DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE (GRAS) NOTICE (Subpart E of Part 170)

Form Approved: OMB No. 0910-0342; Expiration Date: 09/30/2019
(See last page for OMB Statement)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
000790	
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration,5001 Campus Drive, College Park, MD 20740-3835.

SECTION A – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3 Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd)*: N/A

☐
☐

SECTION B – INFORMATION ABOUT THE NOTIFIER

1a. Notifier

Name of Contact Person	Position or Title
Simon Springett	Vice President of Operations

Organization *(if applicable)*: GLG Life Tech Corporation

Mailing Address *(number and street)*: 10271 Shellbridge Way, Suite 100

City	State or Province	Zip Code/Postal Code	Country
Richmond	British Colombia (BC)	V6X 2W8	Canada

Telephone Number	Fax Number	E-Mail Address
604-285-2602	604-661-8858	simon.springett@glglifetech.com

1b. Agent or Attorney *(if applicable)*

Name of Contact Person	Position or Title
Steven Overgaard	President

Organization *(if applicable)*: GRAS Associates, LLC

Mailing Address *(number and street)*: 27499 Riverview Center Blvd., Suite 212

City	State or Province	Zip Code/Postal Code	Country
Bonita Springs	Florida	34134	United States of America

Telephone Number	Fax Number	E-Mail Address
239-444-1724	239-444-1723	smovergaard@gras-associates.com

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

1. Name of notified substance, using an appropriately descriptive term

High Purity Steviol Glycosides (min. 95%)

2. Submission Format: *(Check appropriate box(es))*

☐ Electronic Submission Gateway

☒ Electronic files on physical media

☐ Paper

If applicable give number and type of physical media

_____

4. Does this submission incorporate any information in CFSAN's files? *(Check one)*

☒ Yes *(Proceed to Item 5)* ☐ No *(Proceed to Item 6)*

5. The submission incorporates information from a previous submission to FDA as indicated below *(Check all that apply)*

☒ a) GRAS Notice No. GRN 493

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☐ e) Other or Additional *(describe or enter information as above)* _____

6. Statutory basis for conclusions of GRAS status *(Check one)*

☒ Scientific procedures *(21 CFR 170.30(a) and (b))* ☐ Experience based on common use in food *(21 CFR 170.30(a) and (c))*

7. Does the submission (including information that you are incorporating) contain information that you view as trade secret or as confidential commercial or financial information? (see 21 CFR 170.225(c)(8))

☒ Yes *(Proceed to Item 8*

☐ No *(Proceed to Section D)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*

☒ Yes, information is designated at the place where it occurs in the submission

☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*

☒ Yes, a redacted copy of the complete submission

☐ Yes, a redacted copy of part(s) of the submission

☐ No

SECTION D – INTENDED USE

1. Describe the intended conditions of use of the notified substance, including the foods in which the substance will be used, the levels of use in such foods, and the purposes for which the substance will be used, including, when appropriate, a description of a subpopulation expected to consume the notified substance.

Intended for use as a general purpose non-nutritive sweetener for incorporation into conventional foods and certain meat products.

2. Does the intended use of the notified substance include any use in product(s) subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture?

(Check one)

☒ Yes ☐ No

3. If your submission contains trade secrets, do you authorize FDA to provide this information to the Food Safety and Inspection Service of the U.S. Department of Agriculture?

(Check one)

☒ Yes ☐ No , you ask us to exclude trade secrets from the information FDA will send to FSIS.

SECTION E – PARTS 2 -7 OF YOUR GRAS NOTICE

(check list to help ensure your submission is complete – PART 1 is addressed in other sections of this form)

☒ PART 2 of a GRAS notice: Identity, method of manufacture, specifications, and physical or technical effect (170.230).

☒ PART 3 of a GRAS notice: Dietary exposure (170.235).

☒ PART 4 of a GRAS notice: Self-limiting levels of use (170.240).

☒ PART 5 of a GRAS notice: Experience based on common use in foods before 1958 (170.245).

☒ PART 6 of a GRAS notice: Narrative (170.250).

☒ PART 7 of a GRAS notice: List of supporting data and information in your GRAS notice (170.255)

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☒ Yes ☐ No

Did you include this other information in the list of attachments?

☒ Yes ☐ No

SECTION F – SIGNATURE AND CERTIFICATION STATEMENTS

1. The undersigned is informing FDA that GLG Life Tech Corporation *(name of notifier)*

has concluded that the intended use(s) of High Purity Steviol Glycosides (min. 95%) *(name of notified substance)*

described on this form, as discussed in the attached notice, is (are) not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the substance is generally recognized as safe recognized as safe under the conditions of its intended use in accordance with § 170.30.

2. GLG Life Tech Corporation *(name of notifier)* agrees to make the data and information that are the basis for the conclusion of GRAS status available to FDA if FDA asks to see them; agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so; agrees to send these data and information to FDA if FDA asks to do so.

10271 Shellbridge Way, Suite 100, Richmond, BC V6X 2W8 Canada *(address of notifier or other location)*

The notifying party certifies that this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, pertinent to the evaluation of the safety and GRAS status of the use of the substance.The notifying party certifies that the information provided herein is accurate and complete to the best or his/her knowledge. Any knowing and willful misinterpretation is subject to criminal penalty pursuant to 18 U.S.C. 1001.

3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
(b) (6)	Katrina Emmel on behalf of Steven Overgaard, President	06/07/2018

SECTION G – LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Multiple Appendices---Appendix 1-3	

#790

GRAS ASSOCIATES, LLC

GRAS Associates, LLC
27499 Riverview Center Blvd.
Bonita Springs, FL 34134
T: 239.444.1724 | F: 239.444.1723
www.gras-associates.com

June 7, 2018

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety (HFS-255)
5001 Campus Drive
College Park, MD 20740-3835

Attention: Dr. Paulette Gaynor
Re: High Purity Steviol Glycosides (≥95%) to Include Proposed Uses in Certain Meat Products

Dear Dr. Gaynor:

GRAS Associates, LLC, acting as the agent for GLG Life Tech Corporation (Canada), is submitting for FDA review Form 3667 and the enclosed CD, free of viruses, containing a GRAS Notification for *High Purity Steviol Glycosides (≥ 95%) to Include Proposed Uses in Certain Meat Products*. Along with GLG's determination of safety, an Expert Panel of qualified persons was assembled to assess the composite safety information of the subject substance with the intended use as a table top sweetener and as a general purpose non-nutritive sweetener for incorporation into food in general, including certain meat products. The attached documentation contains the specific information that addresses the safe human food uses for the subject notified substance as discussed in the GRAS guidance document.

GLG has designated the information contained in Appendices 1 and 2 as confidential commercial information, as indicated on the accompanying Form 3667. A redacted copy of the complete submission has also been provided.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via telephone or email. We look forward to your feedback.

Sincerely,

(b) (6)

Steven Overgaard
President
GRAS Associates, LLC
27499 Riverview Center Blvd., Suite 212
Bonita Springs, FL 34134

• • •

(416) 399-1665
smovergaard@gras-associates.com

Enclosure: GRAS Notification for GLG Life Tech Corporation –*High Purity Steviol Glycosides (≥ 95%) to Include Proposed Uses in Certain Meat Products.*

GRAS Notification

of

High Purity Steviol Glycosides (≥ 95%) with Proposed Uses in Certain Meat Products

Food Usage Conditions for General Recognition of Safety

on behalf of

GLG Life Tech Corporation

Suite 100-10271 Shellbridge Way
Richmond, B.C. V6X 2W8
Canada

6/7/18

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FOREWORD

GLG Life Tech Corporation (hereinafter "GLG") have based our GRAS assessment primarily on the composite safety information, i.e., scientific procedures with corroboration from history of use. The safety/toxicity of steviol glycosides, history of use of steviol glycosides, and compositional details, specifications, and method of preparation of the subject ingredient were previously reviewed in GRN 493. The previous safety evaluation was augmented by a search of the scientific and regulatory literature extending through March 12, 2018, and the additional proposed uses in cured meat products were reviwed in concert with related safety documentation. The finished product purity for the steviol glycosides that are the subject of this GRAS assessment remains at ≥ 95% steviol glycosides. Those references that were deemed pertinent to this supplement are listed in Part 7. The composite safety/toxicity studies, in concert with dietary exposure information---contained in GRN 493 as well as herein---ultimately provide the specific scientific foundation for the GRAS conclusion.

At GLG's request, GRAS Associates, LLC ("GA") convened an Expert Panel to complete an independent safety evaluation of proposed uses in certain meat products in addition to those previously proposed in GRN 493, which received FDA's "no questions" letter on May 30, 2014. The purpose of the evaluation is to ascertain whether GLG's conclusion that the sum of the previously proposed food uses described in GRN 493 and the intended additional food uses of its high purity steviol glycosides (≥95%) preparations as described in Part 3 are generally recognized as safe, i.e. GRAS, under the intended conditions of use. In addition, GLG has asked GA to act as agent for the submission of this GRAS notification.

PART 1. SIGNED STATEMENTS AND CERTIFICATION

A. Basis of Exclusion from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR 170.36(c)(1)[1]

GLG has previously concluded that our high purity steviol glycosides (≥95%) preparations, referred to herein as GLG-SG, are Generally Recognized as Safe (GRAS) in accordance with Section 201(s) of the Federal Food, Drug, and Cosmetic Act, as reported in GRN 493. This GRAS evaluation includes proposed uses and supporting data that GLG's high purity steviol glycosides (≥95%) preparations are suitable for use in cured meat products. This determination was supported by a review by an appropriately convened panel of experts who are qualified by scientific training and experience. The GRAS determination is based on scientific procedures as described in the following sections. The evaluation accurately reflects the intended conditions of food use for GLG's high purity steviol glycosides products.

[1] See 81 FR 54960, 17 August 2016. Accessible at: https://www.gpo.gov/fdsys/pkg/FR-2016-08-17/pdf/2016-19164.pdf (Accessed 5/1/18).

Signed:

(b) (6)

Agent for GLG

Steven Overgaard
President
GRAS Associates, LLC
27499 Riverview Center Blvd.
Suite 212
Bonita Springs, FL 34134

Date: 6/7/18

B. Name and Address of Responsible Party

GLG Life Tech Corporation
10271 Shellbridge Way
Suite 100
Richmond, BC V6X 2W8 Canada

As the Responsible Party, GLG accepts responsibility for the GRAS conclusion that has been made for our high purity steviol glycosides (≥95%) preparations as described in the subject safety evaluation; consequently, the purified steviol glycosides preparations having acceptable steviol glycosides compositions which meet the conditions described herein, are not subject to premarket approval requirements for food ingredients.

C. Common Name and Identity of Notified Substance

High purity steviol glycosides is the common name for the notified substance.

D. Conditions of Intended Use in Food

The GLG-SG high purity steviol glycosides preparations, primarily containing rebaudioside A and stevioside, are intended to be used as a table top sweetener and as general purpose non-nutritive sweeteners for incorporation into foods in general, other than infant formulas, at per serving levels reflecting good manufacturing practices principles as described in GRN 493. GLG also intends to use the high purity steviol glycosides preparations as an ingredient in cured meat products, at a maximum use level of 2,500 ppm, as described herein.

E. Basis for GRAS Conclusion

Pursuant to 21 CFR 170.30(a) and (b), GLG's high purity steviol glycosides (≥95%) preparations have been concluded to be GRAS on the basis of scientific procedures as discussed in GRN 493 and the detailed description provided below.

Purified steviol glycosides are not subject to premarket approval requirements of the Federal Food, Drug, and Cosmetic (FD&C) Act based on GLG's conclusion that the substance is GRAS under the conditions of its intended food use.

GLG certifies, to the best of our knowledge, that this GRAS notice is a complete, representative, and balanced assessment that includes all relevant information, both favorable and unfavorable, available and pertinent to the evaluation of safety and GRAS status of high purity steviol glycosides.

F. Availability of Information

The data and information that serve as the basis for this GRAS notice will be maintained at the offices of GLG Life Tech Corporation, 10271 Shellbridge Way, Suite 100, Richmond, BC V6X 2W8 Canada, and will be made available during customary business hours.

GLG certifies that no data or information contained in the body of this document are exempt from disclosure under the Freedom of Information Act (FOIA); however, Appendices 1 and 2 considered confidential as they contain information on technical work on a developmental product, and contain information regarding use levels and organoleptic studies. None of the information contained in Appendices 1 and 2 is safety related, and no non-public, safety-related data were used by GLG or the Expert Panel to reach a GRAS conclusion.

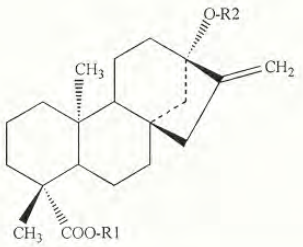
PART 2. IDENTITY, METHOD OF MANUFACTURE, SPECIFICATIONS, AND PHYSICAL OR TECHNICAL EFFECT

The identity, method of manufacture, and specifications of GLG's high purity steviol glycosides preparations remain unchanged from that which was described in GRN 493. GLG continues to utilize product specifications for its high purity steviol glycosides preparations that meet or exceed recommendations set by The Joint FAO/WHO Expert Committee on Food Additives (JECFA).

A. Chemical Identity of Ingredient

In the scientific literature, steviol glycosides have been referred to as stevia, stevioside, steviol glycosides, and stevia glycoside. JECFA adopted the term, steviol glycosides, for the family of steviol derivatives with sweetness properties that are derived from the stevia plant. Presently, the term, stevia, is used more narrowly to describe the plant or crude extracts of the plant. The chemical structures of various steviol glycosides that can be extracted from *Stevia rebaudiana* leaf are shown in Figure 1.

Figure 1. Chemical Structures of Various Steviol Glycosides[a,b]



	Compound name	C.A.S. No.	R1	R2
1	Steviol	471-80-7	H	H
2	Steviolbioside	41093-60-1	H	β-Glc-β-Glc(2→1)
3	Stevioside	57817-89-7	β-Glc	β-Glc-β-Glc(2→1)
4	Rebaudioside A	58543-16-1	β-Glc	β-Glc-β-Glc(2→1) | β-Glc(3→1)
5	Rebaudioside B	58543-17-2	H	β-Glc-β-Glc(2→1) | β-Glc(3→1)
6	Rebaudioside C (dulcoside B)	63550-99-2	β-Glc	β-Glc-α-Rha(2→1) | β-Glc(3→1)
7	Rebaudioside D	63279-13-0	β-Glc-β-Glc(2→1)	β-Glc-β-Glc(2→1) | β-Glc(3→1)
8	Rebaudioside E	63279-14-1	β-Glc-β-Glc(2→1)	β-Glc-β-Glc(2→1)
9	Rebaudioside F	438045-89-7	β-Glc	β-Glc-β-Xyl(2→1) | β-Glc(3→1)
10	Rubusoside	63849-39-4	β-Glc	β-Glc
11	dulcoside A	64432-06-0	β-Glc	β-Glc-α-Rha(2→1)

[a] From FAO (2007a).

[b] The indicated C.A.S. No. for Rubusoside as reported in the cited reference is incorrect and should be 64849-39-4.

More recently, Chaturvedula et al. (2013) reported isolating rebaudioside M, a minor component of total steviol glycosides in commercially available *Stevia rebaudiana* Bertoni extracts.

There are no known toxicants that have been identified in stevia.

A recent publication by Kumari et al. (2016) addressed the content and distribution of Total Phenolic Content (TPC), Total Flavonoid Content (TFC), and Total Antioxidant Capacity (TAC) of different portions of *Stevia rebaudiana.* TPC, TFC, and TAC were observed in all portions of the stevia plant, with the highest levels noted in the leaves; the relative TPC, TFC, and TAC amounts reflect the following order: leaf > flower > stem > branch > root. The higher levels in the leaves were attributed to an increased content of phenolics, flavonoids, and pigments in the stevia leaf. The authors also reported that TPC, TFC, and TAC amounts decreased with leaf maturity.

B. Manufacturing Processes

The method of manufacture of GLG's high purity steviol glycosides preparations remains unchanged from that which was described in GRN 493.

C. Product Specifications

1. JECFA Specifications for Steviol Glycosides

The composition of extracts of *Stevia rebaudiana* Bertoni depends upon the composition of the harvested leaves, which are, in turn, influenced by soil, climate, and the manufacturing process itself (FAO, 2007c).

In 2007, JECFA recommended that the method of assay should include a minimum requirement of 95% of the total of 7 specific steviol glycosides on a dried weight basis, and JECFA finalized food grade specifications at the 68th JECFA meeting with publication in the FAO JECFA Monograph 4 (FAO, 2007b). Stevioside and rebaudioside A (Reb A) are the major component glycosides of interest because of their sweetening property. The five other associated glycosides found in preparations of steviol glycosides accepted by the JECFA specifications with the 95% requirement are rebaudioside C (Reb C), dulcoside A, rubusoside, steviolbioside, and rebaudioside B (Reb B). These, however, are typically found at much lower levels than stevioside or rebaudioside A. JECFA updated the specifications for steviol glycosides in 2008 (FAO, 2008), and then again in 2010, when the specifications were expanded to include the original seven specific steviol glycosides plus rebaudioside D (Reb D) and rebaudioside F (Reb F) (FAO, 2010). Recently, rebaudioside M (Reb M) has garnered interest as an additional naturally-occurring sweet steviol glycoside.

JECFA describes steviol glycosides as a white to yellow powder, odorless to having a slight characteristic odor, and exhibiting a sweetness that is 200-300 times greater than sucrose. The ingredient must consist of a minimum of 95% of nine specific steviol glycosides. The steviol glycosides are freely soluble in water and ethanol, and the 1 in 100 solutions exhibit pH values between 4.5 and 7.0. The product should not have more than 1% ash, with no more than a 6% loss on drying at 105^{o}C for 2 hours. Any residual methanol levels should not exceed 200 ppm, and ethanol residues should not exceed 5,000 ppm. Arsenic levels should not exceed 1 ppm as determined by the atomic absorption hydride technique. Lead levels should not exceed 1 ppm.

2. Specifications for GLG's High Purity Steviol Glycosides Preparations and Supporting Methods

The specifications of GLG's high purity steviol glycosides preparations remain unchanged from that which was described in GRN 493. GLG continues to utilize product specifications for its high purity steviol glycosides preparations that meet or exceed recommendations set by The Joint FAO/WHO Expert Committee on Food Additives (JECFA).

