and appropriate medical treatment for their UTIs. Another comment expressed concerns that consumption of sweetened cranberry products such as cranberry juice cocktail would increase the dietary intake of added sugars, possibly leading to weight gain and an increased risk of chronic diseases.

This letter sets forth the basis of FDA's determination that the current scientific evidence regarding the relationship between cranberry and recurrent UTI is appropriate for consideration of a qualified health claim on conventional foods and dietary supplements. In addition, this letter sets forth (in the "Conclusions" section) qualified health claim language for which FDA intends to exercise enforcement discretion. This letter also sets forth the factors that FDA intends to

[1] See FDA "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003). [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-interim-procedures-qualified-health-claims-labeling-conventional-human-food-and (accessed March 31, 2020)]

consider in the exercise of its enforcement discretion for a qualified health claim with respect to the consumption of cranberry products and a reduced risk of recurrent UTI in healthy women.

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 United States population, or an identified United States 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

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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 (accessed August 16, 2019)]

[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.

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 relationship. 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 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; National Research Council (NRC), 2011). 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. 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 United States 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

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

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.[9] 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 United States population or target subgroup, whether study results supporting the proposed claim have been replicated,[10] and the overall consistency[11] of the total body of evidence.[12] 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 a dietary supplement (21 CFR 101.14(a)(2)).

The petition identified "cranberry" as the substance that is the subject of the proposed claim and defined it to include both the whole cranberry fruit (*Vaccinium macrocarpon*) and the juice of the cranberry fruit. The petition further explained that "cranberry" includes forms of the fruit and juice that vary in moisture content (water may be removed through concentration, dehydration, drying or other processing methods), which allows the substance to be used in a variety of conventional foods and dietary supplement products. We note that none of the studies described in the petition used the whole cranberry fruit, dried cranberries, cranberry sauce, cranberry-containing cereals or baked products, or any other conventional foods that contain cranberries in the experimental group.

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[9] See *supra*, note 3 [Section III.F].

[10] Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990).

[11] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B., The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300); 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."

[12] See *supra*, note 3 [Section III.F].

The petition defined "cranberry product" as a conventional food or dietary supplement product that contains adequate amounts of the "cranberry" ingredient(s) to be eligible to bear the health claim on a per serving basis. As summarized in Table I (Scope of "Cranberry" Substance) in section IV.A.1. (Petition at page 20), the petitioners explained that the cranberry substance can exist in the form of whole cranberry fruit (including fresh, frozen, dried, and powdered) or as cranberry juice (including 100% cranberry juice expressed or extracted from cranberries, cranberry juice concentrate, enriched cranberry juice, or powdered cranberry juice).

The petition noted that the various forms of cranberries – including fresh whole cranberries, dried cranberries, expressed and reconstituted cranberry juice, cranberry juice concentrate, and dehydrated and powdered forms of whole cranberries and cranberry juice – all qualify as a "food" within the meaning of section 201(f) or 201(ff) of the Act. Cranberries as a food have a long and established history of use. The petition also noted that most harvested cranberries are used in beverages (mainly cranberry juice cocktails[13]), sauces, or processed into sweetened dried cranberries. Cranberries also are used in various forms of dietary supplements (e.g., capsules, tablets, soft gels, and powders) which are regulated as foods by the FDA. FDA agrees with these statements about cranberries, and therefore concludes that "cranberry" and "cranberry products," the substances identified in the petition, meet the definition of a substance in the health claim regulation (21 CFR 101.14(a)(2)). However, we note that all of the studies identified in this petition that evaluated the reduction in risk of UTI among healthy women with recurrent UTI used either a cranberry juice beverage or a cranberry dietary supplement.

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 dysfunction (21 CFR 101.14(a)(5)). The petition has identified recurrent urinary tract infection as the disease or health-related condition that is the subject of the proposed claim. The agency concludes that recurrent urinary tract infection is a disease and therefore the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5) (U.S. FDA CDER, 2018)[14].

[13] FDA considers the terms "cranberry juice cocktail," "cranberry juice drink," and "cranberry juice beverage" to be equally appropriate and acceptable terms for describing a cranberry juice beverage that contains less than 100 percent and more than 0 percent cranberry juice. According to 21 CFR 102.33(a), the common or usual name for a carbonated or noncarbonated beverage that contains less than 100 percent and more than 0 percent fruit or vegetable juice shall be a descriptive name that meets the requirements of 21 CFR 102.5(a) and, if the common or usual name uses the word "juice," shall include a qualifying term such as "beverage," "cocktail," or "drink" appropriate to advise the consumer that the product is less than 100 percent juice (e.g., "diluted grape juice beverage" or "grape juice drink").

[14] U.S. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Office of New Drugs OND), Division of Anti-Infective Products (DAIP). Memorandum on the scientific/clinical rationales for the definition, diagnosis and management of urinary tract infections (UTI) and recurrent UTIs. February 2018.

C. Safety Review

Under 21 CFR 101.14(b)(3)(i), if the substance is to be consumed at other than decreased dietary levels, 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 technical 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. 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 (21 CFR 101.14(b)(3)(ii)).

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)). Dietary ingredients[15] in dietary supplements are not subject to the food additive provisions of the Act (see section 201(s)(6) of the Act (21 U.S.C. § 321(s)(6)). Rather, they are subject to the adulteration provisions in section 402 of the Act (21 U.S.C. 342). The applicable adulteration provisions of the Act require, for example, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the Act (21 U.S.C. 342(f)(1)(A))). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (section 402(f)(1)(D) of the Act (21 U.S.C. 342(f)(1)(D))). Dietary ingredients that were not marketed in the United States before October 15, 1994, are also subject to the new dietary ingredient requirements in section 413 of the Act (21 U.S.C. 350b) and the corresponding adulteration provision in section 402(f)(1)(B) of the Act (21 U.S.C. 342(f)(1)(B)).

