http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=grasListing&id=18

http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm171539.htm

U.S. Food and Drug Administration

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Agency Response Letter GRAS Notice No. GRN 000275

CFSAN/Office of Food Additive Safety

June 11, 2009

Claire L. Kruger, Ph.D., D.A.B.T.
Spherix Incorporated
6430 Rockledge Drive
Suite 503
Bethesda, MD 20817

Re: GRAS Notice No. GRN 000275

Dear Dr. Kruger:

The Food and Drug Administration (FDA) is responding to the notice, dated December 23, 2008, that you submitted on behalf of McNeil Nutritionals, LLC (McNeil) in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on December 30, 2008, filed it on January 2, 2009, and designated it as GRAS Notice No. GRN 000275.

The subject of the notice is purified steviol glycosides with rebaudioside A as the principal component (hereinafter referred to as SG-R in this letter). SG-R is obtained from the leaves of *Stevia rebaudiana* (Bertoni) Bertoni. The notice informs FDA of the view of McNeil that SG-R is GRAS, through scientific procedures, for use as a tabletop sweetener. McNeil notes that rebaudioside A has recently been the subject of two GRAS notices, GRN 000252 and GRN 000253.[1]

The SG-R that is the subject of GRN 000275 is a highly purified component of the stevia plant. As such, FDA notes that the GRAS notice for the use of a specific purified

component of stevia, such as SG-R, and FDA's response do not necessarily apply to the uses of other stevia products.

Title 21 CFR 101.4 states that all ingredients must be declared by their common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Our use of "SG-R," "steviol glycosides," or "purified steviol glycosides with rebaudioside A as the principal component" in this letter should not be considered an endorsement or recommendation of any of these terms as an appropriate common or usual name for the purpose of declaring the substance in the ingredient statement of foods that contain that ingredient. Issues associated with labeling and the appropriate common or usual name of a food are the responsibility of the Office of Nutrition, Labeling, and Dietary Supplements in the Center for Food Safety and Applied Nutrition.

As part of its notice, McNeil includes a summary of conclusions of a panel of individuals (McNeil's GRAS panel) who evaluated the data and information that are the basis for McNeil's GRAS determination. McNeil considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. McNeil's GRAS panel evaluated the identity, method of manufacture, product specifications, and the potential exposure resulting from the intended uses of SG-R as well as published and unpublished studies on SG-R and related substances. Based on this review, McNeil's GRAS panel concluded that SG-R, produced consistent with current good manufacturing practice and meeting appropriate purity and food grade specifications, is GRAS, by scientific procedures, under the conditions of its intended use.

McNeil provides information about the identity and composition of SG-R. SG-R is obtained from the leaves of *S. rebaudiana* (Bertoni) Bertoni using water or ethanol extraction processes. McNeil describes the SG-R product as a white to light yellow powder composed of not less than 95% (on a dried weight basis) steviol glycosides, a group of structurally-related sweet compounds that are natural constituents of the stevia leaf. Rebaudioside A (CAS Reg. No. 58543-16-1) is the principal steviol glycoside component of McNeil's SG-R product and accounts for greater than 85% of the steviol glycoside content. Other steviol glycosides, including stevioside (CAS Reg. No. 578 17-89-7), rebaudioside C (CAS Reg. No. 63550-99-2), dulcoside A (CAS Reg. No. 64432-06-0), rubusoside (CAS Reg. No. 64849-39-4), steviolbioside (CAS Reg. No. 41093-60-1), and rebaudioside B (CAS Reg. No. 58543-17-2), may also be present.

McNeil describes two methods of manufacture for SG-R and provides specifications for the final product. McNeil states that both methods of manufacture result in a product that meets the specifications described below. In the first method of manufacture, stevia leaves are dried, crushed and extracted with hot water (50-60 °C), followed by centrifugation of the extract to remove plant debris and other particulates. An adsorption resin is used to trap the steviol glycosides of the leaf extract. The resin is washed with ethanol to release the glycosides. The ethanol in the elutant is removed by evaporation. The elutant is then demineralized and decolorized using ion exchangers, concentrated by

an evaporation process and spray-dried to recover the steviol glycosides. The resulting powder is dissolved in hot ethanol and recrystallized by cooling to enrich rebaudioside A in the product. The crystals are separated by centrifugation, washed with cold ethanol and redissolved in water. The solution is then concentrated by evaporation under reduced pressure, filtered through a microfilter and spray-dried to yield the final SG-R product that is obtained through the first manufacturing method. In the second method of manufacture, stevia leaves are dried, crushed and extracted with a mixture of ethanol and demineralized water, followed by membrane filtration of the extract to remove plant debris and other particulates. An adsorption resin is then used to trap the steviol glycosides of the leaf extract. The resin is washed with ethanol/water mixture to release the glycosides and the elutant is concentrated by an evaporation process. The concentrated solution is crystallized by a rate controlled cooling process to enrich rebaudioside A in the product. The crystals are then recovered by centrifugation, dissolved in hot ethanol/water mixture, and recrystallized by cooling. The refined crystals from this step are recovered by centrifugation, redissolved in water, and spray-dried to yield the final SG-R product that is obtained through the second manufacturing method. McNeil states that all chemical reagents, adsorption and ion exchange resins used in both manufacturing methods are food grade. McNeil provides specifications for SG-R that include, in addition to steviol glycosides content (= 95% by weight (w/w)), limits on ash (= 1% w/w), residual methanol (= 200 milligrams per kilogram (mg/kg)), residual ethanol (= 5000 mg/kg), arsenic (= 1 mg/kg), and lead (= 1 mg/kg). McNeil states that the SG-R product fully complies with the specifications for steviol glycosides established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in its 69th meeting in June 2008.