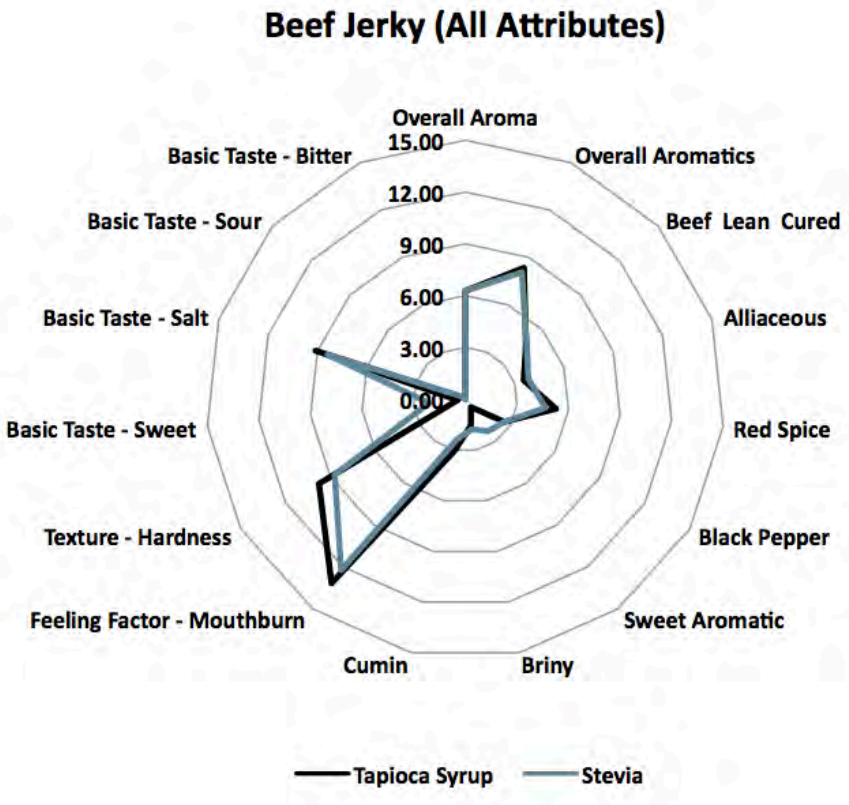
D. Physical or Technical Effect

GLG's high purity steviol glycosides are intended for use as a table top sweetener and as a non-nutritive sweetener, as described in GRN 493. This purpose of this supplement is to evaluate the safety of use of GLG's high purity steviol glycosides preparations as an ingredient in cured meat products.

GLG has conducted organoleptic studies to demonstrate sweetness and palatability in two developmental jerky products using Rebsweet™ RA80, a high purity steviol glycosides preparation.

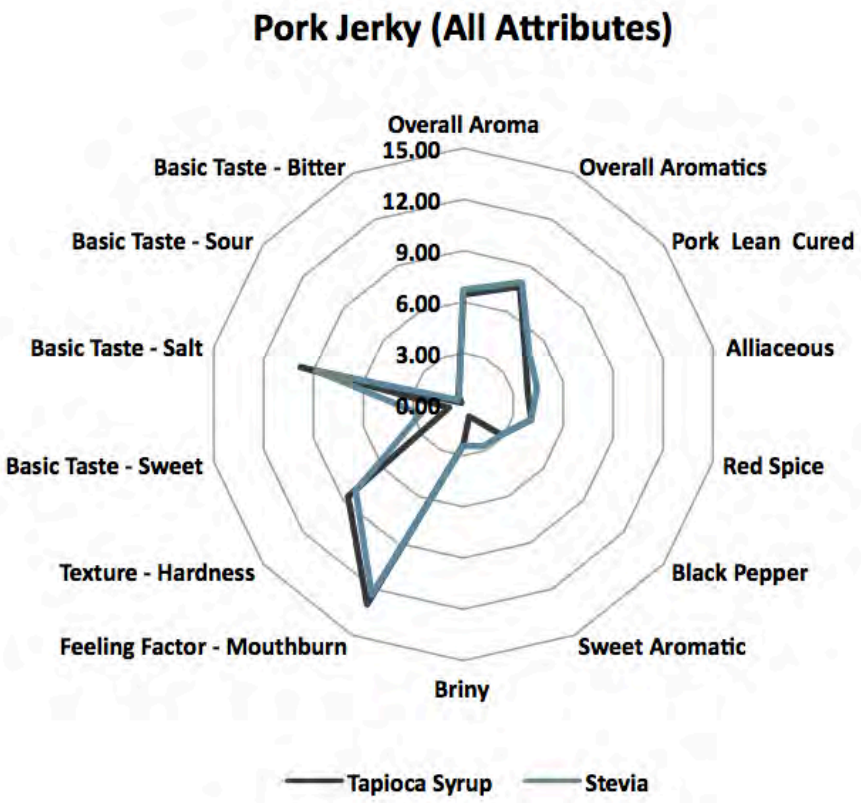
Beef was marinated in a mixture containing soy, spices, apple cider vinegar, water, and 940 ppm Rebsweet™ RA80. After preparing the jerky, the final concentration of Rebsweet™ RA80 was ~2,100 ppm. When compared with beef jerky made with tapioca syrup, beef jerky made with Rebsweet™ RA80, was found to have higher mean scores for basic sweet taste and sweet aromatic attributes. However, many of the other organoleptic attributes were found to be similar, demonstrating that GLG's high purity steviol glycosides preparations are a suitable sweetener to provide consumers with desired sweetness and lower calories in beef jerky applications. A comparison of the means of the beef jerky attributes, as determined in the organoleptic study, is provided in Figure 2. The sensory evaluation report on beef jerky is provided in Appendix 1.

Figure 2. Comparison of Beef Jerky Attributes



An analogous organoleptic study was performed for pork jerky. Pork was marinated in a mixture containing soy, spices, apple cider vinegar, water, and 940 ppm Rebsweet™ RA80. After preparing the jerky, the final concentration of Rebsweet™ RA80 was ~2,000 ppm. It was found that pork jerky prepared with GLG's high purity steviol glycosides product, Rebsweet™ RA80, had higher mean scores for basic sweet taste and sweet aromatic attributes when compared with pork jerky made with tapioca syrup. Many of the other organoleptic attributes had similar means, demonstrating that GLG's high purity steviol glycosides preparations are a suitable sweetener to provide consumers with desired sweetness levels and lower calories in pork jerky applications. A comparison of the means of the beef jerky attributes, as determined in the organoleptic study, is provided in Figure 3. The sensory evaluation report on pork jerky is provided in Appendix 2.

Figure 3. Comparison of Pork Jerky Attributes



E. Stability

1. Stability Data on Steviol Glycosides

Steviol glycosides have been reported to be stable over the pH range 3-9 and can be heated at 100°C for 1 hour, but, at pH levels greater than 9, it rapidly decomposes (Kinghorn, 2002). At pH

10, steviolbioside would be the major decomposition product produced from stevioside by alkaline hydrolysis (Wood et al., 1955). Chang and Cook (1983) investigated the stability of pure stevioside and Reb A in carbonated phosphoric and citric acidified beverages. Some degradation of each sweetening component after 2 months of storage at 37°C was noted. However, no significant change at room temperature or below, following 5 months of storage of stevioside and 3 months of storage of Reb A, was observed. Exposure to one week of sunlight did not affect stevioside, but approximately 20% loss of rebaudioside A was detected. Heating at 60°C for 6 days resulted in 0-6% loss of rebaudioside A.

Merisant (2008) conducted stability testing on rebaudioside A (1) as a powder, (2) as a pure sweetener in solution, and (3) on both cola-type and citrus carbonated beverages. In these investigations, no degradation was detected when the powder was stored at 105˚C for 96 hours. It was concluded that the powder was stable when stored for 26 weeks at 40±2˚C with relative humidity of 75±5%. Both published and unpublished testing results from Merisant revealed that rebaudioside A in carbonated citric acid beverages and phosphoric acid beverages did not significantly degrade during prolonged storage at refrigeration, normal ambient, or elevated ambient temperatures. Minimal loss of rebaudioside A was detected after storage at 60˚C with considerable degradation noted after 13 hours at 100˚C for carbonated beverage solutions and pure sweetener solutions (Merisant, 2008).

Cargill (2008) also conducted extensive stability testing on rebaudioside A as a powder under various storage conditions and under a range of pH and temperatures. Additionally, Cargill also investigated rebaudioside A stability in several representative food matrices at room temperature and elevated temperatures. Stability profiles were created for table top sweetener applications, mock beverages including cola, root beer and lemon-lime, thermally processed beverages, yogurt, and white cake. The results of stability testing revealed some degradation products that had not been detected in bulk rebaudioside A. These degradation products were structurally related to the steviol glycosides that are extracted from the leaves of *Stevia rebaudiana* Bertoni. All the degradation products were found to share the same steviol aglycone backbone structure as found in stevioside and rebaudioside A, but they differ by virtue of the glucose moieties present. The results of stability testing revealed that rebaudioside A is stable in various food matrices following several days or weeks of storage. The extent and rate of degradation is dependent on pH, temperature, and time. When placed in beverages, rebaudioside A is more stable in the pH range 4 to 6, and at temperatures from 5˚C to 25˚C (Cargill, 2008).

Photostability studies of the dry powder and mock beverages were performed to ascertain rebaudioside A behavior under defined conditions of fluorescent and near UV light exposure. Rebaudioside A was found to be photostable under the defined conditions of analysis (Clos et al., 2008).

In addition to the above described stability reports for purified rebaudioside A, in a GRAS notification by Sunwin and WILD Flavors (2010)---regarding purified steviol glycosides with

rebaudioside A and stevioside as the principal components---stability was investigated using a 0.04% solution of Reb A 80% in acidic solutions between pH 2.81 and 4.18. In this study, the solutions were stored at 32°C for 4 weeks, and the Reb A content was determined at 1, 2, and 4 weeks. Reb A 80% was found to be very stable at pH 3.17 and above. At pH 2.81, after 4 weeks of storage under accelerated conditions, only a 7% loss of Reb A was noted. Sunwin and WILD Flavors also studied the stability of Reb A 80% in simulated beverages using 0.1% citric acid (pH 3.2). The solutions were pasteurized and stored for 8 weeks at 4°C and 32 °C, and little difference in sweetness perception was found under these conditions.

2. Stability Data for GLG's High Purity Steviol Glycosides Preparations

The stability of GLG's high purity steviol glycosides preparations remain unchanged from that which was described in GRN 493.

PART 3. DIETARY EXPOSURE

The subject GLG-SG preparations with steviol glycosides (≥95%), containing rebaudioside A and stevioside as the principal components, are intended to be used as a table top sweetener and general purpose non-nutritive sweetener in various foods as defined in 21 CFR 170.3(o)(19)[2], as described in GRN 493, and in cured meat products, as described in this GRAS assessment. GLG's high purity steviol glycosides preparations are not intended for use in infant formulas. The intended use levels will vary by actual food category, but the actual levels are self-limiting due to organoleptic factors and consumer taste considerations. However, the amounts of GLG-SG preparations to be added to foods will not exceed the amounts reasonably required to accomplish its intended technical effect in foods as required by FDA regulation.[3]

A. Estimate of Dietary Exposure to the Substance

There have been many scholarly estimates of potential dietary intake replacement of sweeteners, including steviol glycosides, that have been published (FSANZ, 2008; Renwick, 2008; WHO, 2003) or submitted to FDA (Merisant, 2008). These were previously summarized in GRN 493.

In GRAS notification 301, a simplified estimate was proposed to, and accepted by, FDA based on the estimates of exposure in "sucrose equivalents" (Renwick, 2008) and the sweetness intensity of any particular sweetener (BioVittoria, 2009). As summarized in GRN 301, the 90th percentile consumer (in any population subgroup) of a sweetener which is 100 times as sweet as sucrose when used as a total sugar replacement would have a maximum intake of 9.9 mg per kg body weight (bw) per day.

[2] Non-nutritive sweeteners: Substances having less than 2 percent of the caloric value of sucrose per equivalent unit of sweetening capacity.
[3] See 21 CFR 182.1(b)(1).

GLG intends to use its high purity steviol glycosides preparation in the same foods and at the same levels as described in GRN 493, in addition to use as a non-nutritive sweetener in cured meat products. As the use of GLG-SG in cured meat products is expected to replace caloric sweeteners such as sugar, molasses, and tapioca syrup in these products, there is no expectation of significant increased dietary intake beyond the maximum exposure determined for replacement of all dietary sugars as described in GRN 493, as replicated below.

GLG's steviol glycoside preparations have varying sweetness intensities when compared with sucrose; specific sweetness intensities are provided in Table 1.

Table 1. Sweetness Intensity of GLG-SG Preparations Relative to Sucrose

PRODUCT	SWEETNESS INTENSITY
Anysweet RA50 Plus	280
Anysweet RA60 Plus	320
Rebsweet RA80	360
Rebsweet RA85	380

Therefore, the highest 90th percentile consumption by any population subgroup of GLG's high purity steviol glycosides preparations would be approximately 3.54 mg per kg bw per day (for Anysweet RA50). A weighted sum estimate was used to determine the steviol equivalency factor, on a worst-case scenario basis. For example, GLG's Anysweet RA50 steviol equivalence factor was calculated from the molecular weight ratios of steviol to rebaudioside A, stevioside, and remaining steviol glycosides (as steviolbioside), on a percent composition basis, as follows:

Based on a weighted sum estimate for steviol equivalents,[4] the consumption would be less than 1.37 mg per kg bw per day steviol equivalents for any population group, on a worst-case scenario basis. These calculations are summarized in Table 2.

The values in Table 2 assume that GLG's high purity steviol glycosides preparations would be the only sweetener used in food products, which makes these estimates extremely conservative since the likelihood of this occurrence is minimal. In all population groups, the estimated daily intake of GLG-SG preparations, expressed as steviol equivalents, is well below the JECFA-established acceptable daily intake (ADI) of 4.0 mg per kg bw per day of steviol equivalents.

In addition, based on the maximum use level of GLG's high purity steviol glycosides preparations of 1,000 mg per kg of marinade, which corresponds to a maximum of 2.5 g GLG-SG per kg jerky

[4] 38.7% as calculated as a percent of molecular weight of steviol to the molecular weight of rebaudioside A, stevioside, and steviol glycosides (as steviolbioside), on a percent composition basis. The total steviol glycosides content was assumed to be 100%. All steviol glycosides, with the exception of Reb A and stevioside, were treated as steviolbioside for calculation purposes.

product, the maximum exposure to steviol glycosides can be calculated from United States Department of Agriculture (USDA) survey data (2013-2014) for cured meats (U.S. Department of Agriculture et al., 2014). The mean consumption of all users over the age of 2 years of cured meat is approximately one ounce (28 g per day). The daily consumption for a 90th percentile user of cured meat products can be estimated using a value of twice the mean (56 g per day). Therefore, the maximum steviol glycosides consumption from use in cured meats at a maximum use level of 2.5 g per kg as a replacement for sugar, molasses, honey and other sugar-based syrups would be 140 mg per day (equivalent to 54.3 mg steviol equivalents per day), or 2.33 mg per kg bw per day steviol glycosides for a 60-kg individual (equivalent to 0.91 mg per kg bw per day steviol equivalents).

While this level is not trivial compared to the total estimate of steviol glycoside consumption, the total intake (i.e., the sum of the additional proposed used in cured meat products and the previously proposed use in GRN 493) is unlikely to exceed the JECFA-established ADI of 4.0 mg per kg bw per day of steviol equivalents.

Table 2. Daily Intake of Sweeteners (In Sucrose Equivalents) & Estimated Daily Intakes of High Purity GLG-SG Preparations

Population Group	Intakes of Sweeteners (g sucrose/kg bw/day)[a]		Intake of RA50 (mg/kg bw/day)[b]		Intake of RA50 as Steviol Equivalents[c]	
	Low	High	Low	High	Low	High
Healthy Population	255	675	0.91	2.41	0.35	0.93
Diabetic Adults	280	897	1.00	3.20	0.39	1.24
Healthy Children	425	990	1.52	3.54	0.59	1.37
Diabetic Children	672	908	2.40	3.24	0.93	1.25
Population Group	**Intakes of Sweeteners (g sucrose/kg bw/day)[a]**		**Intake of RA60 (mg/kg bw/day)[b]**		**Intake of RA60 as Steviol Equivalents[c]**	
	Low	**High**	**Low**	**High**	**Low**	**High**
Healthy Population	255	675	0.80	2.11	0.30	0.80
Diabetic Adults	280	897	0.88	2.80	0.33	1.07
Healthy Children	425	990	1.33	3.09	0.51	1.18
Diabetic Children	672	908	2.10	2.84	0.80	1.08
Population Group	**Intakes of Sweeteners (g sucrose/kg bw/day)[a]**		**Intake of RA80 (mg/kg bw/day)[b]**		**Intake of RA80 as Steviol Equivalents[c]**	
	Low	**High**	**Low**	**High**	**Low**	**High**
Healthy Population	255	675	0.71	1.88	0.26	0.68
Diabetic Adults	280	897	0.78	2.49	0.28	0.90
Healthy Children	425	990	1.18	2.75	0.43	1.00
Diabetic Children	672	908	1.87	2.52	0.68	0.91

Population Group	Intakes of Sweeteners (g sucrose/kg bw/day)[a]		Intake of RA85 (mg/kg bw/day)[b]		Intake of RA85 as Steviol Equivalents[c]	
	Low	High	Low	High	Low	High
Healthy Population	255	675	0.67	1.78	0.24	0.63
Diabetic Adults	280	897	0.74	2.36	0.26	0.83
Healthy Children	425	990	1.12	2.61	0.40	0.92
Diabetic Children	672	908	1.77	2.39	0.63	0.85

[a] Source: Renwick (2008).

[b] Calculated by dividing the sucrose intake by the average relative sweetness values from Table 1.

[c] Calculated based on the ratio of molecular weights of rebaudioside A, steviol, and steviol glycosides, as described above.

B. Estimated Dietary Exposure to Any Other Substance That is Expected to be Formed In or On Food

This section is not applicable to GLG's high purity steviol glycosides preparations, which would be chemically stable under conditions of use.

C. Dietary Exposure to Contaminants or Byproducts

While a recent publication by Kumari et al. (2016) has demonstrated the presence of TPC, TFC, and TAC in *S. rebaudiana* leaf --- and the observed activity has been attributed to naturally-occurring phytochemicals such as phenolics, flavonoids, and pigments in the plant --- the study has minimal relevance with regard to the safety considerations of the highly purified stevia extract, of which ≥ 95% consists of the most familiar steviol glycosides. These contaminants, if present, are in low amounts and were likely similarly present in purified test materials that were used in the toxicology studies.

Furthermore, no concerns regarding dietary exposure to contaminants or byproducts have been raised by expert regulatory bodies, including the World Health Organization/Joint FAO/WHO Expert Committee on Food Additives (WHO/JECFA), European Food Safety Authority (EFSA), Food Standards Australia New Zealand (FSANZ), and FDA, since JECFA's first steviol glycosides review was performed in 2000 (WHO, 2000).

PART 4. SELF-LIMITING LEVELS OF USE

It has been well-documented in the published literature that the use of steviol glycosides is self-limiting due to organoleptic factors and consumer taste considerations (Brandle et al., 1998; Carakostas et al., 2008; Gerwig et al., 2016; Gupta et al., 2016; Kochikyan et al., 2006; Prakash et al., 2008). These organoleptic factors include bitterness and astringency, as well as a lingering metallic aftertaste (Gerwig et al., 2016).

PART 5. EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958

A. Other Information on Dietary Exposure

1. History of Traditional Medicinal and Human Food Use

The history of stevia use through October 2013 was previously reviewed in GRN 493.

In October 2014, Zenith International reported that worldwide stevia sales were on course to increase 14% to 4,670 tons, associated with a market value of $336 million. Furthermore, it has been projected that the total market for stevia in 2017 will be 7,150 tons with an associated market value of $578 million (Zenith, 2014).

NewHope360 reported that the global market for stevia in 2014 was $347 million, and the market is expected to increase to $565.2 million by 2020. In addition, consumption is expected to increase from 2014 levels of 5,100.6 tons to 8,506.9 tons by 2020 (NewHope360, 2015).