The petition noted that both whole cranberry fruit and cranberry juice have commonly been used in the United States before January 1, 1958, and are GRAS based on longstanding experience and use as foods. The longstanding history of cranberry use in food includes both whole cranberry fruit and cranberry juice in various forms (e.g., fresh, frozen, heat processed, concentrated, dried/dehydrated). Cranberry fruit and cranberry juice provide nutritive value in the diet by providing vitamin C and several minerals, thereby meeting the requirements in 21 CFR 101.14(b)(3)(i). The definition of "nutritive value" means "a value sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or

[15] The term "dietary ingredient" is defined in section 201(ff)(1) of the Act (21 U.S.C. 321(ff)(1)) and includes vitamins; minerals; herbs and other botanicals; dietary substances for use by man to supplement the diet by increasing the total daily intake; and concentrates, metabolites, constituents, extracts, and combinations of the preceding types of ingredients.

providing energy" (21 CFR 101.14(a)(3))." The petition also noted that substances such as powdered whole cranberries have been used as dietary ingredients in dietary supplements before October 15, 1994 (§ 413 (21 U.S.C. § 350b of the Act)). FDA is not aware of any substantive safety issues that have been identified with respect to consumption of cranberries or cranberry products.

FDA agrees that whole cranberry fruit and cranberry juice are GRAS, and that powdered whole cranberries are safe and lawful for use in dietary supplements. Therefore, FDA concludes that under the preliminary requirements of 21 CFR 101.14(b)(3)(i) and (ii) the petitioner has demonstrated to FDA's satisfaction that the use of cranberry and cranberry products in conventional foods and dietary supplements is safe and lawful.

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

FDA has identified "incidence of urinary tract infection" as the disease endpoint for evaluating the potential effect of cranberry and/or cranberry products on recurrent UTI risk reduction in healthy women with a history of UTI.

The petition cited 96 unduplicated publications[16] as evidence to substantiate the relationship for the proposed claim (see Docket No. FDA-2018-Q-0739), which included 13 intervention studies[17] that evaluated the relationship between cranberry consumption and risk of recurrent UTI. In addition, the petition cited 12 review articles,[18] three meta-analyses,[19] 14 *in vitro* studies,[20] four *ex vivo* studies,[21] three animal studies,[22] four documents from government agencies,[23] and one report in a foreign language.[24] The remaining 42 publications did not evaluate the substance-disease relationship.[25] We identified one meta-analysis article through a literature search that evaluated the relationship between cranberry consumption and risk of

[16] The petition cited 53 references in Appendix A, one reference in Appendix B, and 64 references in Appendix C. There were 22 duplicated references that were cited in both Appendices, A and C.
[17] Barbosa-Cesnik et al., 2011; Di Martino et al., 2006; Kontiokari et al., 2001; Lavigne et al., 2011; Maki et al., 2016; Mathison et al., 2014; Sengupta et al., 2011; Stapleton et al., 2012; Stothers, 2002; Takahashi et al., 2013; Valentova et al., 2007; Vostalova et al., 2015; Walker et al., 1997.
[18] Flores-Mireles et al., 2015; Howell et al., 2007; Jepson et al., 2004, 2007, 2008, 2012; Liska et al., 2016; Micali et al., 2014; Pappas et al., 2009; Schnarr and Smaill 2008; Vasileiou et al., 2013; Wang 2013.
[19] Beerepoot et al., 2013; Luis et al., 2017; Wang et al., 2012.
[20] de Llano et al., 2015; Denis et al., 2015; Foo et al., 2000; Greenberg et al., 2005; Hidalgo et al., 2011; Huang et al., 2009; Johnson-White et al., 2006; Lavigne et al., 2008; Lutay et al., 2013; Martin et al., 2015; Pinzon-Arango et al., 2009, 2011; Rosen et al., 2007; Sun et al., 2015.
[21] Howell and Foxman 2002; Howell et al., 2010, 2015; Kaspar et al., 2015.
[22] Glisan et al., 2016; Hannan et al., 2010, 2014.
[23] CDC National Health Statistics Reports, August 2010; CDC Vital Statistics and Health Statistics, April 2011; Dietary Guidelines for Americans 2015-2020; FDA Guidance on Scientific Evaluation of Health Claims, 2009.
[24] ANSES, 2011.
[25] Kahlmeter et al., 2015; Schito et al., 2009; Zhanel et al., 2006; Gu et al., 2004; Harnly et al., 2006; Howell et al., 2005; Vinson et al., 2001; White et al., 2011; de Pascual-Teresa et al., 1998; Prior et al., 2010; Reed et al., 2005; Slinkard and Singleton 1977; Kimble et al., 2014; Duffey and Sutherland 2013, 2015; Monk et al., 2016; Novotny et al., 2015; Sebastian et al., 2017; Wing et al., 2010; Epp et al., 2010; Foxman, 1990; Ikaheimo et al., 199; Cai et al., 2012; Kaas, 1957, 1960; Romero et al., 1989; Oxford Encyclopedia of Food and Drink in America, 2013; Whitman-

recurrent UTI in healthy women with a history of UTI (Fu et al., 2017). This meta-analysis article was not included in the current health claim evaluation for the reasons described in this section (Section II. A).

A. Assessment of Review Articles, Meta-analysis, and Other Background Materials

"Background materials" here refers to review articles, meta-analyses, reports from federal agencies and other articles that provides background information on cranberry and UTI. Although useful for background information and identifying additional studies, these materials do not contain sufficient information on the individual studies reviewed and, therefore, FDA could not draw any scientific conclusions regarding the substance-disease relationship from this information. FDA could not determine factors such as the study population characteristics or the nutrient composition of the products used (e.g., food, dietary supplement). 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. As a result, the background materials supplied by the petitioner and through comments submitted to this petition did not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship claimed by the petitioner.

B. Assessment of *In Vitro, Ex Vivo,* and Animal Studies

FDA uses *in vitro, ex vivo,* and animal studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. They can also be used to generate hypotheses, investigate biological plausibility of hypotheses, or to explore a mechanism of action. However, these types of studies cannot adequately support a relationship between the substance and disease in humans. FDA did not consider the *in vitro, ex vivo,* or 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 UTI, nor can the studies mimic the human body's response to the consumption of cranberry. Therefore, FDA could not draw any scientific conclusions regarding cranberry consumption and the reduction of risk of UTI from the *in vitro, ex vivo,* and animal studies cited in the petition.

