#821

16 November 2018

Dr. Paulette Gaynor
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition (CFSAN)
Food and Drug Administration
5001 Campus Drive
College Park, MD
20740 USA

Dear Dr. Gaynor:

Re: GRAS Notice for High-Purity Glucosylated Steviol Glycosides

In accordance with 21 CFR §170 Subpart E consisting of § 170.203 through 170.285, Haigen-BGG Natural Ingredients (HBNI) Limited [11038, 11/F, Tower A, Gateway Square No. 18, Xiaguangli, North Road East Third Ring, Chaoyang District, Beijing, China], as the notifier, is submitting one hard copy and one electronic copy (on CD), of all data and information supporting the company's conclusion that high-purity glucosylated steviol glycosides, as manufactured by HBNI, is GRAS under the specified conditions of use as a food ingredient on the basis of scientific procedures, and therefore are not subject to the premarket approval requirements of the *Federal Food, Drug and Cosmetic Act*. Information setting forth the basis for HBNI's GRAS conclusion, as well as a consensus opinion of an independent panel of experts, also are enclosed for review by the agency.

I certify that the enclosed electronic files were scanned for viruses prior to submission and are thus certified as being virus-free using Symantec Endpoint Protection 12.1.5.

Should you have any questions or concerns regarding this GRAS notice, please do not hesitate to contact me at any point during the review process so that we may provide a response in a timely manner.

Sincerely,

(b) (6)

Varuzhan H. Abelyan, Sc.D.
Chief of Science & Technology
Haigen-BGG Natural Ingredients Limited

GRAS Notice for High-Purity Glucosylated Steviol Glycosides

Submitted by:
Haigen-BGG Natural Ingredients Limited
11038, 11/F, Tower A
Gateway Square No. 18
Xiaguangli, North Road East Third Ring
Chaoyang District, Beijing
China

Submitted 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

November 16, 2018

GRAS Notice for High-Purity Glucosylated Steviol Glycosides

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GRAS Notice for High-Purity Glucosylated Steviol Glycosides

Part 1. Signed Statements and Certification (21 CFR § 170.225)

Haigen-BGG Natural Ingredients (HBNI) Limited hereby informs the United States Food and Drug Administration (U.S. FDA) that their high-purity glucosylated steviol glycosides consisting of ≥80% glucosylated steviol glycosides and ≥95% steviol glycosides, meeting the specifications as described below, are Generally Recognized as Safe (GRAS) under the conditions of intended use as described below, and are therefore not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act. This conclusion was made by a convened panel of experts who are qualified by scientific training and experience who have reviewed all unfavorable and favorable information known to HBNI that are pertinent to the safety evaluation of the high-purity glucosylated steviol glycosides for use as a general purpose sweetener.

All data and information presented in Parts 2 through 7 of this GRAS Notice do not contain any trade secret, commercial, or financial information that is privileged or confidential. Therefore, the data and information that are presented herein are not exempt from the Freedom of Information Act (5 U.S. Code § 552).

Signed, (b) (6)

(b) (6)

Name: Varuzhan H Abelyan
Title: Chief of Science & Technology
Email: v.abelyan@hbnaturalingredients.com

Date: 14.11.2018

1.1 Name and Address of Notifier

Haigen-BGG Natural Ingredients Limited
11038, 11/F, Tower A
Gateway Square No. 18
Xiaguangli, North Road East Third Ring
Chaoyang District, Beijing
China

1.2 Common Name of Notified Substance

The notified substance is glucosylated steviol glycosides and is also known as enzyme-modified steviol glycosides.

1.3 Conditions of Use

HBNI intends to market their high-purity glucosylated steviol glycosides (≥80% glucosylated steviol glycosides) for use as a table top sweetener and as a general purpose sweetener in conventional food, other than infant formula and meat and poultry products under the jurisdiction of the United States Department of Agriculture. The use levels of the high-purity glucosylated steviol glycosides (≥80% glucosylated steviol glycosides) will be limited by the inherent organoleptic properties of the ingredient. Therefore, the high-purity glucosylated steviol glycosides (≥80% glucosylated steviol glycosides) will be used at levels to achieve its intended sweetening effect in accordance with current Good Manufacturing Practices (cGMP). HBNI anticipates that the uses and use levels of their high-purity glucosylated steviol glycosides (≥80% glucosylated steviol glycosides) will reflect those of other glucosylated steviol glycoside preparations that are currently on the United States (U.S.) market (GRAS Notice [GRN] 337, 375, 448, 452, 607, 656, 662).