Most recently, Nutritional Outlook reported that Mintel data indicated a 48% increase in stevia-containing products over the last five years (Decker and Prince, 2018).

B. Summary of Regulatory History of High Purity Steviol Glycosides

Stevia-derived sweeteners are permitted as food additives in South America and in several countries in Asia, including China, Japan, and Korea. In recent years, these sweeteners have received food usage approvals in Mexico, Australia, New Zealand, Switzerland, France, Peru, Uruguay, Colombia, Senegal, Russia, Malaysia, Turkey, Taiwan, Thailand, Israel, Canada, and Hong Kong (EFSA, 2010; Health Canada, 2012; Watson, 2010). In the US, steviol glycosides have been used as a dietary supplement since 1995 (Geuns, 2003).

1. U.S. Regulatory History

Based on available information from FDA's GRAS Notice Inventory website (FDA, 2018) as of March 20, FDA has issued 48 "no questions" letters on GRAS notices on rebaudioside A, rebaudioside D, rebaudioside M, or steviol glycosides, including those undergoing enzyme treatment. A summary of these filings is presented in Table 3.

Table 3. FDA's GRAS Notice Inventory on Rebaudioside & Steviol Glycosides Preparations[a,c]

COMPANY	FDA GRAS IDENTIFIER	MATERIAL IDENTITY	INTENDED FOOD USES
1. Merisant	GRN 252	High-Purity Reb A ≥95%	Variety of food categories & table top sweetener
2. Cargill Inc.	GRN 253	High-Purity Reb A ≥97%	General-purpose sweetener, excluding

COMPANY	FDA GRAS IDENTIFIER	MATERIAL IDENTITY	INTENDED FOOD USES
			meat & poultry products
3. McNeil Nutritionals LLC	GRN 275	Purified Steviol Glycosides – Reb A Principal Component	Table top sweetener
4. Blue California	GRN 278	High-Purity Reb A ≥97%	General-purpose & table top sweetener
5. Sweet Green Fields LLC	GRN 282	High-Purity Reb A ≥97%	General-purpose sweetener, excluding meat & poultry products
6. Wisdom Natural Brands	GRN 287	Purified Steviol Glycosides >95% – Reb A and Stevioside Principal Component	General-purpose sweetener, excluding meat, poultry products & infant formulas
7. Sunwin USA LLC & WILD Flavors	GRN 303	High-Purity Reb A ≥95%/ ≥98%	General-purpose sweetener, excluding meat, poultry products & infant formulas
8. Sunwin USA LLC & WILD Flavors	GRN 304	Purified Steviol Glycosides >95% – Reb A and Stevioside Principal Component	General-purpose sweetener, excluding meat, poultry products & infant formulas
9. Pyure Brands, LLC	GRN 318	High-Purity Reb A 95%/ 98%	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
10. PureCircle USA Inc	GRN 323	Purified Steviol Glycosides – Reb A Principal Component	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
11. GLG Life Tech Ltd[c]	GRN 329	High-Purity Reb A ≥97%	General-purpose sweetener, excluding meat & poultry products
12. NOW Foods	GRN 337	Enzyme Modified Steviol Glycosides Preparation (EMSGP)	General-purpose sweetener in foods, excluding meat & poultry products, at levels determined by good manufacturing practices
13. GLG Life Tech Ltd[c]	GRN 348	High-Purity Stevioside ≥95%	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
14. GLG Life Tech Ltd[c]	GRN 349	High-Purity Steviol Glycosides ≥97%	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
15. Guilin Layn Natural Ingredients, Corp.	GRN 354	High-Purity Reb A ≥97%	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
16. BrazTek International Inc.	GRN 365	Purified Reb A	General-purpose sweetener, excluding meat & poultry products
17. Sinochem Qingdao Co. Ltd.	GRN 367	High-Purity Steviol Glycosides ≥95%	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
18. Shanghai Freemen Americas LLC	GRN 369	Purified Reb A	General-purpose sweetener, excluding meat & poultry products
19. Toyo Sugar Refining Co., Ltd. & Nippon Paper Chemicals Co., Ltd.	GRN 375	Enzyme Modified Steviol Glycosides	General-purpose sweetener in foods, excluding meat and poultry products, at levels determined by good manufacturing practices

COMPANY	FDA GRAS IDENTIFIER	MATERIAL IDENTITY	INTENDED FOOD USES
20. GLG Life Tech Ltd[b]	GRN 380	Purified Reb A	General purpose & table top sweetener, excluding meat & poultry products
21. Chengdu Wagott Pharmaceutical	GRN 388	Purified Reb A	General purpose & table top sweetener, excluding meat & poultry products
22. Chengdu Wagott Pharmaceutical	GRN 389	Steviol Glycosides with Stevioside as the Principal Component	General purpose & table top sweetener, excluding meat & poultry products
23. Daepyung Co., Ltd.	GRN 393	Purified Reb A	General purpose & table top sweetener, excluding meat & poultry products
24. Daepyung Co., Ltd.	GRN 395	Steviol Glycosides with Reb A and Stevioside as the Principal Components	General purpose & table top sweetener, excluding meat & poultry products
25. MiniStar International, Inc.	GRN 418	Purified Reb A	General-purpose sweetener, excluding meat, poultry products & infant formulas.
26. Daepyung Co., Ltd.	GRN 448	Enzyme Modified Steviol Glycosides	General-purpose sweetener, excluding meat, poultry products & infant formulas.
27. Daepyung Co., Ltd.	GRN 452	Enzyme Modified Steviol Glycosides	General-purpose sweetener, excluding meat, poultry products & infant formulas.
28. PureCircle USA, Inc.	GRN 456	High-Purity Reb D $\geq$95%	General-purpose sweetener, excluding meat, poultry products & infant formulas.
29. Almendra, Ltd.	GRN 461	High-Purity Reb A $\geq$97%	General-purpose sweetener, excluding meat, poultry products & infant formulas.
30. Qufu Xiangzhou Stevia Products Co., Ltd.	GRN 467	High-Purity Reb A $\geq$98%	General-purpose sweetener, excluding meat, poultry products & infant formulas.
31. PureCircle USA, Inc.	GRN 473	Purified Steviol Glycosides – Reb M (Reb X) Principal Component	General-purpose sweetener, excluding meat, poultry products & infant formulas.
32. GLG Life Tech Corp.	GRN 493	High purity steviol glycosides $\geq$95%	General-purpose sweetener, excluding meat, poultry products.
33. GLG Life Tech Corp.	GRN 512	High purity Reb M $\geq$95%	General-purpose sweetener, excluding meat, poultry products & infant formulas.
34. Almendra Limited	GRN 516	Steviol Glycosides with Reb A and Stevioside as the Principal Components	General-purpose sweetener, excluding meat, poultry products & infant formulas.
35. GLG Life Tech Corp.	GRN 536	High purity Reb C and Steviol glycosides with Reb C as the Principal Component	General-purpose sweetener, excluding meat, poultry products & infant formulas.
36. GLG Life Tech Corp.	GRN 548	High purity Reb D	General-purpose sweetener, excluding meat, poultry products & infant

COMPANY	FDA GRAS IDENTIFIER	MATERIAL IDENTITY	INTENDED FOOD USES
			formulas.
37. Productora Alysa SpA	GRN 555	Steviol Glycosides with Reb A as the Principal Component	General-purpose sweetener, excluding meat, poultry products & infant formulas.
38. PureCircle, Ltd.	GRN 607	Glucosylated steviol glycosides (minimum purity 80%)	Use as a flavoring agent and flavor modifier at levels ranging from 100 to 1,000 ppm
39. PureCircle, Ltd.	GRN 619	Steviol Glycosides ≥95%	General-purpose sweetener, excluding meat, poultry products & infant formulas.
40. Cargill, Inc.	GRN 626	Steviol glycosides (Reb M and Reb D) produced in *Saccharomyces cerevisiae*	General-purpose sweetener
41. DSM Nutritional Products, LLC.	GRN 632	Rebaudioside A from *Yarrowia lipolytica*	General-purpose sweetener, excluding meat, poultry products & infant formulas.
42. Hunan Huacheng Biotech Inc.	GRN 638	High purity steviol glycosides with Reb A as the principal component	General-purpose sweetener, excluding meat, poultry products & infant formulas.
43. GLG Life Tech Corporation	GRN 656	Enzyme-modified steviol glycosides	General-purpose sweetener, excluding meat, poultry products & infant formulas.
44. PureCircle USA	GRN 662	Glucosylated steviol glycosides	General-purpose sweetener, excluding meat, poultry products & infant formulas.
45. Blue California	GRN 667	Rebaudioside M	General-purpose sweetener, excluding meat, poultry products & infant formulas.
46. Xinghua GL Stevia Co., Ltd	GRN 702	Purified steviol glycosides	General-purpose sweetener
47. Blue California	GRN 715	Rebaudioside D	General-purpose sweetener, excluding meat, poultry products & infant formulas.
48. Shandong Shengiangyuan Biotechnology	GRN 733	Purified steviol glycosides	General-purpose sweetener, excluding meat, poultry products & infant formulas.

[a] This table was derived, in part, from (McQuate, 2011).

[b] The name of this company is now GLG Life Tech Corporation.

[c] GRN 744, submitted by PureCircle Limited, regarding steviol glycosides consisting primarily of rebaudioside M, was filed by FDA and is presently under review; GRN 745, submitted by PureCircle Limited, regarding steviol glycosides consisting primarily of rebaudioside M, was filed by FDA and is presently under review; GRN 759, submitted by DSM Food Specialties/DSM Nutritional Products of North America, regarding steviol glycosides consisting primarily of rebaudioside M produced in *Yarrowia lipoytica*, was filed by FDA and is presently under review; GRN 764, submitted by Sichuan Ingia Biosynthetic Co., Ltd., regarding rebaudioside D, was filed by FDA and is presently under review.

In addition, the Flavor and Extract Manufacturers Association (FEMA) has included several steviol glycosides preparations on their GRAS lists as shown in Table 4.

Table 4. FEMA GRAS Status for Steviol Glycoside Preparations

STEVIOL GLYCOSIDES PREPARATION	FEMA NUMBER	REFERENCE
Rebaudioside A	4601	(Smith et al., 2009)
Rebaudioside C; dulcoside B	4720	(Leffingwell, 2011)
Glucosyl steviol glycosides; enzymatically modified stevia extract	4728	(Leffingwell and Leffingwell, 2014; Marnett et al., 2013)
Stevioside	4763	(Leffingwell and Leffingwell, 2014; Marnett et al., 2013)
Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside A 60%	4771	(Marnett et al., 2013)
Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside A 80%	4772	(Marnett et al., 2013)
Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 30%	4796	(Cohen et al., 2015a; Cohen et al., 2015b)
Steviol glycoside extract, *Stevia rebaudiana,* Rebaudioside A 22%	4805	(Cohen et al., 2015a; Cohen et al., 2015b)
Steviol glycoside extract, *Stevia rebaudiana* Rebaudioside C 22%	4806	(Cohen et al., 2015a; Cohen et al., 2015b)

2. Canadian Regulatory History

On September 18, 2009, based on a review of the international regulation of *Stevia rebaudiana* and the clinical evidence for safety and efficacy, the Natural Health Products Directorate, Health Canada (2009) adopted the following guidelines for the use of *stevia* and steviol glycosides in Natural Health Products (NHPs) (Health Canada, 2009). The revised recommendation for the maximum limit for steviol glycosides in NHPs is in accordance with the full acceptable daily intake (ADI) of 4 mg steviol per kg bw established by JECFA (WHO, 2008).

On November 30, 2012, Health Canada published its final clearance for use of steviol glycosides as a sweetener in foods (Health Canada, 2012). In March 2014, Health Canada updated the List of Permitted Sweeteners (Lists of Permitted Food Additives) to include steviol glycosides in applications as a table-top sweetener and as an ingredient in a variety of foods, beverages, baked goods, meal replacement bars, condiments, and confectionary and gums (Health Canada, 2014). On January 15, 2016, Health Canada approved the use of Reb M for use as a high-intensity sweetener under the same conditions as the previously approved steviol glycosides (Health Canada, 2016).

Health Canada's Food Directorate updated its "List of Permitted Sweeteners" to allow for the use of steviol glycosides as a sweetener in 'unstandardized snack bars,' including granola bars, cereal bars, fiber bars, and protein isolate-based bars (Health Canada, 2017b). Health Canada (2017a) also modified the "List of Permitted Sweeteners" to include "all the steviol glycosides in the Stevia rebaudiana Bertoni plant (stevia plant)."

3. European Regulatory History

The Joint Expert Committee on Food Additives (JECFA) reviewed steviol glycosides at its 51st, 63rd, 68th and 73rd meetings. In 2000, JECFA published the original review on steviol glycosides (WHO, 2000). JECFA established a temporary ADI (acceptable daily intake) of 0-2 mg per kg (on a steviol basis) at its 63rd meeting (WHO, 2006). Additionally, JECFA finalized food grade specifications (FAO, 2007c), although they were subsequently updated in 2008 (FAO, 2008) and 2010 (FAO, 2010) (see below). At the 69th meeting, the temporary status of the ADI was removed, and the ADI was raised to 0-4 mg per kg bw per day (on a steviol basis) as a result of the JECFA review of more recently completed clinical studies with steviol glycosides (WHO, 2008). In 2009, JECFA published a final monograph addendum on steviol glycosides (WHO, 2009).

In early 2009, a number of parties, including the government of Australia and the Calorie Control Council, submitted a request to the Codex Committee on Food Additives in which it was proposed that the JECFA specifications for steviol glycosides should be modified to allow inclusion of rebaudioside D and rebaudioside F as specifically named acceptable glycosides that would be considered as part of the minimum 95% steviol glycosides composition (CCFA, 2009). This proposed modification was endorsed by the Codex Alimentarius Committee in July 2009; it was on the agenda for discussion at the JECFA Meeting in June, 2010 (FAO/WHO, 2009), and JECFA subsequently took final action in approving the modified steviol glycosides specifications to include rebaudioside D and rebaudioside F (FAO, 2010).

In 2008, Switzerland's Federal Office for Public Health approved the use of stevia as a sweetener citing the favorable actions of JECFA (Health, 2008). Subsequently, France published its approval for the food uses of rebaudioside A with a purity of 97% (AFSSA, 2009a; AFSSA, 2009b).

In light of JECFA's 2008 findings, and in response to a June 2008 request by the European Commission for European Food Safety Authority (EFSA) to deliver a scientific opinion on the safety of steviol glycosides as a sweetener for use in the food categories specified in the dossiers from three petitioners, EFSA reexamined the safety of steviol glycosides (EFSA, 2010). After considering all the data on stability, degradation products, metabolism and toxicology, the EFSA Panel established an ADI for steviol glycosides, expressed as steviol equivalents, of 4 mg per bw per day, which is similar to JECFA's determination.[5] In addition, on May 25, 2011, EFSA published

[5] From a historical perspective, it is noted that the UK's Advisory Committee on Novel Foods and Processes for the Ministry of Agriculture, Fisheries and Food on September 24, 1998 rejected an application for use of steviol glycosides as a sweetener in herbal teas because "the applicant had not provided all of the information necessary to enable an assessment to be made" MAFF. 1998. Advisory Committee on Novel

a determination that the daily dietary intake for use of rebaudioside A as a flavoring substance in a variety of foods would be less than the ADI for steviol glycosides (EFSA, 2011). In 2014, EFSA evaluated extending the use of steviol glycosides as ingredients in food categories to include coffee, tea, and herbal and fruit infusions (assessed at 10 mg per L steviol glycosides). Exposure estimates were lower than those determined by the Panel in 2011 due to available data, and remained below the ADI of 4 mg per kg bw per day, with the exception of toddlers from one country at the 95th percentile exposure level of 4.3 mg per kg bw per day (EFSA, 2014). More recently, exposure estimates, based on maximum permitted levels (MPLs) and proposed use levels increased to 29 mg per L steviol glycosides, were found to have a "negligible" impact on dietary intake for all population groups, with the mean exposure estimate below the ADI of 4 mg per kg bw per day, with the exception of toddlers from one country at the 95th percentile exposure level of 4.3 mg per kg bw per day. The EFSA panel concluded that "dietary exposure to steviol glycosides (E 960) is similar to the exposure estimated in 2014 and therefore does not change the outcome of the safety assessment" (EFSA, 2015).

The appropriate European regulatory bodies, including the joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA), have now agreed that steviol glycosides are safe for all populations to consume and are a suitable sweetening option for diabetics. Effective December 2, 2011, the EU approved their use as food additives (EU, 2011). In March 2016, the EU approved the use of steviol glycosides in mustard (Michail, 2016).

Most recently, an amendment to the EU food additives regulation 231/2012, which became active on November 3, 2016, removed the previous requirement for stevia blends to contain at least 75% reb A or stevioside. In addition, the updated regulation ---(EU) 2016/1814---now permits the following steviol glycosides in stevia blends: stevioside, rebaudiosides A, B, C, D, E, F and M, steviolbioside, rubusoside, and dulcoside (Searby, 2016).

The EFSA Panel of Food Additives and Nutrient Sources reviewed an application for glucosylated steviol glycoside preparations for use as a new food additive. The Panel concluded that the data supplied by the applicant were "insufficient to assess the safety" of the glucosylated steviol glycosides preparation. It should be noted that no safety concerns were raised by the EFSA Panel, and that their decision was based on the "limited" data provided in the dossier submitted by the applicant (EFSA, 2018).

Foods and Processes for the Ministry of Agriculture, Fisheries and Food. In.). In 1999, the Scientific Committee on Food for the European Commission concluded that "there are no satisfactory data to support the safe use of these stevia plants and leaves" EuropeanCommission. 1999a. Opinion on Stevia Rebaudiana Bertoni plants and leaves. Scientific Committee on Food (CS/NF/STEV/3 Final, 17 June 1999). In another opinion also dated June 17, 1999, the Committee also reiterated "its earlier opinion that stevioside is not acceptable as a sweetener on the presently available data" EuropeanCommission. 1999b. Opinion on stevioside as a sweetener. Scientific Committee on Food (CS/ADD/EDUL/167Final, 17 June 1999).

4. Asian Regulatory History

As of May 2010, the government of Hong Kong amended its food regulations to allow the use of steviol glycosides as a permitted sweetener in foods (Safety, 2010). This action followed in the aftermath of the detailed safety evaluation and favorable findings as reported by JECFA.

The international community continued to exhibit much interest in the food uses of steviol glycosides, with additional advances reported in early July 2011. The Codex Alimentarius Commission has adopted proposed maximum use levels for steviol glycosides in all major food and beverage categories, and this action was expected to favorably influence authorizations of stevia uses in India, Indonesia, Thailand, and the Philippines (FoodNavigator, 2011). An article published online by FoodNavigator (2013) states the following: “with approvals now in Vietnam, the Philippines, Malaysia, Singapore and Thailand, Indonesia is the only [Southeast Asian nation] where stevia hasn’t been given the rubber stamp” (Whitehead, 2013). Furthermore, the International Alliance of Dietary/Food Supplement Associations (IADSA) reported that the Codex Alimentarius Commission agreed to adopt the use of steviol glycosides for addition to chewable food supplements as had been requested by IADSA (NewHope360, 2011).