C. Assessment of Intervention Studies

FDA evaluated eight scientific publications describing nine intervention studies that evaluated the relationship between cranberry consumption and risk of recurrent UTI in healthy women with a history of UTI. The effect of cranberry juice beverage was reported in six publications (Barbosa-Cesnik et al., 2011; Kontiokari et al., 2001; Maki et al., 2016; Stapleton et al., 2012;

Salkin, 2013; Bent et al., 2002; Colgan and Williams 2011; Dason et al., 2011; Foxman and Brown 2003; Grabe et al., 2013; Gupta et al., 2011; Heytens et al., 2017; Hooton et al., 2013; Mabeck 1972; Nicolle et al., 2005; O'Brien et al., 2016; Vidal et al., 2015; Scottish Intercollegiate Guidelines Network (SIGN), 2012; Mayo Clinic 2016.

Stothers, 2002; Takahashi et al., 2013), while the effect of cranberry dietary supplement was reported in three publications (Stothers, 2002; Vostalova et al., 2015; Walker et al., 1997). One scientific publication (Stothers, 2002) reported the effect of both, cranberry juice beverage and cranberry dietary supplement, on the risk of recurrent UTI. Scientific conclusions could not be drawn from one publication (Kontiokari et al., 2001) since the study did not evaluate the independent effect of cranberry on recurrent UTI risk.[26] Therefore, for the purpose of a qualified health claim, we evaluated seven publications reporting on eight intervention studies (five intervention studies on cranberry juice beverage and three intervention studies on cranberry dietary supplement) from which scientific conclusions could be drawn on the relationship between cranberry consumption and risk of recurrent UTI in healthy women with a history of UTI. These studies are discussed below.

Cranberry Juice Beverages

Stothers, 2002 conducted a 12-month randomized, double-blind, placebo-controlled parallel design study of high methodological quality to investigate the effect of a cranberry juice beverage and cranberry dietary supplement[27] on recurrent UTI among healthy women with a history of UTI.[28] Women enrolled in the study were sexually active, aged 21-72 years old (mean age of 42 years old), and they were randomly assigned to either the cranberry (n = 50) or placebo (n = 50) group.[29] No statistically significant differences were observed in the number of UTIs in the preceding year between the cranberry (mean: 3.3 UTIs) and placebo (mean: 3.5 UTIs) groups ($P > 0.05$). In the cranberry group, subjects took a placebo tablet twice a day, and 250 mL of pure unsweetened cranberry juice beverage (at least 1:30 parts of concentrated cranberry juice) three times a day; those in the placebo group took a placebo tablet twice a day, and 250 mL of placebo beverage[30] three times a day.[31] Subjects who experienced a symptomatic UTI[32] during the study were treated with a culture-specific antibiotic for three days, after which, the subjects resumed their supplementation regimen. The number of women experiencing at least one UTI during the study was 10 out of 50 (20%) in the cranberry group versus 16 out of 50 (32%) in the placebo group ($P < 0.05$). The mean number of UTIs in a calendar year was 0.30 in the cranberry group versus 0.72 in the placebo group ($P < 0.05$).[33]

Maki et al. (2016) conducted a 24-week multicenter, randomized, double-blind, placebo-controlled, parallel design study of high methodological quality that investigated the effect of a

[26] The juice used in the treatment group contained a mixture of cranberry and lingonberry juices. Lingonberry fruit also contains proanthocyadins (PACs) (Kylli et al., 2011), the active compound present in cranberry fruit that may confer its potential protective effect against UTI.
[27] Results are reported in the cranberry dietary supplement section of this letter (Section II. C.).
[28] In Stothers, 2002, a history of UTI was defined as having at least two symptomatic, single-organism, culture-positive UTIs in the previous calendar year but without currently having a UTI, as determined by urinalysis and culture test.
[29] No information on sample size estimation has been provided in Stothers, 2002.
[30] Placebo beverage contained filtered water with food coloring plus 20 mL of pineapple juice.
[31] The compliance rate ranged between 75-90% and it was measured by self-report of the study beverage intake.
[32] A symptomatic UTI was diagnosed by having symptoms and equal or more than 100,000 single organism/mL.
[33] It is unclear whether the analysis was adjusted for antibiotic use or any other factor.

cranberry juice beverage on recurrent symptomatic UTI among healthy women with a recent history of UTI.[34] The study was conducted in 17 clinical research centers in the United States and one clinical research center in France. Data from 373 women (mean age of 40.9 years) who were randomly assigned to the cranberry (n = 185) or placebo (n = 188) groups were included in an intention-to-treat analysis.[35,36] In this study, subjects were assigned to consume one 8 oz. (240 mL) bottle per day of either a cranberry juice beverage[37] (27% of cranberry juice) or a placebo beverage[38] that was similar in appearance, smell and taste to the cranberry juice beverage. Subjects were instructed to record their beverage consumption and any UTI symptoms on a validated daily diary.[39,40] Almost every two weeks (at weeks 2, 4, 6, 10, 12, 14, 18, 20 and 22), subjects received a phone call to remind them to keep their daily diary, as well as to capture any UTI symptoms or adverse events that might have occurred. Besides the phone calls, subjects visited the clinic five times, at screening, baseline, and at weeks 8, 16, and 24 to collect clean-catch urine samples for urinalysis and culture, and to review their daily diaries. During the clinic visits, subjects completed questionnaires that assessed sexual history, food and beverage consumption, and presence and severity of gastrointestinal symptoms. If subjects had any symptoms of UTI throughout the study, they were instructed to visit the clinic for a pelvic examination. Subjects who were diagnosed[41] with a symptomatic UTI were treated with a standard antibiotic treatment while they continued consuming the study beverages. At the end of the study, a total of 106 investigator-diagnosed symptomatic UTIs occurred (39 UTIs in the

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[34] In Maki et al. 2016, a recent history of UTI was defined as having two or more episodes of UTI (self-reported) that were treated by a health care professional in the past year, of which one or more UTI had been treated within 6 months of the screening visit.

[35] Intention-to-treat analysis includes the results from all subjects as originally allocated after randomization, regardless of non-compliance, withdrawal, or deviation from the study protocol. The intention-to-treat principle asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance with the planned course of treatment (See FDA, "Guidance for Industry, E9 Statistical Principles for Clinical Trials" (September 1998). [https://www.fda.gov/media/71336/download].

[36] The number of subjects that did not complete the study was 26 in the placebo group and 25 in the cranberry group, but they were included in the intention-to-treat analysis. The authors originally estimated a sample size of 145 women per group. This estimation was based on 80% power and a two-tailed α level of 5% to detect a 18% reduction in the incidence of recurrent UTI in the cranberry group compared to the placebo, with the consideration that 32% of women would experience a recurrent UTI. Then, the authors increased their estimation by 40 subjects to account for a possible lower rate of a first UTI than they had anticipated.