McNeil estimates the intake of SG-R resulting from its intended use in foods. McNeil provides two estimates of daily intake, using data from Market Research Corporation of America (MRCA) in addition to food consumption data reported in the United States Department of Health and Human Services 2003-2004 National Health and Nutrition Examination Survey (NHANES). Based on the 14-day MRCA survey data, McNeil estimates the daily intake of SG-R (all ages, eaters only) to be 20 milligrams per day (mg/d) and 50 mg/d at the mean and 90th percentile level of intake, respectively. McNeil notes that the SG-R product is 36% steviol equivalents by weight and estimates the daily intake of steviol equivalents to be 7 mg/d and 18 mg/d at the mean and 90th percentile level of intake, respectively. Based on the two-day NHANES survey data, McNeil estimates the daily intake of SG-R (adults, eaters only) to be 46 mg/d and 98 mg/d at the mean and 90th percentile level of intake, respectively, and the daily intake of steviol equivalents to be 17 mg/d and 35 mg/d at the mean and 90th percentile level of intake, respectively.[2]

McNeil discusses published studies about the absorption, distribution, metabolism, and excretion of stevioside, rebaudioside A, steviol glycoside mixtures, and steviol in animals and humans. McNeil states that the results from studies which evaluate the absorption and fate of stevioside in both animals and humans indicate that it is appropriate to extrapolate results from toxicity studies in rats and hamsters to humans. McNeil further states that based on the similarity of the metabolism of stevioside in the rat and humans to

that of rebaudioside A, both human studies and rodent toxicology studies conducted with stevioside are also relevant to the safety assessment of rebaudioside A.

McNeil discusses published and unpublished studies related to the safety evaluation of SG-R, including an unpublished subchronic toxicity study of SG-R in rats and various published animal studies conducted with rebaudioside A, stevioside, steviol, and crude stevia extracts. The published animal studies McNeil discusses include acute toxicity studies in rats, mice, and hamsters; subchronic toxicity studies in rats and hamsters; chronic toxicity/carcinogenicity studies in rats and hamsters; reproductive/developmental toxicity studies in rats, hamsters, and chickens. Additional published studies that McNeil discusses include *in vitro* and *in vivo* genotoxicity studies.

McNeil discusses published and unpublished clinical studies on rebaudioside A, stevioside, steviol glycoside mixtures, and crude stevia extracts in diabetics and nondiabetics, and in hypertensive, normotensive, and hypotensive subjects. McNeil concludes that steviol glycosides are well tolerated in humans and unlikely to have adverse effects on blood pressure or on glucose homeostasis at consumption levels well exceeding the maximum expected intakes.

In its discussion of the published literature, McNeil also considers reports on stevia or stevia derived substances that raised safety concerns about the use of such substances as food ingredients. McNeil states that more recent, pivotal studies on well defined extracts that address comparative metabolism, acute, repeat-dose, chronic, genetic and reproductive toxicity, and clinical safety have become available to document the safety of steviol glycosides and concludes that SG-R is safe under the conditions of its intended use.

To further support its view that SG-R is safe for the intended use, McNeil describes recent decisions by JECFA and the Food Standards Australia New Zealand (FSANZ) on the safety of steviol glycosides for use in food as sweeteners. McNeil notes that in 2006, JECFA established a temporary acceptable daily intake (ADI) for steviol glycosides of 0–2 mg/kg body weight per day (mg/kg bw/d; expressed as steviol), pending requirements for further studies on the effects of steviol glycosides on blood glucose and blood pressure in humans.[3] McNeil also notes that in 2008, FSANZ established an ADI for steviol glycosides of 4 mg/kg bw/d (expressed as steviol).[4]

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FFDCA)

The Food and Drug Administration Amendments Act of 2007, that was signed into law on September 27, 2007, amends the FFDCA to, among other things, add section 301(ll). Section 301(ll) of the FFDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FFDCA, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In its review of McNeil's notice that SG-R is GRAS for use as a

tabletop sweetener, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing SG-R. Accordingly, this response should not be construed to be a statement that foods that contain SG-R, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information provided by McNeil, as well as other information available to FDA, the agency has no questions at this time regarding McNeil's conclusion that SG-R is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of SG-R. As always, it is the continuing responsibility of McNeil to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000275, as well as a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying via the FDA home page at http://www.fda.gov. To view or obtain an electronic copy of the text of the letter, follow the hyperlinks from the "Food" topic to the "Food Ingredients and Packaging" section to the "Generally Recognized as Safe (GRAS)" page where the GRAS Inventory is listed.

Sincerely,

Laura M. Tarantino, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition

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[1] On December 17, 2008, FDA responded to these GRAS notices informing the notifiers that the agency had no questions at that time regarding their conclusion that the rebaudioside A that is the subject of their respective notice is GRAS for its intended use as a sweetener in food.

[2] FDA notes that, as a general observation, a shorter survey period will tend to have a greater estimated daily intake as compared to a longer survey period.

[3] At its 69th meeting in June 2008, JECFA reviewed new data on the effects of steviol glycosides on blood glucose and blood pressure in humans. JECFA concluded that the

results of the new studies showed no adverse effects of steviol glycosides at the levels tested. At this meeting, the temporary designation was removed and JECFA established an ADI of 0–4 mg/kg bw/d (expressed as steviol). FDA notes that the equivalent ADI for rebaudioside A is 0-12 mg/kg bw/d, due to the relative molecular weights of rebaudioside A of 967 g/mol and steviol of 318 g/mol.

[4]The FSANZ issued a final assessment report on August 6, 2008, stating that the agency has established a full ADI of 4 mg/kg bw/d and recommended the approval of steviol glycosides as a food additive in specified food categories.

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