The Food Safety and Standards Authority of India (FSSAI) convened on September 20, 2012, at which time they approved the use of steviol glycosides as a non-nutritive sweetener in a variety of foods. The FSSAI specified that: the steviol glycosides must meet the specifications and purity as established by JECFA; table top sweetener tablets may contain 7 mg of steviol equivalents per 100 mg carrier/filler, as well as established maximum use levels specific to 11 distinct food categories including dairy, beverage, and chewing gum applications (FSSAI, 2012).

Since December 10, 2012, over thirty registrations have been granted by FDA Philippines to stand-alone steviol glycosides sweeteners or foods containing steviol glycosides as ingredients, including: FR-104390, Steviten Light Brand Steviol Glycosides 95% Sweetener Powder; FR-109427, Del Monte Pineapple Chunks in Extra Light Syrup Reduced Calorie with Steviol Glycosides from Stevia; FR-101120, Diebetamil Zero Calorie Sweetener with Stevia (stick pack); and FR-102127, Sawayaka Stevia Sweetener (1 g sticks) (Philippines, 2014).

Steviol glycosides are also listed under INS number 960 in the Food Additives Permitted Under the Singapore Food Regulations document prepared by the Agri-Food & Veterinary Authority (AVA) of Singapore (AVA, 2014).

5. Other Regulatory History

In 2008, the Food Standards Australia New Zealand (FSANZ) completed its evaluation of an application for use of steviol glycosides in foods. FSANZ recommended that the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) amend the Australia New Zealand Food Standards Code to allow the use of steviol glycosides in food (FSANZ, 2008). In December 2010, FSANZ recommended accepting the increased usage levels as requested since

no public health and safety issues were identified (FSANZ, 2010). Subsequently, FSANZ approved an increase in the maximum permitted level (MPL) of steviol glycosides (expressed as steviol equivalents) in ice cream, water based beverages, brewed soft drinks, formulated beverages, and flavored soy beverages up to 200 mg per kg, and in plain soy beverages up to 100 mg per kg (FSANZ, 2011). In a recent risk assessment, FSANZ concluded that the use of Reb M does not pose any "public health and safety issues" (FSANZ, 2015b). In addition, FSANZ proposed to add Reb M to the list of permitted steviol glycosides (FSANZ, 2015a). On January 14, 2016, Reb M was approved for use "as a food additive in accordance with the current permissions for steviol glycosides" (FSANZ, 2016a).

Most recently, FSANZ called for submissions on permitting all minor steviol glycosides extracted from stevia leaf to be included in the definition of steviol glycosides in the Food Standards Code, noting that "[no] evidence was found to suggest that the proposed changes pose any public health and safety concerns." The submission period ended on December 19, 2016 (FSANZ, 2016b). Subsequently, on February 8, 2017, FSANZ approved a draft variation of the definition of steviol glycosides to include all steviol glycosides present in the *Stevia rebaudiana* leaf (FSANZ, 2017).

On September 10, 2012, the South African Department of Health issued an amendment to labeling regulations indicating: "in the case of the sweetener steviol glycosides, it shall be described as 'Steviol Glycosides' or 'Steviol Extract.'" On the same date, steviol glycosides were added to the List of Permissible Sweeteners (RSADH, 2012a; RSADH, 2012b).

PART 6. NARRATIVE

GRAS Associates submitted GRAS notification 493 on behalf of GLG on December 9, 2013. The key safety information in GRN 493 included multiple published toxicology studies, along with favorable reviews and subsequent regulations issued by respected scientific regulatory bodies, including JECFA, FSANZ, WHO, and FDA. FDA issued a "no questions" letter to GRN 493 on May 30, 2014. As of March 20, 2018, 48 "no questions" letters have been issued by FDA for various steviol glycosides preparations, as reported on FDA's GRAS Notice Inventory website (FDA, 2018). The collective evaluation of steviol glycosides safety studies apply to the high purity steviol glycosides mixture described herein.

An updated review of the scientific literature was performed covering the time period of December 2013 to the present to ascertain whether or not any new safety information has been published or any adverse effects have been reported due to ingestion of steviol glycosides. The references that were identified in the search with the key words "stevia" and "steviol glycosides" are discussed below.

The updated literature reveals a growing body of evidence that steviol glycosides are safe for human consumption. From the safety perspective, only a few references are worthy of elaboration, as portrayed in the following paragraphs:

1. In a recent review, Urban et al. (2013) examined the extensive genotoxicity database on steviol glycosides because some concern has been expressed in two recent publications (Brahmachari et al., 2011; Tandel, 2011) in which the authors concluded that additional testing is necessary to adequately address the genotoxicity profile (Urban et al., 2013). The review aimed to address this matter by evaluating the specific genotoxicity studies of concern, while evaluating the adequacy of the database that includes more recent genotoxicity data not noted in these publications. The results of this literature review showed that the current database of *in vitro* and *in vivo* studies for steviol glycosides is robust and does not indicate that either stevioside or rebaudioside A are genotoxic. This finding, combined with the lack of evidence for neoplasm development in rat bioassays, supports the safety of all steviol glycosides with respect to their genotoxic/carcinogenic potential.

2. Subsequently, Urban et al. (2015) reviewed the potential allergenicity of steviol glycosides. The authors noted that: “hypersensitivity reactions to stevia in any form are rare” and concluded that current data do not support claims that steviol glycosides are allergenic. In addition, the authors stated that there is “little substantiated scientific evidence” to warrant consumer warning labels for highly purified stevia extracts (Urban et al., 2015).

3. Additional studies have been conducted on some of the steviol glycosides present in the Sinochem product. A recently published study compared the anaerobic *in vitro* metabolism of rebaudiosides A, B, D, and M (Purkayastha et al., 2014). In all cases, the rebaudiosides were hydrolysed to steviol within 24 hours with the majority of metabolism occurring within the first 8 hours. Metabolism of rebaudiosides took longer at higher concentrations (2.0 mg per mL vs. 0.2 mg per mL). There were no marked differences in the rate or extent of hydrolysis observed between male and female fecal homogenates or the individual rebaudiosides (Purkayastha et al., 2014). Results from this study corroborate the presumption of safety of rebaudioside D, given that it is observed to have a similar metabolism to that of Reb A.

4. Similarly, Nikiforov et al. (2013) reported similar *in vitro* metabolism for Reb A and Reb D in simulated gastrointestinal fluids, rat liver microsomes, and rat cecal contents, as well as through plasma analysis in a rat toxicity study. Furthermore, a repeated exposure dietary toxicity study demonstrated comparable results between rats administered 2,000 mg per kg per day Reb D and those administered 2,000 mg per kg per day Reb A. These results further support the presumption of safety of rebaudioside D.

5. Shannon et al. (2016) investigated the endocrine disrupting potential of stevioside, rebaudioside A, and steviol in a series of *in vitro* bioassays. Steviol was observed to antagonize progesterone nuclear receptor transcriptional activity, increase progesterone production, and induce an agonistic response on the progesterone receptor of sperm cells (Catsper). While the authors conclude that stevia may not be a safe alternative to sugar or

synthetic sweeteners, it is important to note that it is difficult to translate *in vitro* concentrations to local concentrations *in vivo* at receptors, and that no adverse effects were observed in reproductive studies.

6. Roberts et al. (2016) suggested that a higher ADI for steviol glycosides than assigned by JECFA is justified based on metabolic factors to reduce the 100X safety factor. A chemical-specific adjustment factor (CSAF), as defined by the WHO in 2005, was determined by comparative studies in rats and humans. A CSAF that is less than the standard 100X safety factor will result in an increase in the ADI, independent of the no observed adverse effect level (NOAEL). The authors determined that using a CSAF results in an ADI value of 6-16 mg per kg bw per day for steviol glycosides, depending on whether area under the plasma-concentration time curve (AUC) or maximum concentration (C_{max}) data are used when considering the 400 mg per kg per day NOAEL for stevioside reported by Toyoda et al. (1997).

7. Recently, JECFA published a safety evaluation of a number of food additives, including steviol glycosides. The JECFA committee reviewed information supporting the safety of a *Yarrowia lipolytica* fermentation-produced rebaudioside A, which included a 90-day rat toxicity study and two *in vitro* genotoxicity studies, as well as *in vitro* colonic microflorae hydrolysis studies in several steviol glycosides, toxicokinetic studies of stevioside in humans and rats, and literature published since the 69th meeting.

   The Committee noted that the most recent short-term toxicity studies were consistent with those reviewed at or prior to the 69th meeting, and that the new toxicokinetic study in humans did not have a large enough subject pool to provide reliable toxicokinetic estimates to derive an update ADI for steviol glycosides. The Committee confirmed the current ADI of 0-4 mg per kg bw steviol. In addition, the Committee prepared new “tentative” specifications for steviol gycosides, which were expanded to include “any mixture of steviol glycosides compounds derived from *S. rebaudiana* Bertoni” while retaining the requirement that the total percentage of steviol glycosides is $\geq$ 95% (WHO, 2017).

8. Recent studies have investigated the *in vitro* and *in vivo* effects of stevioside on pro-inflammatory cytokines in rats. Noosud et al. (2017) reported that the consumption of stevioside inhibited the release of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in lipopolysaccharide-stimulated peripheral blood mononuclear cells in rats.

9. Panagiotou et al. (2018) observed that steviol and steviol glycosides exert glucocorticoid receptor-mediated effects in human leukemic T-cells (Jurkat cells) but not in normal human peripheral blood mononuclear cells, which they concluded was due to a cell-type specific manner of glucocorticoid receptor-modulation.

10. Philippaert et al. (2017) demonstrated that stevioside, rebaudioside A, and steviol potentiate the activity of transient receptor potential cation channel subfamily melastatin member 5 (TRPM5), a Ca^{2+} -activated cation channel that is expressed in type II taste receptor cells and pancreatic β-cells. The authors found that the steviol glycosides increased the perception of bitter, sweet, and umami tastes, and also enhanced glucose-induced insulin secretion in a TRPM5-dependent manner. Furthermore, *in vivo* studies indicated that daily consumption of stevioside prevents high-fat-induced diabetic hyperglycemia development in wild-type mice. No adverse events or animal deaths were discussed.

11. A commercially available steviol glycoside extract (>99%, composition and brand unknown) was used to investigate genotoxicity in human peripheral blood lymphocytes. Uçar et al. (2017) observed no significant differences in chromosomal aberration induction or micronuclei between the control and treatment groups at 24 and 48 h. These data support previous findings that steviol glycosides are not genotoxic.

None of the updated literature located and summarized above trigger any safety concerns for the intended uses of steviol glycosides in food, including the articles published after JECFA's most recent safety review (WHO, 2017). GLG agrees with the safety conclusions of the 48 GRAS Expert Panels in the notifications for steviol glycosides previously submitted to FDA that resulted in "no questions" responses from FDA (as summarized in Table 3), JECFA (WHO, 2006; WHO, 2008; WHO, 2017), and Renwick (2008) that a sufficient number of good quality health and safety studies exist to support the determination that purified preparations of steviol glycosides when added to food at levels up to full replacement of sucrose on a sweetness equivalency basis meet FDA's definition of safe.

Furthermore, GLG has reviewed this safety information and has concluded that their high purity steviol glycosides product is generally recognized as safe for the proposed uses in cured meat products.

A. GRAS Criteria

FDA defines "safe" or "safety" as it applies to food ingredients as:

> "…reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."[6]

Amplification is provided in that the conclusion of safety is to include probable consumption of the substance in question, the cumulative effect of the substance and appropriate safety factors. It is

[6] See 21 CFR 170.3 (e)(i) and 81 FR 54959 Available at: https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe (Accessed on 4/15/17).

FDA's operational definition of safety that serves as the framework against which this evaluation is provided.

Furthermore, in discussing GRAS criteria, FDA notes that:

> "…General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances directly or indirectly added to food, that there is reasonable certainty that the substance is not harmful under the conditions of its intended use."
>
> "'Common knowledge' can be based on either "scientific procedures" or on experience based on common use of a substance in food prior to January 1, 1958." [7]

FDA discusses in more detail what is meant by the requirement of general knowledge and acceptance of pertinent information within the scientific community, i.e., the so-called "common knowledge element," in terms of the two following component elements:[8]

- Data and information relied upon to establish safety must be generally available, and this is most commonly established by utilizing published, peer-reviewed scientific journals; and
- There must be a basis to conclude that there is consensus (but not unanimity) among qualified scientists about the safety of the substance for its intended use, and this is established by relying upon secondary scientific literature such as published review articles, textbooks, or compendia, or by obtaining opinions of expert panels or opinions from authoritative bodies, such as JECFA and the National Academy of Sciences.

General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive. General recognition of safety through scientific procedures shall be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.

The apparent imprecision of the terms "appreciable," "at the time," and "reasonable certainty" demonstrates that the FDA recognizes the impossibility of providing absolute safety in this or any other area (Lu, 1988; Renwick, 1990; Rulis and Levitt, 2009).

[7] See 81 FR 54959 Available at: https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe (Accessed on 4/15/17).
[8] See Footnote 1.

As noted below, this safety assessment to ascertain GRAS status for high purity steviol glycosides for the specified food uses meets FDA criteria for reasonable certainty of no harm by considering both the technical and common knowledge elements.

B. Expert Panel Findings on Safety of GLG's High Purity Steviol Glycosides

An evaluation of the safety and GRAS status of the intended use of GLG's high purity steviol glycosides (≥95%) preparations in cured meat products has been conducted by an Expert Panel convened by GRAS Associates; the Panel consisted of Richard Kraska, Ph.D., as Panel Chair; Katrina Emmel, Ph.D.; and Kara Lewis, Ph.D. The Expert Panel reviewed GLG's dossier as well as other publicly available information available to them. The individuals who served as Expert Panelists are qualified to evaluate the safety of foods and food ingredients by merit of scientific training and experience.

The GRAS Expert Panel report is provided in Appendix 3.

C. Common Knowledge Elements for GRAS Conclusions

The first common knowledge element for a GRAS conclusion requires that data and information relied upon to establish safety must be generally available; this is most commonly established by utilizing studies published in peer-reviewed scientific journals. The second common knowledge element for a GRAS conclusion requires that consensus exists within the broader scientific community.

1. Public Availability of Scientific Information

The majority of the studies reviewed on steviol glycosides and steviol have been reviewed in detail in previous GRAS submissions, including GRN 555, GRN 548, and GRN 536.

With regard to the safety documentation, the key pharmacokinetic data establish that steviol glycosides are not absorbed through the gastrointestinal (GI) tract, *per se*; they are converted to steviol by bacteria normally present in the large intestine, and the steviol is absorbed but rapidly metabolized and excreted. It has been well-established experimentally from various published studies that the steviol glycoside molecules are not absorbed from the GI tract (Gardana et al., 2003; Koyama et al., 2003b). The action of bacteria in the large intestine is directly supported by the published study that steviol glycosides can be converted to steviol in the large intestine by normal anaerobic GI flora as demonstrated by an *in vitro* study in fecal homogenates (Koyama et al., 2003a; Renwick and Tarka, 2008). The ADI for steviol glycosides has been set largely based on a published chronic study in rats (Toyoda et al., 1997) and several published clinical studies that there are no pharmacological effects in humans at doses several fold higher than the ADI (Barriocanal et al., 2006; Barriocanal et al., 2008; Wheeler et al., 2008). Recently, Roberts et al. (2016) noted that the ADI could be higher. The toxicity of the metabolite steviol has been well reviewed in the published literature (Geuns, 2003; Urban et al., 2013; WHO, 2006).

In addition, there is a large publicly available collection of GRNs regarding steviol glycosides on FDA's website.

2. Scientific Consensus

The second common knowledge element for a GRAS conclusion requires that there must be a basis to conclude that consensus exists among qualified scientists about the safety of the substance for its intended use.

A number of well-respected regulatory agencies, including JECFA, EFSA, FSANZ, the Switzerland Office of Public Health, and Health Canada, as well as numerous well-respected individual scientists, have indicated that steviol glycosides are safe for human consumption at doses in the range of the JECFA ADI (EFSA, 2010; FAO, 2010; FSANZ, 2008; Geuns, 2003; Health, 2008; HealthCanada, 2012; Toyoda et al., 1997; Williams, 2007; Xili et al., 1992). The Panel also notes that, since December 2008, over 45 GRAS notifications have been submitted to FDA for stevia-derived sweetener products, and FDA detailed reviews have consistently yielded "no questions" letters.

In summary, a compelling case can be made that scientific consensus exists regarding the safety of steviol glycosides when of sufficiently high purity. The central role of conversion to steviol and subsequent elimination with these naturally occurring steviol glycosides extends to the manner in which the various steviol glycosides molecules are metabolized and eliminated from the body. While the scientific conclusions are not unanimous regarding the safe human food uses of steviol glycosides, the Panel believes that a wide consensus does exist in the scientific community to support a GRAS conclusion as evidenced by several publications (Brusick, 2008; Carakostas, 2012; Geuns, 2007; Urban et al., 2013; Waddell, 2011; Williams, 2007) that refute safety concerns expressed by a minority of scientists. In addition, a recent publication by Roberts et al. (2016) suggests that the ADI could be higher than has been previously accepted by the scientific community.

D. Conclusion

GLG concludes that no new safety issues are raised with the proposed use of GLG's high purity steviol glycosides (≥95%) preparations in cured meat products as described herein in addition to the proposed uses described in GRN 493, which previously received a "no questions" response from FDA. Accordingly, high purity steviol glycosides (≥95%) as produced by GLG and declared within the subject GRAS assessment meet FDA's definition of safety in that there is "reasonable certainty of no harm under the intended conditions of use" as described herein, and GLG's high purity steviol glycosides (≥95%) preparation is generally recognized as safe (GRAS).

PART 7. LIST OF SUPPORTING DATA AND INFORMATION IN THE GRAS NOTICE.

A. List of Acronyms

ADI	Acceptable daily intake
AUC	Area under the plasma-concentration time curve
AVA	Agri-food & Veterinary Authority
bw	Body weight
CFR	Code of Federal Regulations
C_{max}	Maximum serum concentration
CSAF	Chemical-specific adjustment factor
EFSA	European Food Safety Authority
EU	European Union
FD&C	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturers Association
FOIA	Freedom of Information Act
FSANZ	Food Standards Australia New Zealand
FSSAI	The Food Safety and Standards Authority of India
g	gram
GA	GRAS Associates
GI	Gastrointestinal
GLG	GLG Life Tech Corporation
GRAS	Generally Recognized as Safe
GRN	GRAS notification

h	hour
IADSA	International Alliance of Dietary/Food Supplement Associations
IL-1β	Interleukin-1β
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
kg	kilogram
L	liter
LLC	Limited liability corporation
mg	milligram
mL	milliliter
NHPs	Natural health products
NOAEL	No observed adverse effect level
ppm	parts per million
Reb A	Rebaudioside A
Reb D	Rebaudioside D
Reb M	Rebaudioside M
TAC	Total Antioxidant Capacity
TFC	Total Flavonoid Content
TNF-α	Tumor necrosis factor-α
TPC	Total Phenolic Content
TRPM5	Transient receptor potential cation channel subfamily melastatin member 5
USDA	United States Department of Agriculture

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C. Appendices

Appendix 1 Beef Jerky Sensory Evaluation Report

ADM Confidential

ADM
Sensory

To: [redacted]
From: [redacted]
Project: 17-DAP-CP-BEEFJERKY-095 RETEST

Date: August 14, 2017

OBJECTIVE: To determine the sensory profile that Stevia provides in a Jerky application.