[37] The cranberry juice beverage contained filtered water, cranberry juice from concentrate, fructose, natural flavors, pectin, sodium citrate, acesulfame-potassium, and sucralose. The cranberry beverage was produced from a single lot of cranberry concentrate.

[38] The placebo beverage contained filtered water, fructose, dextrose, citric acid, quinic acid, malic acid, natural flavors, pectin, potassium citrate, sodium citrate, Red 40, Blue 1, acesulfame-potassium, and sucralose.

[39] During the study, subjects agreed to avoid consumption of any food, food products, or supplements containing blueberries, cranberries, or probiotics, and not to consume quantities of carbonated soda and fermented milk products that greatly exceeded the mean US intake for these products.

[40] There was a 98% compliance with the study beverage intake based on the returned unused and empty bottles, as well as, the diary recorded consumption of the study beverage.

[41] A clinical (symptomatic) UTI was diagnosed by the investigator as subjects having one or more of the following symptoms: dysuria, urinary frequency, urinary urgency, or suprapubic pain in absence of other potential etiologies such as vaginal infection or discharge.

cranberry group and 67 UTIs in the placebo group). The number of women experiencing at least one UTI during the study was 33 out of 185 (18%) in the cranberry group versus 50 out of 188 (27%) in the placebo group (HR: 0.67; 95% CI: 0.43, 1.05; *P* = 0.078). The authors indicated that the primary outcome of the study was the investigator-diagnosed symptomatic UTI incidence density, defined as the number of clinical UTI events in each group (including multiple events per subject when applicable) per unit of observation time. The number of UTIs per women-year of observation (incidence density) was 0.48 (95% CI: 0.33, 0.63) in the cranberry group and 0.75 (95% CI: 0.56, 0.94) in the placebo group, with an incidence rate ratio of 0.62 (95% CI: 0.42, 0.92, *P* = 0.017). After adjustment for antibiotic use,[42] the incidence rate ratio was 0.61 (95% CI: 0.41, 0.91, *P* = 0.016). Besides the investigator-diagnosed symptomatic UTI, the authors also analyzed data on probable UTIs.[43] Considering the investigator-diagnosed symptomatic UTI plus probable UTIs, there were 47 UTIs in the cranberry group and 72 UTIs in the placebo group, with an antibiotic-adjusted incidence rate ratio of 0.68 (95% CI: 0.47, 0.99; *P* = 0.043).

Takahashi et al. (2013) conducted a 24-week randomized, double-blind, placebo-controlled, parallel design study of high methodological quality at 40 urology clinics in Japan to investigate the effect of a cranberry juice beverage on recurrent UTI among healthy women with a history of UTI.[44] A total of 170 women[45] aged 20-79 years old with uncomplicated cystitis (also referred to as uncomplicated UTI)[46] participated in the study, they were randomly divided into two groups, the cranberry group (n = 82) or placebo group (n = 88). Subjects were instructed to drink one bottle (125 mL) of a cranberry juice beverage (65% of cranberry juice containing more than 40 mg of proanthocyanidin (PAC)) or a placebo beverage (similar in color and taste to the cranberry juice beverage) once a day. Every four weeks, subjects visited the clinic for an interview on UTI symptoms, adverse event(s), and compliance with intake of the study beverages.[47] After subjects were diagnosed[48] with a UTI they were withdrawn from the study. The UTI episodes occurred in 22 out of 82 (27%) subjects in the cranberry group and 38 out of 88 (39%) subjects in the placebo group (*P* = 0.13). In a sub-group analysis of women aged 50 years and older, the number

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[42] Observation time, which is the susceptible time under observation, was adjusted by subtracting 7 days from the observation time for every instance of antibiotic use regardless of the indication. There were 111 instances in the cranberry group and 139 instances in the placebo group.

[43] Probable UTIs were those from which the investigator did not examine the subject, but a health care provider did examine the subject and prescribed antibiotics.

[44] In Takahashi et al. 2013, a history of UTI was defined as a history of multiple UTI episodes in which a healing by antimicrobial agents had been confirmed by urologists.

[45] No information on the sample size estimation has been provided in Takahashi et al. 2013.

[46] Uncomplicated UTI, also referred to as acute cystitis, is defined as a clinical syndrome characterized by pyuria and a documented microbial pathogen on urine culture, accompanied by local signs and symptoms such as lower abdominal discomfort and dysuria. It occurs in females with normal anatomy of the urinary tract and are not accompanied by systemic signs or symptoms, such as fever greater than 38 degrees Celsius or costovertebral angle pain (FDA Guidance for Industry: Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment-Final, July 2019, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/uncomplicated-urinary-tract-infections-developing-drugs-treatment-guidance-industry).

[47] It was stated in the article that the doctors strictly confirmed the regular intake of the study beverage, but no compliance rate was reported.

[48] The description of a UTI diagnosis was not provided in the article.

of subjects who experienced a UTI episode, 16 out of 55 (29%) subjects in the cranberry group and 31 out of 63 (49%) subjects in the placebo group, was statistically significantly different among the two groups ($P = 0.0425$).[49]

Barbosa-Cesnik et al. (2011) conducted a 6-month randomized, double-blind, placebo-controlled, parallel design study of moderate methodological quality that investigated the effects of cranberry juice beverage on recurring UTI among healthy women with a history of UTI.[50] College women 18-40 years old (mean age of 21.2 years old) were randomly assigned to either the cranberry (n = 155) or the placebo (n = 164) group. However, not all women who participated in the study met the inclusion criteria of having a history of UTI. For our evaluation, only the results from those women who reported a history of one or more UTI were considered, which were 59% (92 out of 155) of women in the cranberry group and 53% (87 out of 164) of women in the placebo group. During the study, subjects were instructed to drink either 8 oz of 27% low-calorie cranberry juice beverage[51] or 8 oz of placebo beverage (similar in flavor, sugar and acidity) twice a day. The beverages were home delivered to subjects every 1-2 weeks.[52] Subjects were also instructed to avoid consuming foods containing cranberry or blueberry during the study. Subjects visited the University Health Clinic at baseline, 3 and 6 months to collect a clean-catch midstream urine sample, self-selected vaginal and rectal specimens, and to complete several questionnaires.[53] Subjects were followed for six months or until they had a confirmed UTI,[54] whichever came first. Among those women who had a history of one or more UTI, the percentage of UTI recurrence was not statistically significantly different between the cranberry (28%) and placebo (16%) groups ($P > 0.05$).[55] However, given the considerable reduction in the number of women included in our evaluation compared to the original estimated sample size,[56] it is possible that the study was underpowered to detect a difference in recurrent UTI incidence, if one existed, between the placebo and treatment groups.