1.4 Basis for GRAS

Pursuant to 21 CFR §170.30 (a) and (b) of the Code of Federal Regulations (CFR), HBNI's high-purity glucosylated steviol glycosides (≥80% glucosylated steviol glycosides), as described herein, has been concluded to have GRAS status for use as an ingredient for addition to conventional food, on the basis of scientific procedures, as described herein.

1.5 Availability of Information

The data and information that serve as the basis for this GRAS Notification will be made available to the U.S. FDA for review and copying upon request during business hours at the offices of:

Haigen-BGG Natural Ingredients Limited
11038, 11/F, Tower A
Gateway Square No. 18
Xiaguangli, North Road East Third Ring
Chaoyang District, Beijing
China

Part 2. Identity, Method of Manufacture, Specifications, and Physical or Technical Effect (21 CFR § 170.230)

2.1 Identity

HBNI's glucosylated steviol glycosides (≥80% glucosylated steviol glycosides) are manufactured by glucosylation of steviol glycosides derived from the leaves of *Stevia rebaudiana* Bertoni. The starting steviol glycosides are extracted and purified in accordance with the methodology described in the Chemical and Technical Assessment (CTA) for steviol glycosides (FAO, 2016) and include stevia extracts (≥95% steviol glycosides) containing <30% rebaudioside A; ≥50% rebaudioside A; >95% rebaudioside D; or >95% stevioside. The glucosylation step results in the formation of a glucosylated form of the starting steviol glycoside (*i.e.,* glucosylated stevioside, glucosylated rebaudioside A, glucosylated rebaudioside D from stevioside, rebaudioside A, and rebaudioside D, respectively). Thus, the final glucosylated steviol glycosides contain a mixture of glucosylated steviol glycosides and steviol glycosides.

HBNI has conducted compositional analyses of several batches of the final product to determine the glucosylated steviol glycoside and steviol glycoside content (see Table 2.1-1 for further details). The final product contains no less than 80% glucosylated steviol glycosides and no less than 95% total steviol glycosides, thus meeting the Joint FAO/WHO Expert Committee on Food Additives (JECFA) purity specifications for steviol glycosides. The glucosylated steviol glycoside content was measured using a method similar to that of the Japanese Ministry of Health, Labour and Welfare method for measuring glucosylated steviol glycosides (MHLW, 2009). The total steviol glycoside content was measured using high-performance liquid chromatography (JECFA, 2008).

Table 2.1-1 Steviol Glycoside Content Present in 3 Non-Consecutive Lots of HBNI's Glucosylated Steviol Glycosides

Content (%)	Glucosylated Reb A[a]	Glucosylated Reb D[a]	Glucosylated Stevioside[a]	Glucosylated Steviol Glycosides (>50% Reb A) [a]	Glucosylated Steviol Glycosides (<30% Reb A) [a]
Stevioside + Reb C + Reb A (<8%)	2.7±0.6%	3.1±0.5%	2.3±0.6%	3.4±1.1%	1.9±0.1%
Mono- and di-glucosyl Steviol Glycosides	35.5±0.2%	36.9±1.6%	43.2±0.6%	36.1±0.3%	38.8±0.5%
Tri- and tetra-glucosyl	33.7±0.4%	32.4±0.9%	39.2±1.5%	32.7±0.2%	32.1±0.4%

Table 2.1-1 Steviol Glycoside Content Present in 3 Non-Consecutive Lots of HBNI's Glucosylated Steviol Glycosides					
Content (%)	**Glucosylated Reb A[a]**	**Glucosylated Reb D[a]**	**Glucosylated Stevioside[a]**	**Glucosylated Steviol Glycosides (>50% Reb A) [a]**	**Glucosylated Steviol Glycosides (<30% Reb A) [a]**
Steviol Glycosides					
Higher α-GSG	25±1.1%	26.4±0.9%	14.1±1.9%	24.5±0.9%	25.3±0.6%
Total Steviol Glycosides (≥95%)	96.9±0.5%	98.8±0.6%	98.8±0.7%	96.7±0.6%	98.1±0.2%
Total α-GSG (≥80%)	94.2±1.0%	95.6±0.2%	96.5±0.1%	93.3±1.1%	96.2±0.2%
Dextrins (<5%)	3.1±0.5%	1.2±0.6%	1.2±0.7%	3.3±0.6%	1.9±0.2%

GSG = glucosylated steviol glycosides; Reb = rebaudioside.
[a] Results are the average and standard deviation of 3 non-consecutive lots of each product.