BACKGROUND: Sensory data is necessary for a GRAS dossier covering the use of Stevia in meat applications. Comparisons between jerky prepared with tapioca syrup as a control and jerky prepared using stevia were placed into a trained sensory panel that allowed for the determination of the sensory profile.

METHODS: Spectrum Descriptive Flavor Evaluation
n = 9 trained descriptive sensory panelists

PRODUCTS:
1. GBB Tapioca Syrup (no sugar or Stevia)
2. GBB GLG Rebsweet RA80*

*Refer to Appendix 1 for product formulations.

KEY FINDINGS:

- The RA 80 jerky had significantly higher means scores for basic taste sweet and sweet aromatic compared to the jerky made with Tapioca syrup.
- The Tapioca syrup jerky provided slightly more intense overall aromatics (driven by red spice and cumin) than the RA 80 jerky.
- The beef jerky made with Tapioca syrup was harder, had a stronger mouth-burn and was saltier than the beef jerky made with RA 80.
- *Please note: A great deal of seasoning variability was noted during evaluation of Jerky pieces. Panelists were advised to assess each piece for each attribute and then average those to give an intensity that was representative of all the pieces evaluated.*

CONCLUSIONS:
GLG Rebsweet RA 80 stevia provided acceptable sweetness in a beef jerky application as shown in the Table 1. A beef jerky formulated with tapioca syrup was utilized for sensorial comparative purposes and GLG's Rebsweet RA 80 provided the required sweetness necessary for consumer acceptance. All other sensory attributes were demonstrated to be acceptable for commercial beef jerky.

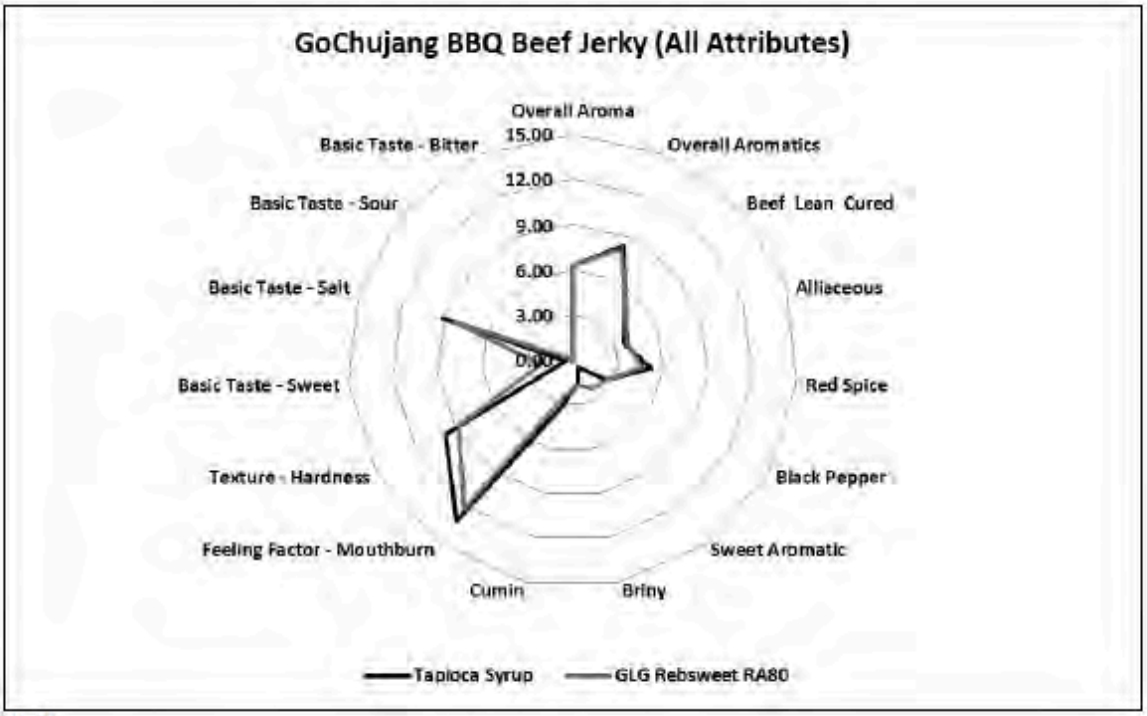
1

Table 1: Flavor Means Comparison – GoChujang BBQ Beef Jerky

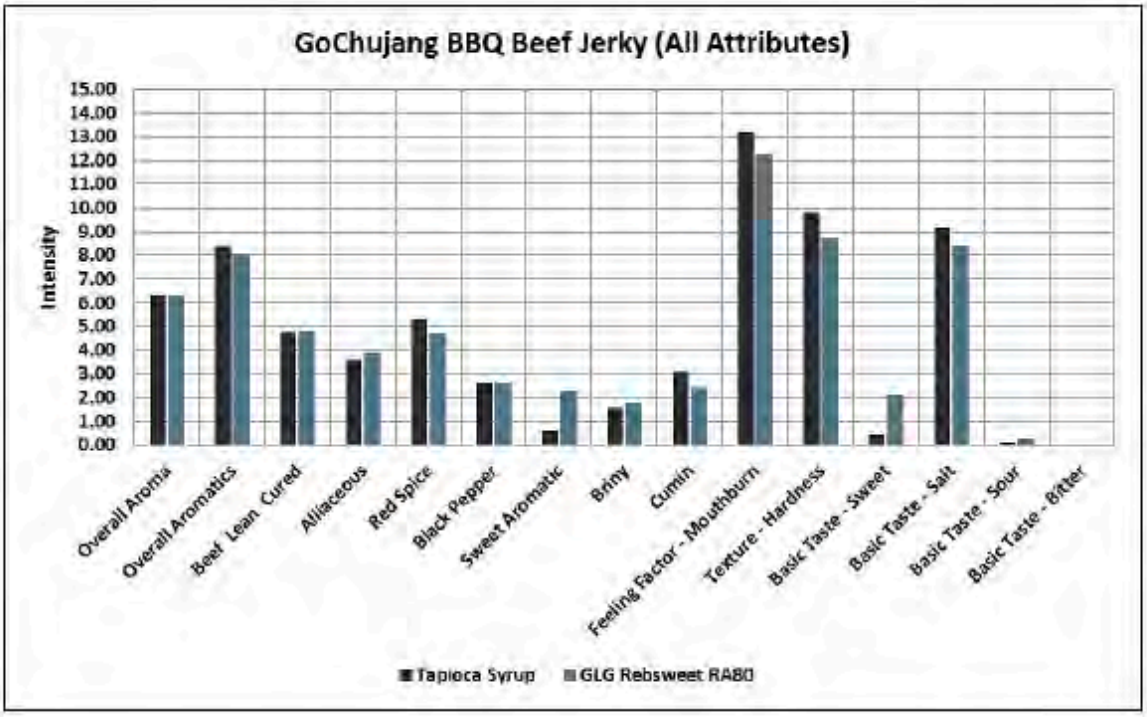
	Tapioca Syrup	GLG Rebsweet RA80	p-value
Aroma			
Overall Aroma	6.28 a	6.28 a	1.0000
Aromatics			
Overall Aromatics	8.33 a*	8.06 b	0.0483
Beef Lean Cured	4.72 a	4.78 a	0.7247
Alliaceous	3.56 a	3.83 a	0.2970
Red Spice	5.28 a*	4.67 b	0.0029
Black Pepper	2.61 a	2.61 a	1.0000
Sweet Aromatic	0.56 b*	2.28 a	< 0.0001
Briny	1.56 a	1.78 a	0.2481
Cumin	3.06 a*	2.39 b	0.0008
Feeling Factors			
Mouthburn	13.17 a*	12.22 b	0.0061
Texture			
Hardness	9.78 a*	8.72 b	0.0003
Basic Tastes			
Sweet	0.44 b*	2.11 a	< 0.0001
Salt	9.11 a*	8.39 b	0.0035
Sour	0.11 a	0.22 a	0.0893
Bitter	0.00 a	0.00 a	1.0000

*Sample means with different letters in the same row are considered significantly different at the 95% confidence level.

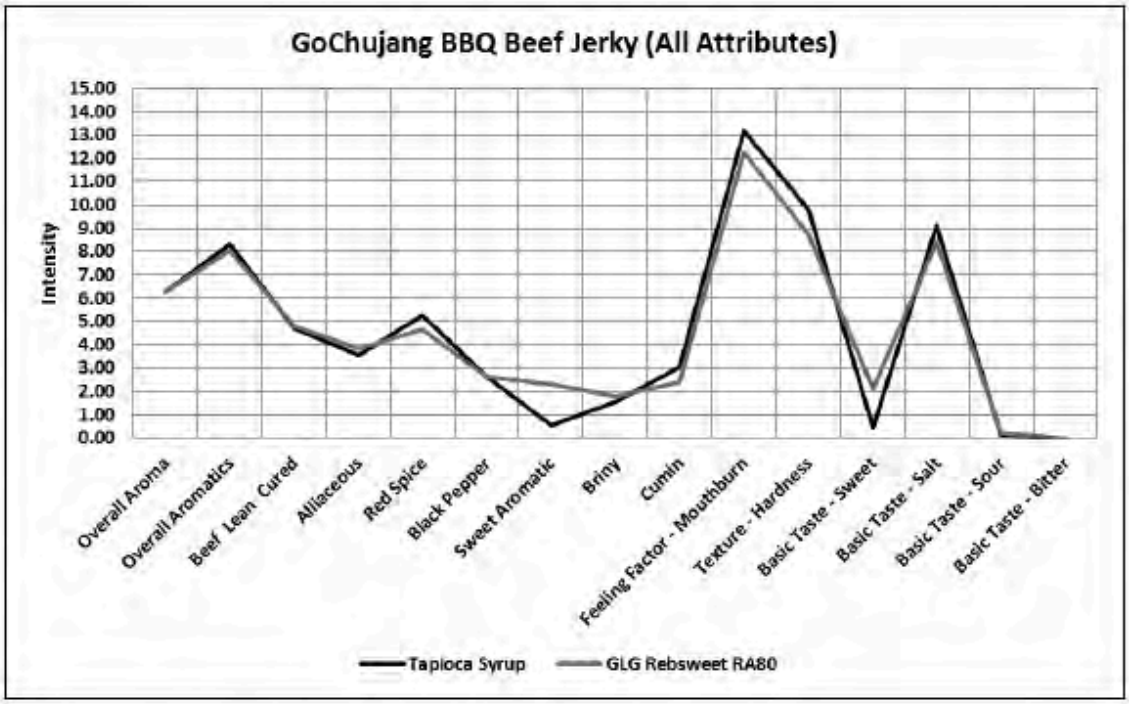
Graph 1:



Graph 2:



Graph 3:



Detailed Methods Summary:

- **Descriptive Method** – Panelists conducted descriptive flavor analysis using the basic taste intensity scales and Spectrum 15 point Universal aromatic scale

Basic Taste / Scale Intensity		2	5	10	15
Sweet	(Sucrose)	2.0%*	5.0%	10%	16%
Salt	(Sodium Chloride)	0.20%	0.35%	0.55%	0.70%
Sour	(Citric Acid)	0.05%	0.10%	0.15%	0.20%
Bitter	(Caffeine)	0.05%	0.08%	0.15%	0.20%

*All solutions are made by dissolving the compounds listed in deionized water.

Universal Flavor Aromatic Scale

- **Sample Preparation** - Samples were cut into pieces and placed into 4 oz plastic soufflé cups and capped the morning of evaluation. The samples were coded with random 3-digit codes. All samples were stored and evaluated room temperature.
- **Sample Evaluation** - Samples were evaluated 1st for overall aroma, then basic taste sweet, followed by the rest of the flavor profile. Samples were evaluated in a round table style format with panelists evaluating individually and group discussion following. A 10 minute break was provided between

4

samples to allow for cleansing with unsalted cracker and water. Refer to Appendix A2 for sample ballot and terms.

- **Test Design/Data Analysis** - All data was collected using Compusense at Hand sensory software. Panelists evaluated all samples using a balanced, complete block design. Samples were evaluated twice, with both evaluations conducted on the same day.
- An analysis of variance (ANOVA) was conducted per attribute using XLSTAT statistical software to determine significance with sample means compared using Fishers LSD. Significance was measured at 95% confidence.

Appendix 2 Pork Jerky Sensory Evaluation Report

ADM
Sensory

To: [redacted]
From: [redacted]
Project: [Pork Jerky Retest]

Date: August 14, 2017

OBJECTIVE: To determine the sensory profile that Stevia provides in a Jerky application.

BACKGROUND: Sensory data is necessary for a GRAS dossier covering the use of Stevia in meat applications. Comparisons between jerky prepared with tapioca syrup as a control and jerky prepared using stevia were placed into a trained sensory panel that allowed for the determination of the sensory profile.

METHODS: Spectrum Descriptive Flavor Evaluation
n = 9 trained descriptive sensory panelists

PRODUCTS: **1.** GBB Tapioca Syrup (no sugar or Stevia)
2. GBB GLG Rebsweet RA80*
*Refer to Appendix 1 for product formulations.

KEY FINDINGS:

- The RA 80 jerky had significantly higher means scores for basic taste sweet and sweet aromatic compared to the jerky made with Tapioca syrup.
- The RA80 syrup jerky provided slightly more intense overall aromatics (driven by alliaceous) than the Tapioca Syrup jerky.
- The pork jerky made with Tapioca syrup was slightly harder, had a stronger mouth-burn and was saltier than the pork jerky made with RA 80.
- *Please note: A great deal of seasoning variability was noted during evaluation of Jerky pieces. Panelists were advised to assess each piece for each attribute and then average those to give an intensity that was representative of all the pieces evaluated.*

CONCLUSIONS:
GLG Rebsweet RA 80 stevia provided acceptable sweetness in a pork jerky application as shown in Table 1. A pork jerky formulated with tapioca syrup was utilized for sensorial comparative purposes and GLG's Rebsweet RA 80 provided the required sweetness necessary for consumer acceptance. All other sensory attributes were demonstrated to be acceptable for commercial pork jerky.

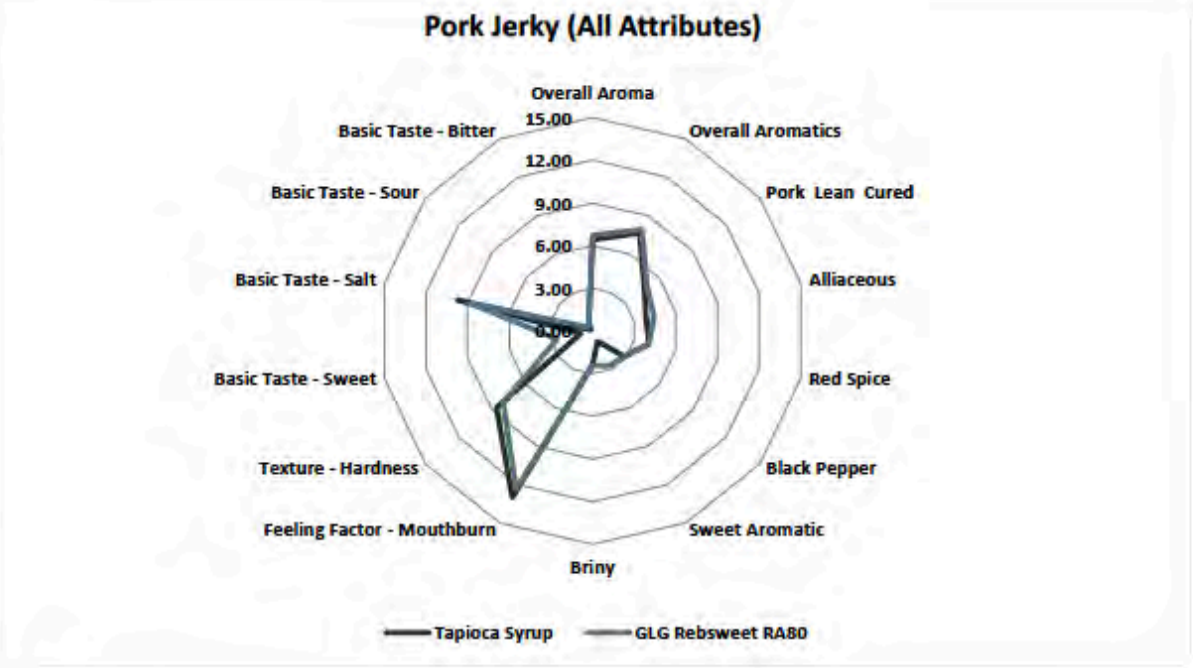
1

Table 1: Flavor Means Comparison – Pork Jerky

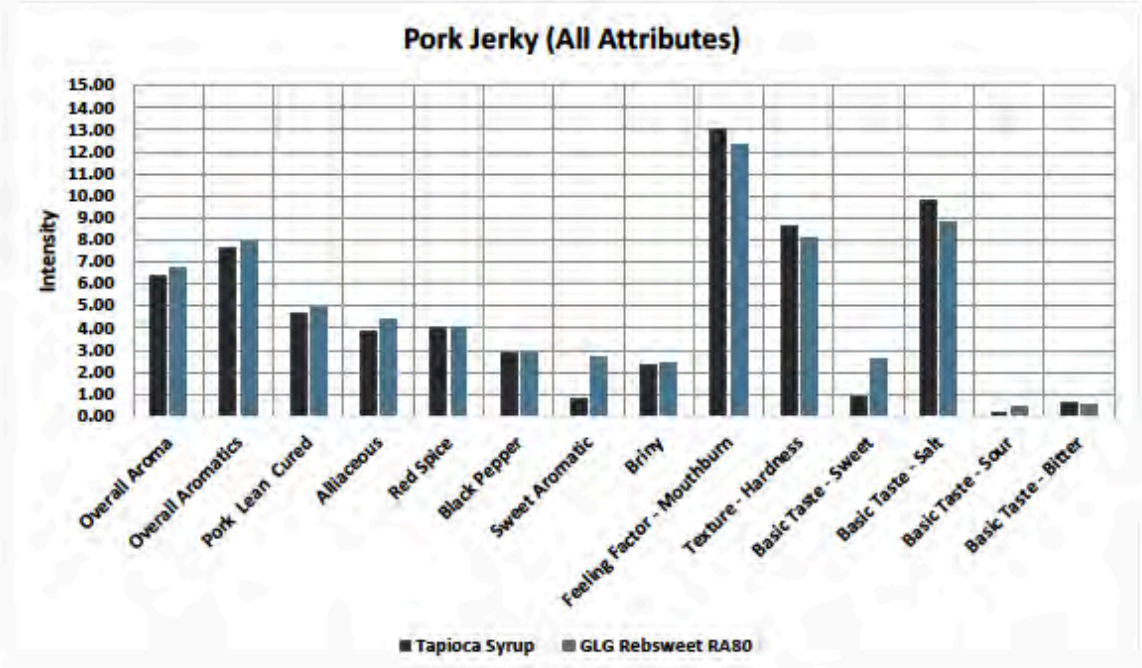
	Tapioca Syrup	GLG Rebsweet RA80	p-value
Aroma			
Overall Aroma	6.43 a	6.71 a	0.1708
Aromatics			
Overall Aromatics	7.64 b*	7.93 a	0.0479
Pork Lean Cured	4.64 a	4.93 a	0.0631
Alliaceous	3.86 b*	4.43 a	0.0046
Red Spice	4.07 a	4.07 a	1.0000
Black Pepper	2.86 a	2.86 a	1.0000
Sweet Aromatic	0.79 b*	2.71 a	< 0.0001
Briny	2.36 a	2.43 a	0.7618
Feeling Factors			
Mouthburn	13.00 a*	12.36 b	0.0053
Texture			
Hardness	8.64 a	8.07 a	0.0524
Basic Tastes			
Sweet	0.86 b*	2.57 a	< 0.0001
Salt	9.79 a*	8.86 b	0.0267
Sour	0.14 b*	0.43 a	0.0125
Bitter	0.64 a	0.57 a	0.3299

*Sample means with different letters in the same row are considered significantly different at the 95% confidence level.