Stapleton et al. 2012 conducted a 6-month randomized, double-blind, placebo-controlled, parallel design study of moderate methodological quality among healthy premenopausal women aged 18-45 years old (mean age of 25 years) with a history of recent UTI.[57] The study was conducted in

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[49] See *supra*, note 30.
[50] Women who had 3 or more urinary symptoms (painful and frequent urination, and report of either urgency, hematuria, or supra-pubic pressure).
[51] An 8 oz bottle of cranberry juice contained 112 ± 14.1 mg (range: 83-136 mg) of PAC.
[52] Compliance with the study beverage intake was self-reported and ranged between 60-75%.
[53] The questionnaires assessed UTI symptoms, behaviors associated with UTI, diet, compliance, gastrointestinal or any other symptoms, and medical history.
[54] Confirmed UTI were those that occurred 15 or more days after the enrollment, or if less than 15 days, was with a different bacteria type or strain than those found in the enrollment episode. In addition, if the recurrence isolates were identical to those found in the enrollment episode, the recurrence was considered a treatment failure and the patient remained in the study
[55] See *supra*, note 30.
[56] It is described in the article that the authors estimated a sample size of 120 women per group based on 80% power and a two-tailed α level of 5% and assuming that 30% of participants would experience a UTI during the study, but that they had planned on recruiting 200 women per group to allow for an intention-to-treat analysis.
[57] History of one or more clinician-diagnosed UTIs in the past 12 months. Women diagnosed with symptomatic UTI had to meet both, the symptoms of dysuria (painful or difficult urination) plus one or more of the symptoms of

two clinical research centers in the United States. The study had four arms, two treatment groups, those receiving 4 oz and 8 oz of cranberry juice beverage (27% cranberry juice), and two placebo groups, those receiving 4 oz and 8 oz of placebo beverage (similar in color and taste to the cranberry beverage).[58] The estimated sample size for this study was 350 women, 210 in the cranberry groups (105 in each group, those taking 4 oz and 8 oz of cranberry juice beverage), 105 in the placebo group, and an additional 35 women to allow for a 10% dropout rate. The authors reported that the recruitment was terminated earlier due to administrative and budgetary issues. Therefore, only 50% of the estimated sample size (n = 176) was enrolled in the study, and were randomly assigned to either the cranberry (n = 120) or placebo (n = 56) group. Among those, 85 out of 120 (71%) women in the cranberry group and 35 out of 56 (63%) women in the placebo group completed the study with a median follow-up time of 168 days per subject. In an intention-to-treat analysis, data from all women enrolled in the study (n = 176) and both doses (4 oz and 8 oz) of cranberry juice beverage were combined for the analysis. A total of 72 UTIs[59] occurred among 50 women. The number of women who experienced at least one UTI was 33 out of 120 (28%) in the cranberry group and 17 out of 56 (30%) in the placebo group ($P = 0.70$). There were no statistically significant differences in the percentage of women having more than one UTI, 8% (10/120) versus 7% (4/56) in the cranberry and placebo groups, respectively ($P > 0.05$). The cumulative rate of UTIs at six months was 0.29 (95% CI: 0.21-0.38) versus 0.37 (95% CI: 0.25-0.54) in the cranberry and placebo groups, respectively ($P = 0.82$). The hazard ratio for UTI was 0.68 (95% CI: 0.33-1.39; $P = 0.29$) adjusted for age, baseline sexual frequency, race, study site, pyelonephritis[60] history, and number of bladder infections. Although the authors performed an intention-to-treat analysis, because of the early termination of recruitment, resulting in 50% of the estimated sample size, combined with a 30% loss to follow up, it might be possible that the study was underpowered to detect a difference in recurrent UTI incidence, if one existed, between the placebo and treatment groups.

Cranberry Dietary Supplements

Walker et al. (1997) conducted a randomized, double-blind, placebo-controlled cross-over design study of moderate methodological quality that investigated the effect of a cranberry dietary supplement on recurrent UTI among healthy women with a history of recurring UTI.[61] Non-pregnant, sexually active women aged 28-44 years old (median age of 37 years) participated in the study. This study had a high rate of attrition with 19 subjects entering the study but only 10

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frequency, urgency, suprapubic pain, hematuria (presence of red blood cells in the urine), and pyuria criteria (white blood cell count > 10/µL in unspun urine by hemocytometer or a positive leukocyte esterase dip-stick result). If the urine was positive (≥ 103 colony forming units (cfu)/mL of a uropathogen), the episode was categorized as culture-confirmed UTI. If urine UTI was negative, alternate diagnoses were excluded, and if symptoms resolved with therapy, the episode was categorized as a clinical UTI.

[58] There was a 90% compliance with the study beverage intake which was calculated by dividing the reported number of ingested doses by the expected number of doses per month.

[59] Among the 72 UTIs, there were 18 clinical UTIs and 54 culture-confirmed UTIs.

[60] Pyelonephritis, or kidney infection, is a type of UTI that commonly begins in the bladder and moves upstream to one or both kidneys (National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-infection-pyelonephritis).

[61] In Walker et al. 1997, a history of recurrent UTI was defined as having four UTIs during the previous year or at least one UTI within the previous three months.

subjects completing the study.[62] Only the results for those subjects who completed the study were included in the statistical analysis. The study entry point was a symptomatic UTI, which was followed by a standard 10-day antibiotic treatment. After the antibiotic treatment, subjects were randomly assigned to receive one capsule per day of either cranberry (400 mg of powdered cranberry extract) or placebo (dicalcium phosphate) for three months.[63] Subjects who were diagnosed with a symptomatic UTI during the study were prescribed an antibiotic treatment while continuing with their supplementation regimen. After three months of supplementation, a total of 21 incidents of UTIs occurred, 6 UTIs when subjects were taking the cranberry dietary supplement versus 15 UTIs when subjects were taking the placebo. Therefore, the number of UTIs per subject year[64] was 2.4 when subjects were taking the cranberry dietary supplement versus 6.0 when subjects were taking the placebo, which was a statistically significant difference ($P < 0.005$).