2.2 Method of Manufacture

HBNI utilizes a multi-step process to manufacture the glucosylated steviol glycosides. The general steps include production of the starting steviol glycosides that are subjected to the glucosylation reaction. The starting steviol glycosides are obtained by hot water extraction and a series of concentration, crystallization, and purification steps that are consistent with the methodology described in the CTA for steviol glycosides (FAO, 2016). The starting steviol glycosides contain ≥95% steviol glycosides and thus meet the JECFA purity specifications for steviol glycosides. Next, the starting steviol glycosides undergo a glucosylation reaction in which the starting material is dissolved in tapioca starch[1] that has been liquefied by treatment with commercially available cyclomaltodextrin glucanotransferase (CGTase)[2] (EC 2.4.1.19) or α-amylase (EC 3.2.1.1), and the reaction is carried out at 60°C for 24 to 48 hours to produce the mixture of glucosylated steviol glycosides. If the starting steviol glycoside is rebaudioside A (≥95% rebaudioside A), the resulting glucosylated product can be referred to as α-glucosylated rebaudioside A. Likewise, application of other steviol glycosides as the starting material generates glucosylated stevioside and/or α-glucosylated rebaudioside B, C, D, M, O, N, E, and/or F. Thus, the manufacturing process utilized by HBNI can be extended to produce various glucosylated steviol glycosides from their respective starting steviol glycoside. The enzymes are inactivated at the end of the reaction by heating for 20 minutes at 100°C.

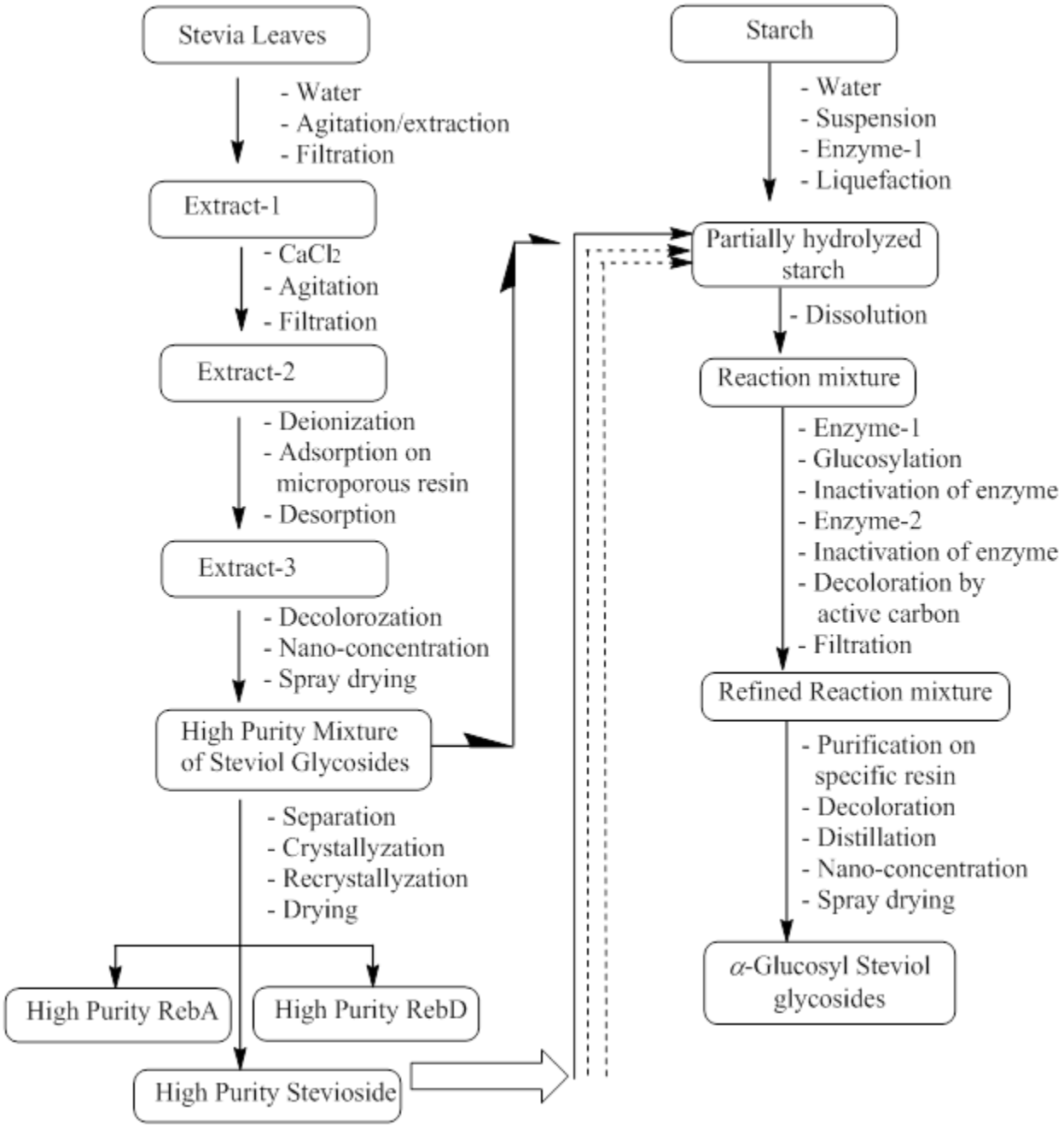
[1] Source of glucose.