Graph 1:



Graph 2:



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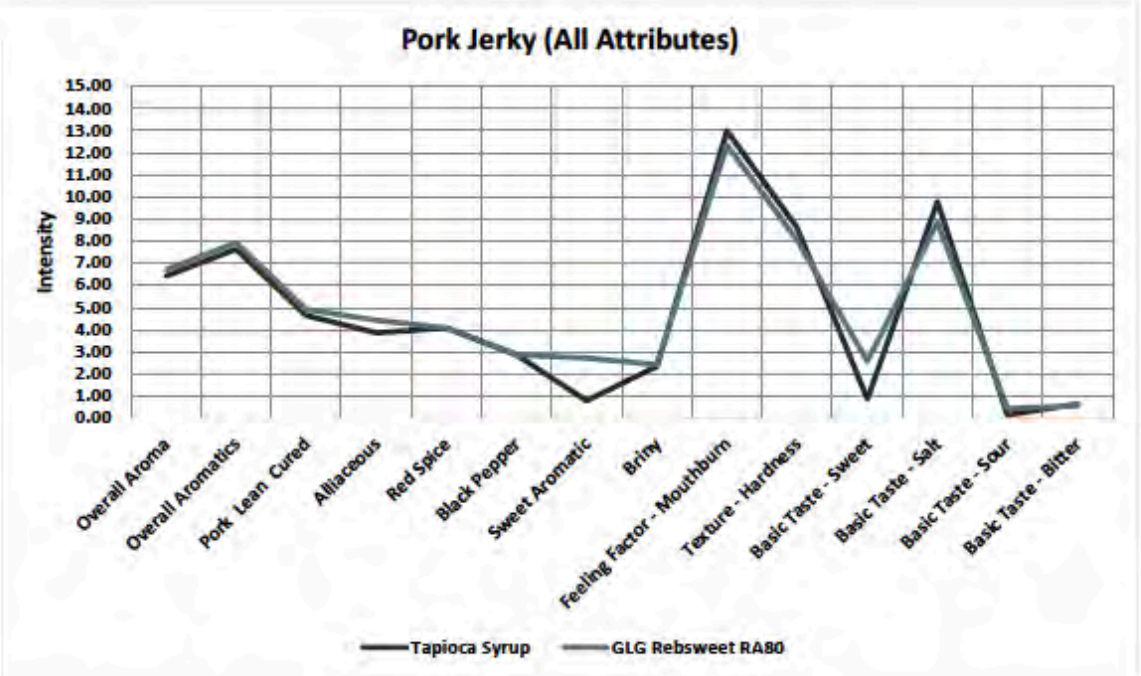
Graph 3:



Detailed Methods Summary:

- **Descriptive Method** – Panelists conducted descriptive flavor analysis using the basic taste intensity scales and Spectrum 15 point Universal aromatic scale

Basic Taste / Scale Intensity		2	5	10	15
Sweet	(Sucrose)	2.0%*	5.0%	10%	16%
Salt	(Sodium Chloride)	0.20%	0.35%	0.55%	0.70%
Sour	(Citric Acid)	0.05%	0.10%	0.15%	0.20%
Bitter	(Caffeine)	0.05%	0.08%	0.15%	0.20%

*All solutions are made by dissolving the compounds listed in deionized water.

Universal Flavor Aromatic Scale

- **Sample Preparation** - Samples were cut into pieces and placed into 4 oz plastic soufflé cups and capped the morning of evaluation. The samples were coded with random 3-digit codes. All samples were stored and evaluated room temperature.
- **Sample Evaluation** - Samples were evaluated 1st for overall aroma, then basic taste sweet, followed by the rest of the flavor profile. Samples were evaluated in a round table style format with panelists

4

evaluating individually and group discussion following. A 10 minute break was provided between samples to allow for cleansing with unsalted cracker and water. Refer to Appendix A2 for sample ballot and terms.

- **Test Design/Data Analysis** - All data was collected using Compusense at Hand sensory software. Panelists evaluated all samples using a balanced, complete block design. Samples were evaluated twice, with both evaluations conducted on the same day.
- An analysis of variance (ANOVA) was conducted per attribute using XLSTAT statistical software to determine significance with sample means compared using Fishers LSD. Significance was measured at 95% confidence.

Appendix 3 GRAS Associates Expert Panel Report

The Generally Recognized as Safe (GRAS) Status of the Proposed Uses of High Purity Steviol Glycosides Preparations in Cured Meat Products

Foreword

An independent panel of experts ("Expert Panel") was convened by GRAS Associates, LLC on behalf of their client, GLG Life Tech Corporation ("GLG"), to evaluate the safety and Generally Recognized as Safe (GRAS) status of GLG's proposed uses of high purity steviol glycosides in cured meat products. The members of this Expert Panel[†] are qualified to serve in this capacity by qualification of scientific training and experience in the safety of food and food ingredients.

Discussion

A significant amount of safety information related to the consumption of steviol glycosides is generally available, and has been presented by GLG in GRN 493, as well as in Part 6 of GLG's GRAS evaluation for proposed uses in cured meat products. First, there is a history of safe consumption of steviol glycosides when used as an ingredient in food products in the U.S., Canada, South America, Europe, Asia, and Australia and New Zealand. Secondly, a number of experimental studies have investigated the safety of steviol glycosides. The composite evidence from historical safe consumption and experimental studies together demonstrate the safety of the subject high purity steviol glycosides for human food consumption.

The majority of the studies reviewed on steviol glycosides and steviol have been discussed in detail in previous GRAS submissions, including GRN 555, GRN 548, GRN 536, and GLG's GRN 493.

With regard to the safety documentation, the key pharmacokinetic data establish that steviol glycosides are not absorbed through the GI tract, *per se*; they are converted to steviol by bacteria normally present in the large intestine, and the steviol is absorbed but rapidly metabolized and excreted. It has been well-established experimentally from various published studies that the steviol glycoside molecules are not absorbed from the GI tract (Gardana et al., 2003; Koyama et al., 2003b). The action of bacteria in the large intestine is directly supported by the published study that steviol glycosides can be converted to steviol in the large intestine by normal anaerobic GI flora as demonstrated by an *in vitro* study in fecal homogenates (Koyama et al., 2003a; Renwick and Tarka, 2008). The ADI for steviol glycosides has been set largely based on a published

[†] Dr. Kraska, the Chair of the Expert Panel, worked on GRAS and food additive safety issues within FDA's GRAS Review Branch earlier in his career, and subsequently continued working within this area in the private sector. Dr. Emmel is a chemist with substantial food safety experience in addressing steviol glycosides and other food ingredients. Dr. Lewis is a biologist with more than 10 years of experience preparing GRAS dossiers. All three panelists have extensive technical backgrounds in the evaluation of food ingredient safety and in participating in deliberations of GRAS Expert Panels.

chronic study in rats (Toyoda et al., 1997) and several published clinical studies showing that there are no pharmacological effects in humans at doses several fold higher than the ADI (Barriocanal et al., 2006; Barriocanal et al., 2008; Wheeler et al., 2008). Recently, Roberts et al. (2016) noted that the ADI could be higher. The toxicity of the metabolite steviol has been well reviewed in the published literature (Geuns, 2003; Urban et al., 2013; WHO, 2006). In addition, FDA has issued "no questions" letters to 48 GRN submissions for steviol glycosides preparations.

The Expert Panel notes that GLG has not changed the manufacturing process for their high purity steviol glycoside preparations or revised its product specifications since GRN 493 was submitted to FDA on May 30, 2014. The updated scientific literature review of steviol glycosides covering the time frame of 2013 through the present revealed no findings raising new safety concerns that would alter the previous GRAS determination.

The GRAS Associates Expert Panel convened on behalf of GLG has reviewed the additional proposed uses for GLG's high purity steviol glycosides in cured meat products, along with the associated utility studies in jerky products. Since the specifications and sweetness intensity of GLG's high purity steviol glycosides preparations remain unchanged from GRN 493, the estimated increase in dietary intake from the proposed uses in cured meat products, at a maximum use level of 2,500 ppm in cured meat products is 0.91 mg per kg bw per day steviol equivalents. When added to the highest estimated intake level in GRN 493 (1.37 mg per kg bw per day steviol equivalents), the total maximum daily intake from all proposed uses is 2.28 mg per kg bw per day steviol equivalents. This estimated intake value is slightly more than half the JECFA ADI of 4 mg per kg bw per day expressed as steviol equivalents. Therefore, the maximum proposed use level of 2,500 ppm steviol glycosides in cured meat products, over and above the uses detailed in GRN 493, is expected to be safe within established allowable limits.

A compelling case can be made that scientific consensus exists regarding the safety of steviol glycosides when of sufficiently high purity. The central role of conversion to steviol and subsequent elimination with these naturally occurring steviol glycosides extends to the manner in which the various steviol glycosides molecules are metabolized and eliminated from the body. While the scientific conclusions are not unanimous regarding the safe human food uses of steviol glycosides, the Panel believes that a wide consensus does exist in the scientific community to support a GRAS conclusion as evidenced by several publications (Brusick, 2008; Carakostas, 2012; Geuns, 2007; Urban et al., 2013; Waddell, 2011; Williams, 2007) that refute safety concerns expressed by a minority of scientists. In addition, a recent publication by Roberts et al. (2016) suggests that the ADI could be higher than has been previously accepted by the scientific community.

In summary, sufficient qualitative and quantitative scientific evidence in the composite is available to support the safety-in-use of GLG's high purity steviol glycosides (≥95%) preparation in cured meat products as long as:

- GLG's high purity steviol glycosides preparations continue to meet the specifications designated in GRN 493;
- the minimum sweetness intensities designated in GRN 493 remain unchanged; and
- the high purity steviol glycosides are produced in accordance with cGMPs.

Conclusion

The Expert Panel critically reviewed the data provided by GLG for their high purity steviol glycosides preparations, as well as publicly available published information obtained from peer reviewed journals and other safety assessments prepared by other Expert Panels and well-respected international regulatory bodies.

The ingestion of GLG's high purity steviol glycosides from the intended uses results in intakes that are safe within the limits of established historical use and published safety studies.

The Expert Panel unanimously concluded that the proposed uses of GLG's high purity steviol glycosides preparations, as described in GRN 493 and declared within the subject notification meet the FDA definition of safety in that there is "reasonable certainty of no harm under the intended conditions of use" as described herein, and GLG's high purity steviol glycosides (≥95%) preparation is generally recognized as safe (GRAS).

(b) (6)

Richard Kraska, Ph.D.

Panel Chair

(b) (6)

Katrina Emmel, Ph.D.

(b) (6)

Kara Lewis, Ph.D.

END

GRAS ASSOCIATES, LLC

GRAS Associates, LLC
27499 Riverview Center Blvd.
Bonita Springs, FL 34134
T: 239.444.1724 | F: 239.444.1723
www.gras-associates.com

June 22, 2018

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety (HFS-255)
5001 Campus Drive
College Park, MD 20740-3835
Attention: Mr. Richard E. Bonnette
Re: GLG's Steviol Glycosides Submission

Dear Mr. Bonnette:

We received an email from you on June 22, 2018 regarding the erroneous designation of "confidential" on page 9 of GLG's Steviol Glycosides GRAS submission. While Appendices 1 and 2 do contain confidential information, the rest of the submission is releasable, and the information on page 9 of the dossier should not be considered confidential.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via email.

We look forward to your feedback.

Thank you,

(b) (6)

Katrina V. Emmel, Ph.D.

Senior Scientist/Associate
GRAS Associates, LLC
27499 Riverview Center Blvd., Suite 212
Bonita Springs, FL 34134
emmel@gras-associates.com

Bonnette, Richard

From: Katrina Emmel <emmel@gras-associates.com>
Sent: Friday, June 22, 2018 2:16 PM
To: Bonnette, Richard
Cc: Steven Overgaard; William J. Rowe; Robert McQuate; Richard Kraska; Kara Lewis
Subject: RE: Submission to FDA GRAS notification program for High Purity Steviol Glycosides
Attachments: FDA Response Ltr GLG GRN Submission 6-7-18.pdf

Dear Mr. Bonnette,

On behalf of our client, GLG, and Steven Overgaard (GRAS Associate's agent on behalf of GLG), I have prepared an official response to your question regarding the notation of "confidential" on page 9 of the GRAS submission, as attached. Please note that the use of the term "confidential" in the footer of page 9 was in error, and no information contained in the body of the dossier is considered confidential, while GLG requests that the information contained in Appendices 1 and 2 remain confidential.

Thank you so much, and please feel free to contact me if you have any further questions.

Kind Regards,

Katrina

Katrina Emmel, Ph.D.
Senior Scientist/Project Manager/Associate
GRAS Associates, LLC.

emmel@gras-associates.com

From:	Katrina Emmel
To:	Perrier, Judith
Cc:	Robert McQuate; William J. Rowe
Subject:	Re: GRN 790 - Steviol Glycosides with Rebaudioside A and Stevioside as the Principal Components
Date:	Wednesday, July 25, 2018 7:50:31 PM
Attachments:	GRN 790 Appendix 1 Beef Jerky Unredacted.pdf GRN 790 Appendix 2 Pork Jerky Unredacted.pdf

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Hello Dr. Perrier,

I apologize for the delay in relaying these documents to you and I appreciate your patience. Attached you will find the unredacted version of Appendices 1 and 2.

Please let me know if you require anything else. We look forward to hearing from you.

Thank you,

Katrina

Katrina Emmel, Ph.D.
Senior Scientist/Project Manager/Associate
GRAS Associates, LLC.

emmel@gras-associates.com

Sensory

To: Dirk Reif, Shawn Sprankle
From: Melissa Kerr, Amanda Jable
Project: 17-DAP-CP-BEEFJERKY-095 RETEST

Date: August 14, 2017

OBJECTIVE: To determine the sensory profile that Stevia provides in a Jerky application.

BACKGROUND: Sensory data is necessary for a GRAS dossier covering the use of Stevia in meat applications. Comparisons between jerky prepared with tapioca syrup as a control and jerky prepared using stevia were placed into a trained sensory panel that allowed for the determination of the sensory profile.

METHODS: Spectrum Descriptive Flavor Evaluation
n = 9 trained descriptive sensory panelists

PRODUCTS: **1.** GBB Tapioca Syrup (no sugar or Stevia)
2. GBB GLG Rebsweet RA80*
***Refer to Appendix 1 for product formulations.

KEY FINDINGS:

- The RA 80 jerky had significantly higher means scores for basic taste sweet and sweet aromatic compared to the jerky made with Tapioca syrup.
- The Tapioca syrup jerky provided slightly more intense overall aromatics (driven by red spice and cumin) than the RA 80 jerky.
- The beef jerky made with Tapioca syrup was harder, had a stronger mouth-burn and was saltier than the beef jerky made with RA 80.
- *Please note: A great deal of seasoning variability was noted during evaluation of Jerky pieces. Panelists were advised to assess each piece for each attribute and then average those to give an intensity that was representative of all the pieces evaluated.*

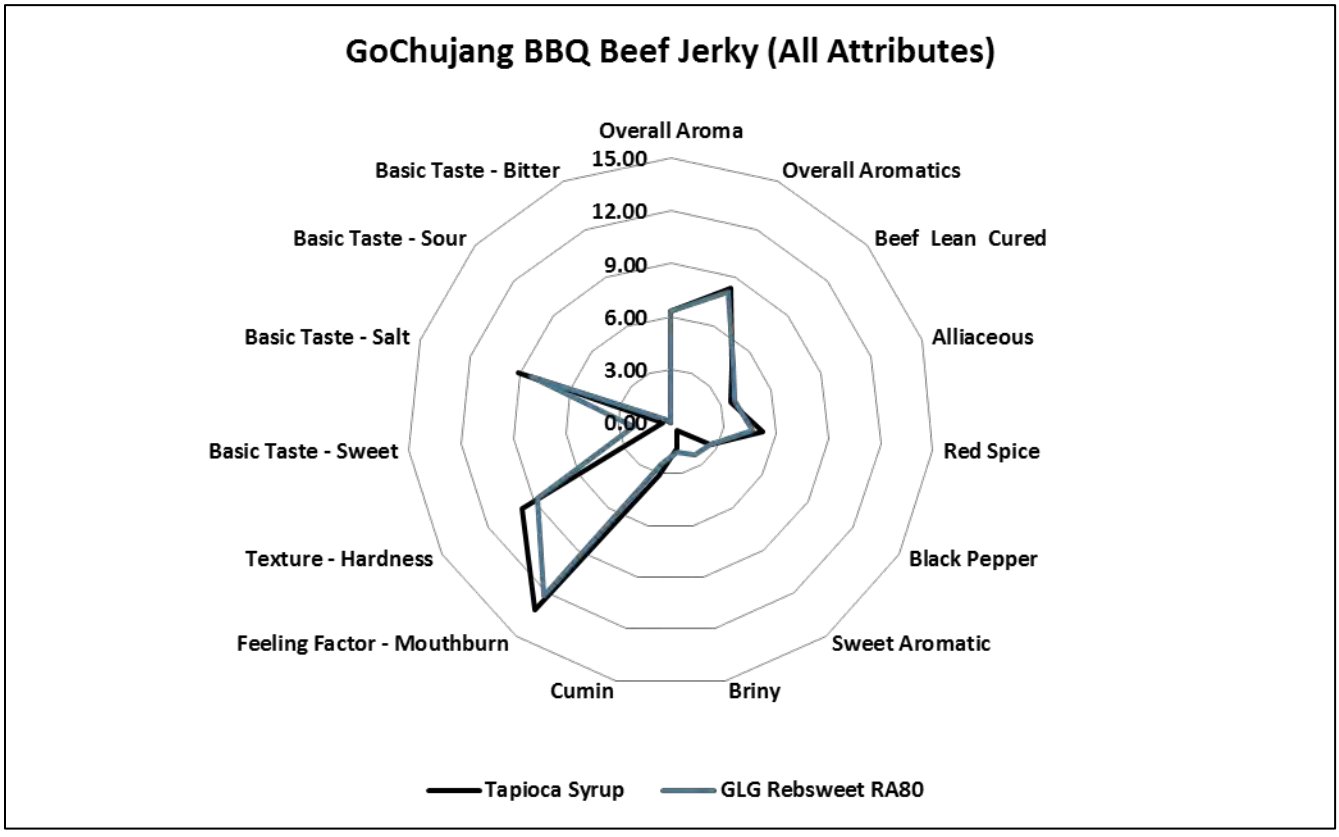
CONCLUSIONS:
GLG Rebsweet RA 80 stevia provided sweetness in a beef jerky application as shown in the table below.