Stothers, (2002) conducted a 12-month randomized, double-blind, placebo-controlled parallel design study of high methodological quality to investigate the effect of a cranberry dietary supplement and cranberry juice beverage[65] on recurrent UTI among healthy women with a history of UTI.[66] Women enrolled in the study were sexually active, aged 21-72 years old (mean age of 42 years), and they were randomly assigned to either the cranberry (n = 50) or placebo (n = 50) groups.[67] No statistically significant differences were observed in the number of UTIs in the preceding year between the cranberry (mean: 3.1 UTIs) and the placebo (mean: 3.5 UTIs) groups ($P > 0.05$). In the cranberry group, subjects took a tablet containing cranberry extracts and concentrated cranberry juice beverage (at least 1:30 parts of concentrated cranberry juice) twice a day, and 250 mL of placebo juice[68] three times a day; those in the placebo group took a placebo tablet twice a day, and 250 mL of placebo beverage three times a day.[69] Subjects who experienced a symptomatic UTI during the study were treated with a culture-specific antibiotic for three days, after which, the subjects resumed their supplementation regimen. The number of women experiencing at least one UTI during the study was 9 out of 50 (18%) subjects in the cranberry group versus 16 out of 50 (32%) subjects in the placebo group ($P < 0.05$). The mean number of UTIs in a calendar year was 0.39 in the cranberry group versus 0.72 in the placebo group ($P < 0.05$).[70]

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[62] Subjects were lost to follow-up due to pregnancy, other infections that required the use of antibiotics, or they had moved from the area.

[63] Subjects returned their bottles and received a new supply of capsules every month during which they were interviewed for compliance. However, no compliance rate was reported in the study.

[64] The number of UTIs per subject year was calculated by dividing the total number of UTIs in each study phase (treatment or placebo) by the number of subjects (i.e., n = 10), then multiplying by 4 (study period of 3 months multiplied by 4 equals 12 months).

[65] Results are reported in the cranberry juice beverage section.

[66] See *supra*, note 28.

[67] See *supra*, note 29.

[68] See *supra*, note 30.

[69] The compliance rate ranged between 85-100% and it was measured by self-report of the study dietary supplement intake.

[70] See *supra*, note 33.

Vostalova et al. (2015) conducted a 6-month randomized, double-blind, placebo-controlled parallel design study of high methodological quality to investigate the effect of a cranberry dietary supplement on recurrent UTI among healthy women aged 18-75 years old with a history of UTI.[71] Data from 176 women who were randomly assigned to the cranberry (n = 83) or placebo (n = 93) groups were included in an intention-to-treat analysis.[72] The subjects were instructed to take two capsules after breakfast containing either 250 mg of the cranberry fruit powder[73] per capsule (for a total daily dose of 500 mg of cranberry fruit powder) or the same amount of placebo.[74,75] The study subjects were also instructed to maintain their lifestyle but to avoid consuming foods rich in phenolics (e.g., berries) and to avoid taking vitamin supplements. Urine samples were collected at baseline, three and six months, or when subjects experienced UTI symptoms. A subject diagnosed[76] with a UTI was treated with a culture-specific antibiotic for 1-3 days. After a resolution of UTI was confirmed, through a urine analysis, the subject resumed her supplementation regimen. After six months of supplementation, a total of 40 incident UTIs occurred in 33 women (10 UTIs when subjects were taking the cranberry dietary supplement versus 30 UTIs when subjects were taking the placebo). The number of UTIs per subject year was 0.12 when subjects were taking the cranberry dietary supplement versus 0.32 when subjects were taking the placebo ($P < 0.03$, after adjusting for age-adjusted 12-month history, age, and age squared). Furthermore, the proportion of women having at least one UTI episode was statistically significantly lower in the cranberry group (9 out of 83, corresponding to 11%) compared to placebo group (24 out of 93, corresponding to 26%) ($P < 0.04$), with age-adjusted 12-month UTI history ($P < 0.01$), age ($P = 0.73$), and age-squared ($P < 0.05$) included in the model. This corresponded to a relative risk reduction of 58% in the cranberry group relative to the placebo group.

D. Assessment of Observational Studies

There were no observational studies that evaluated the relationship between cranberry consumption and risk of recurrent UTI.

III. Strength of the Scientific Evidence

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[71] In Vostalova et al. 2015, a history of UTI was defined as having a medical history of at least two symptomatic UTI episodes treated with antibiotics in the previous 12 months.

[72] For this study, a total of 182 women were enrolled in the study and 17 women did not complete the study, but they were included in the intention-to-treat analysis. However, another six women, all randomized to the cranberry group, were excluded from the intention-to treat analysis due to a violation of the following inclusion criteria: they had less than two UTIs episodes in the previous 12 months (n = 3) or were younger than 18 years old (n = 3). The authors had estimated a sample size of 80 women per group. This estimation was based on 80% power and a two-tailed α level of 5% to detect a 50% reduction in the incidence of recurrent UTI in the cranberry group compared to the placebo, with the consideration that 30% of women would experience a recurrent UTI within 6 months.

[73] Each capsule of cranberry fruit powder contained 1.4 mg of A-type PACs for a total daily intake of 2.8 mg of PACs as determined by the DMAC method.

[74] The placebo capsules contained maltodextrin, canola oil, Red 40 Lake, sodium aluminum silicate, and Blue 1 Lake.

[75] Compliance with the consumption of the study dietary supplement was not reported.

[76] The clinical diagnosis of a UTI was based on a bacteriuria $\geq 10^5$ cfu/mL plus one symptom of UTI (e.g., dysuria, pollakiuria, burning sensation on micturition).

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 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 target subgroup, whether study results supporting the proposed claim have been replicated,[77] and the overall consistency[78] of the total body of evidence.[79] 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.