Table 1: Flavor Means Comparison – GoChujang BBQ Beef Jerky

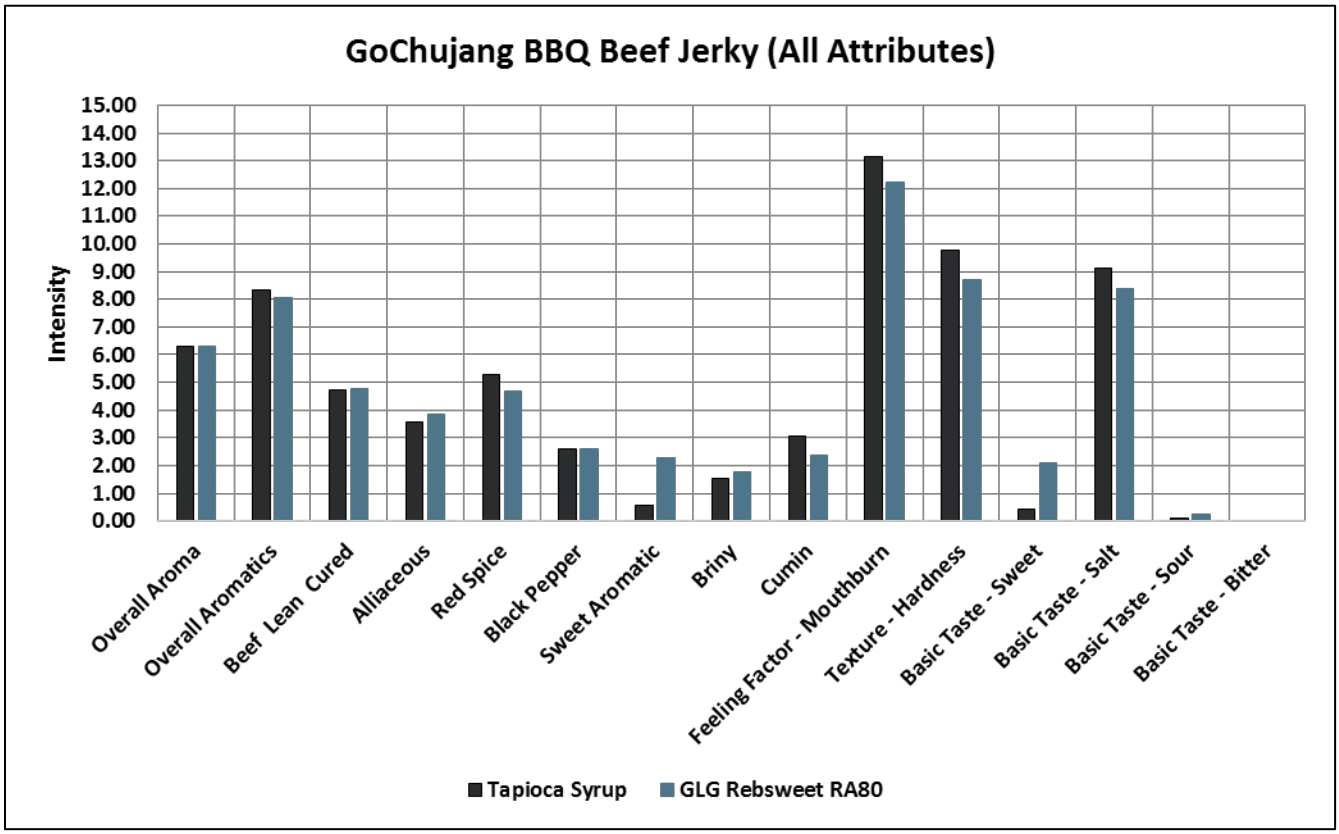
	Tapioca Syrup	GLG Rebsweet RA80	p-value
Aroma			
Overall Aroma	6.28 a	6.28 a	1.0000
Aromatics			
Overall Aromatics	8.33 a*	8.06 b	0.0483
Beef Lean Cured	4.72 a	4.78 a	0.7247
Alliaceous	3.56 a	3.83 a	0.2970
Red Spice	5.28 a*	4.67 b	0.0029
Black Pepper	2.61 a	2.61 a	1.0000
Sweet Aromatic	0.56 b*	2.28 a	< 0.0001
Briny	1.56 a	1.78 a	0.2481
Cumin	3.06 a*	2.39 b	0.0008
Feeling Factors			
Mouthburn	13.17 a*	12.22 b	0.0061
Texture			
Hardness	9.78 a*	8.72 b	0.0003
Basic Tastes			
Sweet	0.44 b*	2.11 a	< 0.0001
Salt	9.11 a*	8.39 b	0.0035
Sour	0.11 a	0.22 a	0.0893
Bitter	0.00 a	0.00 a	1.0000

*Sample means with different letters in the same row are considered significantly different at the 95% confidence level.

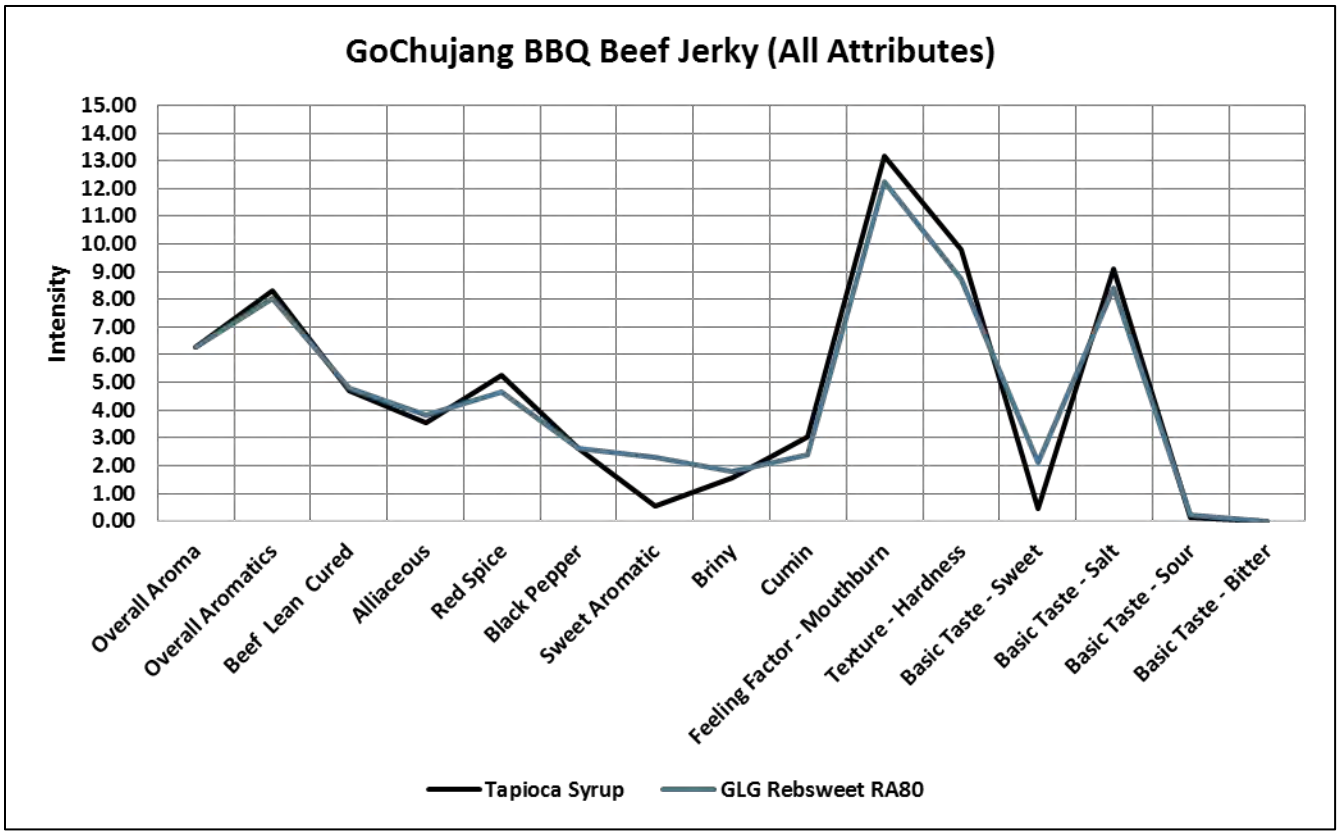
Graph 1:



Graph 2:



Graph 3:



Detailed Methods Summary:

- **Descriptive Method –** Panelists conducted descriptive flavor analysis using the basic taste intensity scales and Spectrum 15 point Universal aromatic scale

Basic Taste / Scale Intensity		2	5	10	15
Sweet	(Sucrose)	2.0%*	5.0%	10%	16%
Salt	(Sodium Chloride)	0.20%	0.35%	0.55%	0.70%
Sour	(Citric Acid)	0.05%	0.10%	0.15%	0.20%
Bitter	(Caffeine)	0.05%	0.08%	0.15%	0.20%

*All solutions are made by dissolving the compounds listed in deionized water.

Universal Flavor Aromatic Scale

- **Sample Preparation -** Samples were cut into pieces and placed into 4 oz plastic soufflé cups and capped the morning of evaluation. The samples were coded with random 3-digit codes. All samples were stored and evaluated room temperature.
- **Sample Evaluation -** Samples were evaluated 1st for overall aroma, then basic taste sweet, followed by the rest of the flavor profile. Samples were evaluated in a round table style format with panelists evaluating individually and group discussion following. A 10 minute break was provided between samples to allow for cleansing with unsalted cracker and water. Refer to Appendix A2 for sample ballot and terms.
- **Test Design/Data Analysis -** All data was collected using Compusense at Hand sensory software. Panelists evaluated all samples using a balanced, complete block design. Samples were evaluated twice, with both evaluations conducted on the same day.
- An analysis of variance (ANOVA) was conducted per attribute using XLSTAT statistical software to determine significance with sample means compared using Fishers LSD. Significance was measured at 95% confidence.

To: Dirk Reif, Shawn Sprankle
From: Melissa Kerr, Amanda Jable
Project: [Pork Jerky Retest]

Sensory **Date: August 14, 2017**

OBJECTIVE: To determine the sensory profile that Stevia provides in a Jerky application.

BACKGROUND: Sensory data is necessary for a GRAS dossier covering the use of Stevia in meat applications. Comparisons between jerky prepared with tapioca syrup as a control and jerky prepared using stevia were placed into a trained sensory panel that allowed for the determination of the sensory profile.

METHODS: Spectrum Descriptive Flavor Evaluation
n = 9 trained descriptive sensory panelists

PRODUCTS: **1.** GBB Tapioca Syrup (no sugar or Stevia)
2. GBB GLG Rebsweet RA80*
***Refer to Appendix 1 for product formulations.

KEY FINDINGS:

- The RA 80 jerky had significantly higher means scores for basic taste sweet and sweet aromatic compared to the jerky made with Tapioca syrup.
- The RA80 syrup jerky provided slightly more intense overall aromatics (driven by alliaceous) than the Tapioca Syrup jerky.
- The pork jerky made with Tapioca syrup was slightly harder, had a stronger mouth-burn and was saltier than the pork jerky made with RA 80.
- *Please note: A great deal of seasoning variability was noted during evaluation of Jerky pieces. Panelists were advised to assess each piece for each attribute and then average those to give an intensity that was representative of all the pieces evaluated.*

CONCLUSIONS:

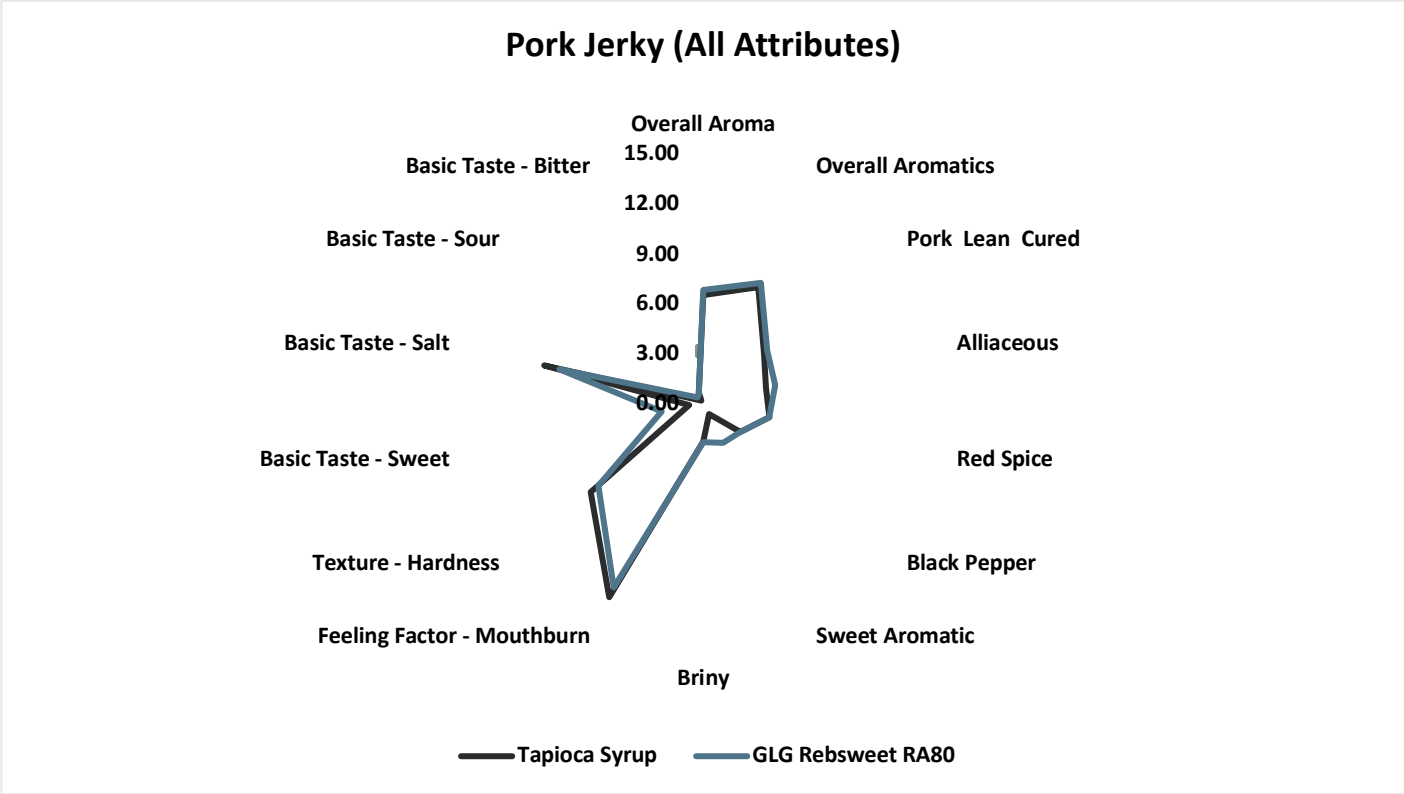
GLG Rebsweet RA 80 stevia provided acceptable sweetness in a pork jerky application as shown in Table 1. A pork jerky formulated with tapioca syrup was utilized for sensorial comparative purposes and GLG's Rebsweet RA 80 provided the required sweetness necessary for consumer acceptance. All other sensory attributes were demonstrated to be acceptable for commercial pork jerky.

Table 1: Flavor Means Comparison – Pork Jerky

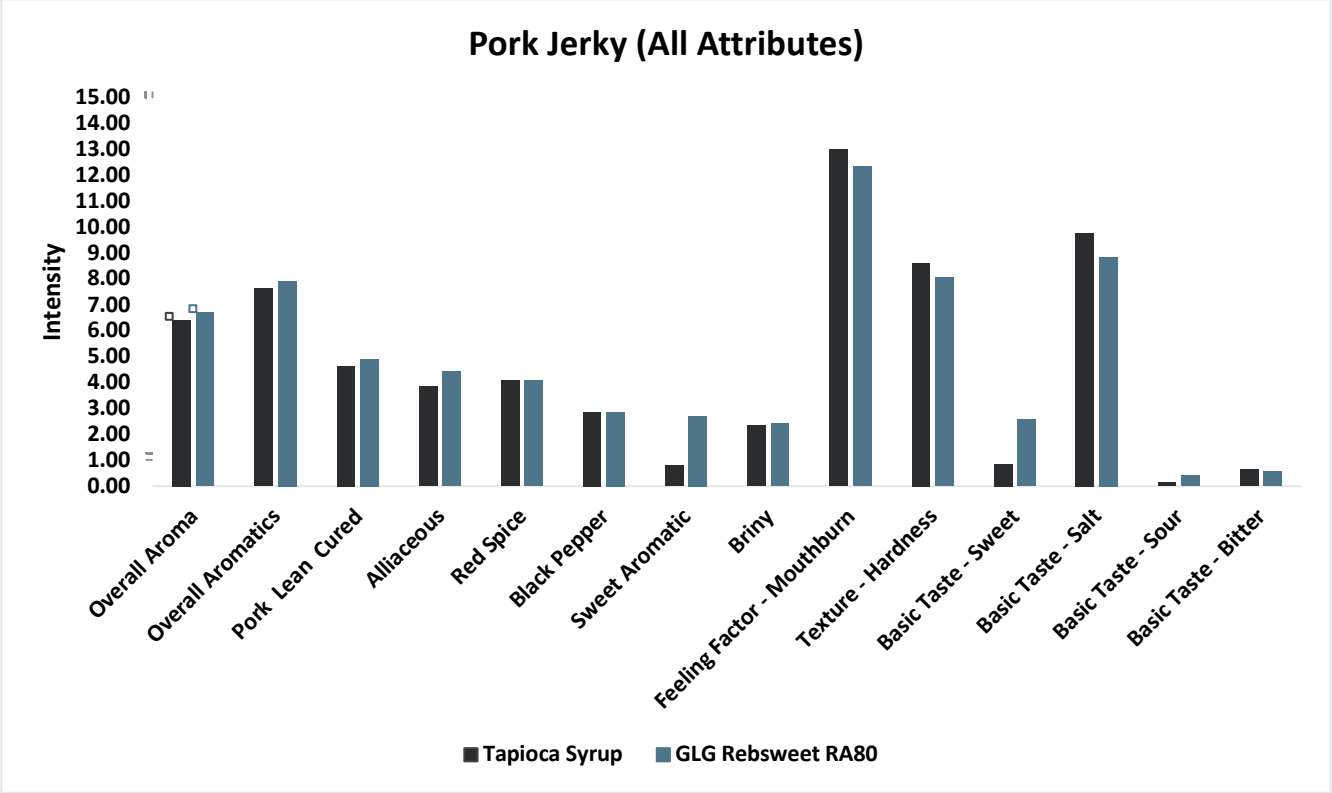
	Tapioca Syrup	GLG Rebsweet RA80	p-value
Aroma			
Overall Aroma	6.43 a	6.71 a	0.1708
Aromatics			
Overall Aromatics	7.64 b*	7.93 a	0.0479
Pork Lean Cured	4.64 a	4.93 a	0.0631
Alliaceous	3.86 b*	4.43 a	0.0046
Red Spice	4.07 a	4.07 a	1.0000
Black Pepper	2.86 a	2.86 a	1.0000
Sweet Aromatic	0.79 b*	2.71 a	< 0.0001
Briny	2.36 a	2.43 a	0.7618
Feeling Factors			
Mouthburn	13.00 a*	12.36 b	0.0053
Texture			
Hardness	8.64 a	8.07 a	0.0524
Basic Tastes			
Sweet	0.86 b*	2.57 a	< 0.0001
Salt	9.79 a*	8.86 b	0.0267
Sour	0.14 b*	0.43 a	0.0125
Bitter	0.64 a	0.57 a	0.3299

*Sample means with different letters in the same row are considered significantly different at the 95% confidence level.