Cranberry Juice Beverages

As discussed in Section II, the totality of the scientific evidence for a possible relationship between a cranberry juice beverage and risk of recurrent UTI in healthy women with a history of UTI includes five intervention studies (Barbosa-Cesnik et al., 2011; Maki et al., 2016; Stapleton et al., 2012; Stothers, 2002; Takahashi et al., 2013) from which scientific conclusions can be drawn. Two out of the five intervention studies demonstrated a statistically significant benefit (Stothers, 2002; Maki et al., 2016). These studies were high quality randomized controlled trials, including one multi-center study involving 18 clinical research centers, 17 of which were in the United States (Maki et al. 2016). The study sample sizes ranged between 100 to 373 subjects, with daily doses of a cranberry juice beverage of 240 and 750 mL, and 6- and 12-months study duration. One study that demonstrated mixed results (Takahashi et al., 2013) was also a high quality randomized controlled multi-center study, involving 40 Japanese urology clinics. No statistically significant beneficial effect was observed when subjects with uncomplicated UTI (n = 170) consumed a daily dose of 125 mL of a cranberry juice beverage (65% of cranberry juice), only in a sub-analysis of women aged 50 years and older (n = 118) a statistically significant beneficial effect was observed.

Another two intervention studies showed no effect of consumption of a cranberry juice beverage on risk reduction of recurrent UTI. Both studies were moderate quality randomized controlled trials (Barbosa-Cesnik et al., 2011; Stapleton et al., 2012) with similar daily doses (240 mL) of a cranberry juice beverage and study duration (6 months) as in the multi-center study that showed a beneficial effect (Maki et al. 2016). In both studies there was a substantial reduction in the number of subjects evaluated for the substance-disease relationship as compared to the original

[77] See *supra*, note 10.
[78] See *supra*, note 11.
[79] See *supra*, note 3 [Section III.F].

estimated sample size. Consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.[80] Lack of consistency among studies evaluating the same substance-disease relationship weakens the strength of the evidence.

Based on FDA's review of the strength of the total body of scientific evidence for the proposed qualified claim, FDA concludes that there is some scientific evidence suggesting a relationship between consumption of cranberry juice beverages and reduced risk of recurrent UTI among healthy women with a history of UTI. Due to the limited number of studies (five randomized controlled trials with high and moderate methodological quality, but with inconsistent results (two beneficial, one mixed, and two non-effect)), FDA has concluded that the evidence provides only qualified support for the scientific validity of the claimed relationship. Therefore, FDA 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 a cranberry juice beverage on the label or in labeling of cranberry juice beverages that includes a truthful and non-misleading description of the strength of the body of scientific evidence, i.e. "limited and inconsistent." Such a description is truthful and not misleading because, while the evidence provides support for the claimed relationship, the evidence is limited and inconsistent. Further, in order for the claim to be truthful and not misleading, the agency will consider, as factors in the exercise of its enforcement discretion, certain other factors discussed below. Based on the above, FDA concludes that there is credible scientific evidence that is limited and inconsistent for a relationship between cranberry juice beverage, and reduced risk of recurrent UTI in healthy women with a history of UTI.

Cranberry Dietary Supplements

As discussed in Section II, the totality of the scientific evidence for a possible relationship between cranberry dietary supplement and risk of recurrent UTI in healthy women with a history of UTI includes three intervention studies (Stothers, 2002; Vostalova et al., 2015; Walker et al., 1997) from which scientific conclusions can be drawn. The three intervention studies were randomized controlled trials of high or moderate methodological quality. All three intervention studies demonstrated a statistically significant benefit of a cranberry dietary supplement consumption on reduced risk of recurrent UTI in healthy women with a history of UTI. Consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.[81] The two intervention studies of high methodological quality had larger sample sizes and longer study durations (n = 100, 176, study period = 12 and 6 months, respectively) compared to the moderate methodological quality study (n = 10, study period = 3 months). The daily doses of the dietary cranberry supplement in these studies ranged from 400 to 500 mg of cranberry powder, with one study not providing the exact amount of cranberry powder that was consumed.

[80] See *supra*, note 3 [Section III.F].
[81] See *supra*, note 5 [Section III.F].

Based on FDA's review of the strength of the total body of scientific evidence for the proposed qualified claim, FDA concludes that there is some scientific evidence that is credible suggesting a relationship between consumption of a cranberry dietary supplement and reduced risk of recurrent UTI among healthy women with a history of UTI. Due to the limited number of studies (three intervention randomized controlled trials with high and moderate methodological quality), FDA has concluded that the evidence provides only qualified support for the scientific validity of the claimed relationship. Therefore, FDA 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 cranberry dietary supplements on the label or in labeling of cranberry dietary supplements that includes a truthful and non-misleading description of the strength of the body of scientific evidence, i.e. "limited." Such a description is truthful and not misleading because, while the evidence provides support for the claimed relationship, the evidence is consistent but limited. Further, in order for the claim to be truthful and not misleading, the agency will consider, as factors in the exercise of its enforcement discretion, certain other factors discussed below. Based on the above, FDA concludes that there is limited credible scientific evidence for a relationship between dietary cranberry supplement and reduced risk of recurrent UTI in healthy women with a history of UTI.

IV. Other Enforcement Discretion Factors

A qualified health claim about reducing the risk of recurrent UTI in healthy women on the label or in the labeling of conventional foods and dietary supplements containing cranberry is required to meet all applicable statutory and regulatory requirements under the Act, with the exception of the requirement that the 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 health claims that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims are discussed below, as well as enforcement discretion factors specific to qualified health claims describing how consuming cranberry and cranberry products may reduce the risk of recurrent UTI in healthy women.

A. Qualifying Level for Cranberry Juice Beverages

For the purpose of this qualified health claim, FDA intends to exercise its enforcement discretion only for certain cranberry juice beverages. The claim would not be allowed for other conventional foods or conventional food products made from or containing cranberries, such as dried cranberries, cranberry sauce, and cranberry-containing cereals or baked products, because FDA did not identify any studies in which these or other cranberry-containing conventional food products were investigated among healthy women with recurrent UTI.

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)).

In order to quantify the amount of "cranberry" (the substance that is the subject of the proposed claim) in a food, the petition proposed the term "cranberry fruit equivalent" (CFE) as a unit to represent the cranberry fruit content of a food, per reference amount customarily consumed (RACC). The petition said the CFE is determined from an analysis of the food's total polyphenol content (i.e., the total phenolics) contributed by all the cranberry-containing ingredients in the food.

However, FDA does not recognize the term "cranberry fruit equivalent" (or CFE) as a unit of measure that is based on the total phenolic content of all cranberry ingredients. As such, FDA does not consider the CFE to be appropriate for representing the cranberry fruit content of a food per RACC. CFE is not a conventional unit of measure in the metric system or other measurement system, and we are not aware that this term is recognized by any authoritative scientific body.