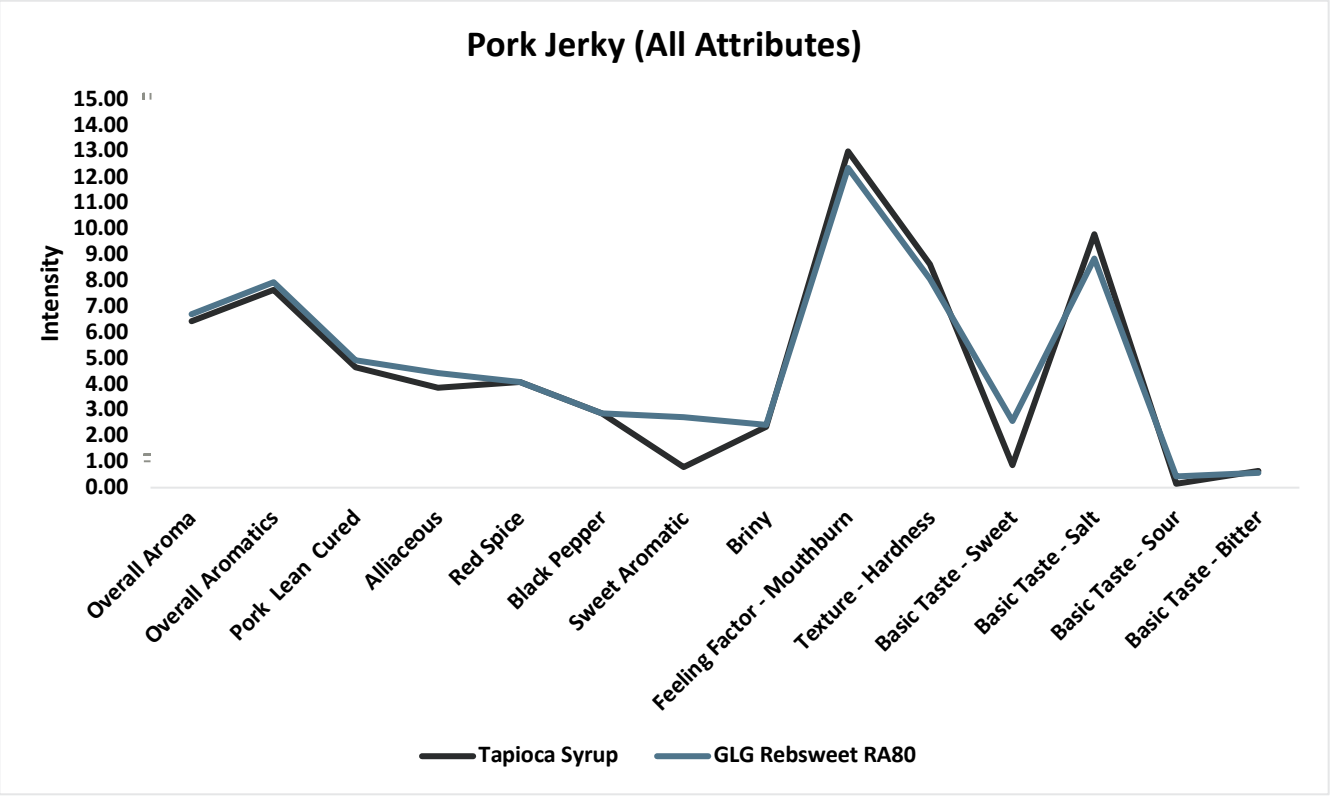
Graph 1:



Graph 2:



Graph 3:



Detailed Methods Summary:

- **Descriptive Method –** Panelists conducted descriptive flavor analysis using the basic taste intensity scales and Spectrum 15 point Universal aromatic scale

Basic Taste / Scale Intensity		2	5	10	15
Sweet	(Sucrose)	2.0%*	5.0%	10%	16%
Salt	(Sodium Chloride)	0.20%	0.35%	0.55%	0.70%
Sour	(Citric Acid)	0.05%	0.10%	0.15%	0.20%
Bitter	(Caffeine)	0.05%	0.08%	0.15%	0.20%

*All solutions are made by dissolving the compounds listed in deionized water.

Universal Flavor Aromatic Scale

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

LOW MODERATE STRONG

- **Sample Preparation -** Samples were cut into pieces and placed into 4 oz plastic soufflé cups and capped the morning of evaluation. The samples were coded with random 3-digit codes. All samples were stored and evaluated room temperature.
- **Sample Evaluation -** Samples were evaluated 1st for overall aroma, then basic taste sweet, followed by the rest of the flavor profile. Samples were evaluated in a round table style format with panelists

evaluating individually and group discussion following. A 10 minute break was provided between samples to allow for cleansing with unsalted cracker and water. Refer to Appendix A2 for sample ballot and terms.

- **Test Design/Data Analysis -** All data was collected using Compusense at Hand sensory software. Panelists evaluated all samples using a balanced, complete block design. Samples were evaluated twice, with both evaluations conducted on the same day.
- An analysis of variance (ANOVA) was conducted per attribute using XLSTAT statistical software to determine significance with sample means compared using Fishers LSD. Significance was measured at 95% confidence.

From:	Katrina Emmel
To:	Perrier, Judith
Cc:	William J. Rowe; Robert McQuate
Subject:	Re: GRN 790 - Follow up Questions from FSIS and FDA
Date:	Thursday, October 04, 2018 3:37:39 PM
Attachments:	FDA Response Ltr GLG GRN 790 10-4-18.pdf

Hello Dr. Perrier,

Attached you will find a response letter addressing the questions provided in your email on September 24, 2018 regarding GRN 790. Please let me know if you have any further questions.

Thank you,

Katrina

Katrina Emmel, Ph.D.
Senior Scientist/Project Manager/Associate
GRAS Associates, LLC.

emmel@gras-associates.com

GRAS Associates, LLC
27499 Riverview Center Blvd.
Bonita Springs, FL 34134
T: 239.444.1724 | F: 239.444.1723
www.gras-associates.com

October 4, 2018

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety (HFS-255)
5001 Campus Drive
College Park, MD 20740-3835

Attention: Dr. Judith Perrier
Re: GRN 790 – High Purity Steviol Glycosides to Include Proposed Uses in Certain Meat Products – Response to Questions Posed in an Email Dated 9/24/18

Dear Dr. Perrier:

Per your request, GRAS Associates, LLC, acting as the agent for GLG Life Tech Corporation ("GLG"), is providing a response to complete FDA and USDA/FSIS's request for additional information as denoted in your email dated September 24, 2018, as follows:

1. *At the requested level of 2500 ppm, what would be the amount of steviol glycosides present in cured ham with a RACC of 114 grams on a ready to cook basis? This is the highest RACC amount for the product category requested.*

   At the requested level of 2,500 ppm, there would be 285 mg steviol glycosides present in cured ham with a RACC of 114 grams on a ready-to-cook basis.

2. *What would be the intended "carrier" for this ingredient? Maltodextrin, glucose, water? Is the ingredient intended to be used dry or as part of a liquid solution? Could we see specification sheets for this ingredient?*

   There is no intended "carrier" for this ingredient. It is intended to be used as an ingredient in cured meat products as a component of a marinade mixture.

   The specifications for the steviol glycosides materials remain unchanged from those provided in Table 3 on p. 19 of GRN 493, which has been duplicated below for reference.

• • •

Table 3. Specifications for GLG-SG Preparations

Parameter	JECFA[a] Specifications Steviol Glycosides	FCC[b] Specifications Rebaudioside A	GLG Specifications			
			Anysweet RA50 Plus	Anysweet RA60 Plus	Rebsweet RA80	Rebsweet RA85
Appearance	White to light yellow powder	White to off-white, hygroscopic fine crystal, granule, or powder	White/off-white hygroscopic powder	White/off-white hygroscopic powder	White/off-white hygroscopic powder	White/off-white hygroscopic powder
Sweetness	200-300 times sweeter than sucrose	NS	NS	NS	NS	NS
Solubility	Freely soluble in water	Freely soluble in water:ethanol (50:50)	Freely Soluble	Freely Soluble	NS	Freely soluble
Rebaudioside A	NS	NLT 95%	NLT 50%	NLT 60.0%	NLT 80%	NLT 85.0%
Stevioside	NS	NS	NLT 25%	NLT 15.0%	NS	NS
Total Steviol Glycosides	NLT 95%	NA	NLT 95%	NLT 95.0%	NLT 95%	NLT 95.0%
Residue on Ignition	NS	NS	NMT 1.0%	NMT 1.0%	NMT 1.0%	NMT 1.0%
Moisture (loss on drying)	NMT 6%	NMT 6%	NMT 4.0%	NMT 4.0%	NMT 4.0%	NMT 4.0%
pH (1% solution)	4.5 - 7.0	4.5 - 7.0	4.5-7.0	4.5-7.0	4.5-7.0	4.5-7.0
Specific Rotation	NS	NS	-30°to -38°	-30°to -38°	NS	NS
Residual Solvent Levels						
Total Solvents	NS	NS	NMT 5200 ppm	NMT 5200 ppm	NMT 5200 ppm	NMT 5200 ppm
Residual Methanol	NMT 200 mg/kg	NMT 0.02%	NMT 200 ppm	NMT 200 ppm	NMT 200 ppm	NMT 200 ppm
Residual Ethanol	NMT 5000 mg/kg	NMT 0.5%	NMT 5000 ppm	NMT 5000 ppm	NMT 5000 ppm	NMT 5000 ppm
Heavy Metals						
Total Metals	NS	NS	NMT 10 ppm	NMT 10 ppm	NMT 10 ppm	NMT 10.0 ppm
Lead	NMT 1 mg/kg	NMT 1 mg/kg	NMT 1.0 ppm	NMT 1.0 ppm	NMT 1.0 ppm	NMT 1.0 ppm
Arsenic	NMT 1 mg/kg	NMT 1 mg/kg	NMT 1.0 ppm	NMT 1.0 ppm	NMT 1.0 ppm	NMT 1.0 ppm
Microbiological						
Total Plate Count (cfu/g)	NA	NA	<1000	<1000	<1000	<1000
Yeast & Mold Plate Count (cfu/g)	NA	NA	<100	<100	<100	<100
Salmonella	NA	NA	Negative	Negative	Negative	Negative
Escherichia coli	NA	NA	Negative	Negative	Negative	Negative
Staphylococcus aureus	NA	NA	Negative	Negative	Negative	Negative

[a] Prepared at 73rd JECFA (2010).
[b] FCC, 2010. Rebaudioside A monograph. Food Chemicals Codex (7th Ed.)
NS = not specified; NA = not applicable; NLT = not less than; NMT = not more than

3. *Does the notifier only intend to use this ingredient in cured meat products? Please note, that as written, this submission would not extend to "uncured" versions of products that are traditionally cured (examples: uncured bacon formulated with naturally occurring sources of nitrite such as cultured celery powder, jerky that does not contain a curing agent).*

   GLG has reevaluated its proposed uses and would like to revise the proposal to uncured versions of the meat products listed in the NHANES cured meat category. We have reviewed the description of NHANES meat categories and believe that survey respondents would have reported consuming a cured meat even if the product was uncured. Certainly that is true for any jerky product as jerky is only listed in the cured meat product. Therefore, we believe our consumption estimate based on total cured meat consumption is a reasonable worst case for the proposed use.

4. *For those cured products that also contain starter cultures, how does the replacement of sugar with Steviol Glycosides impact lactic acid production?*

   Replacement of sugar with steviol glycosides would result in no lactic acid production.

   Steviol glycosides are used solely to provide sweetness; however, sugar provides many technical properties in addition to sweetness. In applications where non-sweet technical properties are required (i.e., ability to ferment, osmolality, water activity, humectancy, viscosity, volume, texture, etc.), steviol glycosides alone will not work. Therefore, another substance would need to be added to deliver the additional technical properties.

5. *Do steviol glycosides have the same dehydration or osmotic effect as sugar?*

   Steviol glycosides do not provide the same dehydration or osmotic effect as sugar.

6. *Although not commonly used anymore, does the substitution of steviol glycosides for sugar impact the conversion of nitrate to nitrite in those products that are still using nitrate?*

   There is no data on the impact of steviol glycosides on the conversion of nitrates to nitrites, but GLG expects that the replacement of sugar with steviol glycosides would reduce the conversion.

7. *How does GLG Life Tech Corporation intend to label the ingredient on the cured meat products?*

   GLG intends to label the ingredient as Stevia.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via email.

We look forward to your feedback.

Katrina Emmel, Ph.D.
Senior Scientist/Project Manager/Associate

GRAS Associates, LLC
27499 Riverview Center Blvd., Suite 212
Bonita Springs, FL 34134

(b)(6)

From:	Katrina Emmel
To:	Perrier, Judith
Cc:	William J. Rowe; Robert McQuate
Subject:	Re: GRN 790 - Follow up Question About Intended Food Categories
Date:	Wednesday, October 31, 2018 11:54:34 PM
Attachments:	FDA Response Ltr GLG GRN 790 10-31-18.pdf

Hello Dr. Perrier,

Attached you will find a response letter addressing the questions provided in your email on October 18, 2018 regarding GRN 790. Please let me know if you have any further questions.

Thank you,

Katrina
Katrina Emmel, Ph.D.
Senior Scientist/Project Manager/Associate
GRAS Associates, LLC.

emmel@gras-associates.com

GRAS Associates, LLC
27499 Riverview Center Blvd.
Bonita Springs, FL 34134
T: 239.444.1724 | F: 239.444.1723
www.gras-associates.com

October 31, 2018

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety (HFS-255)
5001 Campus Drive
College Park, MD 20740-3835

Attention: Dr. Judith Perrier
Re: GRN 790 – High Purity Steviol Glycosides to Include Proposed Uses in Certain Meat Products – Response to a Question Posed in an Email Dated 10/18/18

Dear Dr. Perrier:

Per your request, GRAS Associates, LLC, acting as the agent for GLG Life Tech Corporation ("GLG"), is providing a response regarding the following question posed by FDA and USDA/FSIS in your email dated October 18, 2018, as follows:

In your response to question 3 regarding use of your ingredient in uncured versions of meat products, you requested to modify the intended use of steviol glycosides in 'cured meat products' to 'uncured versions of meat products listed in the NHANES cured meat category.' We agree that it is appropriate, for purposes of exposure estimate, to use consumption data for cured meats as substitutes for uncured versions for which data is not available. However, we could not identify a "cured meat" category among NHANES food codes (e.g. cured meat products are dispersed within the hierarchy of food codes, such as 21602100 – beef jerky, 22002800 – pork jerky, 23321900 – venison jerky). Please provide a list of the meat product categories that are included in your intended uses.

GLG intends to use high purity steviol glycosides in uncured versions of meat products that fall within the following NHANES food codes:

Beef jerky – 21602100
Pork jerky – 22002800
Venison jerky – 23321900

GLG also intends to use high purity steviol glycosides in uncured versions of chicken jerky and turkey jerky; however, we are unable to find the corresponding NHANES food codes for poultry jerky listed in Appendix D, Food Codes for NHANES (Final, August 2012).[1]

[1] Available at: https://oehha.ca.gov/media/downloads/crnr/appendixd2012.pdf; Accessed on 10/29/18.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via email.

We look forward to your feedback.

Katrina Emmel, Ph.D.
Senior Scientist/Project Manager/Associate

GRAS Associates, LLC
27499 Riverview Center Blvd., Suite 212
Bonita Springs, FL 34134

From:	Katrina Emmel
To:	Perrier, Judith; Zhang, Janet
Cc:	Robert McQuate; William J. Rowe
Subject:	Re: GRN 790 - Request for Statement about Confidential Data in the Appendices
Date:	Friday, December 21, 2018 11:18:10 PM
Attachments:	FDA Response Ltr GLG GRN 790 12-21-18.pdf

Hello Dr. Perrier and Dr. Zhang,

Attached you will find a response letter addressing the questions provided in your email on December 19, 2018 regarding GRN 790. Please let me know if you have any further questions.

As I mentioned in our call earlier this week, I will be on vacation from 12/22-1/13; however, I will do my best to respond to any additional communications you may have in as timely a manner as possible. If a response is urgent, please note that in the subject line so I can attend to it as soon as possible.

Thank you and I wish you both happy holidays.

Kind Regards,

Katrina

Katrina Emmel, Ph.D.
Senior Scientist/Project Manager/Associate
GRAS Associates, LLC.

emmel@gras-associates.com

> On Dec 19, 2018, at 8:25 AM, Perrier, Judith <Judith.Perrier@fda.hhs.gov> wrote:
>
> Hello Katrina,
>
> As part of our evaluation of GRN 790, we request input regarding the notifier's request to keep the appendices confidential. Please provide a statement regarding the following:
>
> 1. The rationale as to why Appendices 1 and 2 are confidential, and
>
> 2. Articulate why experts can get to a conclusion of safety without the data in Appendices 1 and 2.

As we discussed, the sooner we receive a response to this request, the sooner we will be able to finalize our response letter.

Thank you.

Regards,

Judy Perrier

Judith D. Perrier, Ph.D., R.D.
Biologist

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Tel: 240-402-2040
Judith.Perrier@fda.hhs.gov

GRAS Associates, LLC
27499 Riverview Center Blvd.
Bonita Springs, FL 34134
T: 239.444.1724 | F: 239.444.1723
www.gras-associates.com

December 21, 2018

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety (HFS-255)
5001 Campus Drive
College Park, MD 20740-3835

Attention: Dr. Judith Perrier and Dr. Janet Zhang
Re: GRN 790 – High Purity Steviol Glycosides to Include Proposed Uses in Certain Meat Products – Response to Questions Posed in an Email Dated 12/19/18

Dear Dr. Perrier:

GRAS Associates, LLC, acting as the agent for GLG Life Tech Corporation ("GLG"), is providing a response regarding the following question posed by FDA in your email dated December 19, 2018 in which GLG was asked to provide input regarding a request to keep the information provided in Appendices 1 and 2 confidential, specifically:

1. *The rationale as to why Appendices 1 and 2 are confidential, and*
2. *Articulate why experts can get to a conclusion of safety without the data in Appendices 1 and 2.*

After careful consideration, GLG would like to withdraw their request for confidentiality of Appendices 1 and 2. GLG understands that the full version of the dossier—including Appendices 1 and 2 in their entirety—will therefore be publicly available.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via email.

We look forward to your feedback.

(b) (6)

Katrina Emmel, Ph.D.
Senior Scientist/Project Manager/Associate

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