The petition indicated that for a cranberry-containing food to be eligible to bear the health claim, the cranberry content of the food should be an amount that is at least equal to the cranberry content of one serving (8 fluid ounces or 240 mL) of a 27% cranberry juice cocktail, which is the most commonly marketed cranberry beverage. A 27% cranberry juice cocktail is also the product that has been used most frequently in clinical trials investigating the relationship between cranberry consumption and the reduced risk of recurrent UTI in healthy women.

Therefore, based on the limited and inconsistent scientific evidence FDA intends to exercise enforcement discretion for cranberry juice beverages with at least 27% cranberry juice to bear a cranberry and recurrent UTI claim.

B. Qualifying Level for Cranberry Dietary Supplements

As a factor in the exercise of our enforcement discretion, we are specifying a minimum amount of cranberry that a dietary supplement bearing a qualified health claim for cranberry and reduced risk of recurrent UTI in healthy women should contain. The purpose of this minimum content enforcement discretion factor is to prevent consumer deception from health claims on the labels of products that contain only trivial or insignificant amounts of cranberry. To identify an appropriate minimum content amount, FDA considered the lowest levels of cranberry evaluated in the studies that demonstrated a benefit in reducing the risk of recurrent UTI in healthy women. As discussed in sections III and IV.A., the scientific evidence for such a benefit does not support the establishment of a recommended daily dietary intake level because it is limited and inconsistent; however, limiting our consideration of enforcement discretion to products that contain cranberry in amounts that have been observed to reduce the risk of recurrent UTI in at least some well-conducted scientific studies will help ensure that consumers do not see the claim on products that contain so little cranberry that such products would be very unlikely to provide any health benefit.

The lowest level of intake among the studies that showed a benefit in reducing the risk of UTI was 400 mg/day in the study by Walker et al. (1997), which was of moderate methodological quality. The next lowest level of intake among studies that showed a benefit in reducing UTI risk was 500 mg/day (Vostalova et al., 2015). Because the study by Vostalova et al. (2015) was of a high methodological quality, we conclude that this study provided the most scientifically appropriate basis for a minimum amount of cranberry in dietary supplements that bear a cranberry/UTI qualified health claim. We do not expect the typical healthy woman in the U.S. to consume cranberry dietary supplements on multiple occasions during the day. Therefore, we are specifying 500 mg of cranberry fruit powder per day as the minimum amount per serving for a dietary supplement to bear a cranberry and recurrent UTI claim. Dietary supplements may declare the amount of cranberry per serving in the "Supplement Facts label," instead of in the claim (see 21 CFR 101.36(b)(3)).

C. Disqualifying Nutrient Levels

Under the general requirements for health claims (21 CFR 101.14(e)(3)), a food may not bear a health claim if the food exceeds any of the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium established in 21 CFR 101.14(a)(4)[82], unless FDA establishes an alternative level. Section 101.14(e)(3) applies to all health claims regardless of types of diseases and health-related conditions. We are not aware of any commercially available cranberry juice or cranberry dietary supplement product that exceeds the disqualifying level for total fat, saturated fat, cholesterol, or sodium, but we expect that any cranberry juice or dietary supplement product that bears the claim would not exceed the disqualifying levels for these nutrients as described in 21 CFR 101.14(a)(4). FDA believes that an appropriately worded qualified health claim about consumption of such cranberry products could assist consumers in maintaining healthy dietary practices by providing consumers with information that could facilitate a reduction in recurrent UTIs in healthy women.

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) of vitamin A, vitamin C, iron, calcium, protein, or fiber per RACC (21 CFR 101.14(e)(6)). The purpose of this requirement is to prevent the use of health claims on foods of minimal nutritional value.

Conventional Foods. The 10 percent minimum content requirement applies to conventional foods that bear a cranberry juice beverage qualified health claim. Cranberry juice beverage products would generally meet the 10 percent minimum nutrient content requirement of 21 CFR 101.14(e)(6) because of their vitamin C content, which is one of the specific nutrients listed in 21 CFR 101.14(e)(6).

[82] 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)).

Dietary Supplements. The 10 percent minimum nutrient content requirement does not apply to dietary supplements (21 CFR 101.14(e)(6)).

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 limited and inconsistent credible scientific evidence for a qualified health claim for consumption of cranberry juice beverage containing at least 27% cranberry juice and reduced risk of recurrent UTI in healthy women. FDA also concludes that there is limited credible scientific evidence for a qualified health claim for consumption of cranberry dietary supplement containing at least 500 mg of cranberry fruit powder (100% fruit) and reduced risk of recurrent UTI in healthy women, provided that both qualified health claims are appropriately worded so as to not mislead consumers.

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

For cranberry juice beverages

"Limited and inconsistent scientific evidence shows that by consuming one serving (8 oz) each day of a cranberry juice beverage, healthy women who have had a urinary tract infection (UTI) may reduce their risk of recurrent UTI."

"Consuming one serving (8 oz) each day of a cranberry juice beverage may help reduce the risk of recurrent urinary tract infection (UTI) in healthy women. FDA has concluded that the scientific evidence supporting this claim is limited and inconsistent."

"Consuming one serving (8 oz) each day of [this identified cranberry juice beverage] may help reduce the risk of recurrent urinary tract infection (UTI) in healthy women. FDA has concluded that the scientific evidence supporting this claim is limited and inconsistent."

And for cranberry dietary supplements

"Limited scientific evidence shows that by consuming 500 mg each day of cranberry dietary supplement, healthy women who have had a urinary tract infection (UTI) may reduce their risk of recurrent UTI."

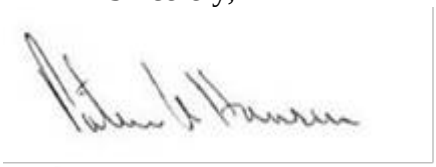
"Consuming 500 mg each day of cranberry dietary supplement may help reduce the risk of recurrent urinary tract infection (UTI) in healthy women. FDA has concluded that there is limited scientific evidence supporting this claim."

"Consuming 500 mg [X capsules/tablets/soft gels] each day of [this identified cranberry dietary supplement] may help reduce the risk of recurrent urinary tract infection (UTI) in healthy women. FDA has concluded that there is limited scientific evidence supporting this claim."

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, or 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,



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