[2] The enzyme preparation (Toruzyme) complies with the current JECFA and FCC purity specifications for food-grade enzyme preparations (JECFA, 2006; FCC, 2018).

In the next steps of production, the reaction mixture is purified, concentrated, and filtered in a series of steps consistent with the CTA for steviol glycosides (FAO, 2016). The reaction mixture is treated with activated carbon to remove the inactivated enzymes and the carbon is separated by a plate-and-frame filter press. The filtrate is purified with macroporous adsorption resin and the remaining maltooligosaccharides are removed by washing the column with deionized water. The adsorbed steviol glycosides are eluted using food-grade ethanol, treated with activated carbon, concentrated, and then spray dried. The final glucosylated steviol glycoside preparation contains ≥80% glucosylated steviol glycosides and ≥95% of total steviol glycosides (sum of glucosylated steviol glycosides and unmodified steviol glycosides), therefore meeting the JECFA purity specifications for steviol glycosides. A schematic of the manufacturing process is presented in Figure 2.2-1.

All raw materials, processing aids, and purification equipment used in the manufacturing process are food-grade or equivalent (*e.g.,* Food Chemical Codex, United States Pharmacopeia, or European Pharmacopeia), and are used in accordance with an applicable federal regulations or are GRAS for their intended use. The enzymes used in the glucosylation reaction, namely CGTase and α-amylase, are derived from non-genetically modified and non-pathogenic strains of *Bacillus licheniformis* and *Bacillus subtilis*, respectively. The use of CGTase and α-amylase in the glucosylation reaction are identical to the uses described in previous GRAS Notifications for glucosylated steviol glycosides (*e.g.,* GRN 337, 375, 448, 452, 656 – U.S. FDA, 2011a,b, 2013a,b, 2016b) and are GRAS when used in accordance with 21 CFR § 184.1012 and 184.1148, respectively (U.S. FDA, 2018).

Figure 2.2-1 Schematic of the Manufacturing Process for HBNI's Glucosylated Steviol Glycosides



2.3 Specifications

HBNI has established specifications for the steviol glycoside starting material (Table 2.3-1) and glucosylated steviol glycosides (Table 2.3-2) based on the specifications for steviol glycosides established by JECFA (2017) and the specifications for steviol glycosides and rebaudioside A

published by the Food Chemicals Codex (FCC) (FCC, 2018). The specifications for HBNI's glucosylated steviol glycosides are consistent with those described in recent GRAS Notices for glucosylated steviol glycosides (GRN 607, 656, 662 – U.S. FDA, 2016a-c) and the specifications for steviol glycosides established by JECFA (2017). The methods of analysis are based on internationally-recognized standards. HBNI's glucosylated steviol glycosides primarily consists of steviol glycosides (≥95%) and is therefore consistent with the purity definition established by JECFA and the FCC.

Table 2.3-1 Specifications for the Steviol Glycoside Starting Materials							
Specification Parameter	**JECFA Specifications for Steviol Glycosides (JECFA, 2017)**	**Steviol Glycoside Starting Material**					**Method of Analysis**
		Stevia extract-S	**Stevia extract-R**	**Reb A**	**Reb D**	**Stevioside**	
Appearance	White to light yellow powder	White to off-white powder	White to off-white powder	White to off-white powder	White to off-white powder	White to off-white powder	Visual inspection
Total steviol glycosides (anhydrous basis) (%)	≥95.0	≥95.0	≥95.0	≥95.0 (Reb A content)	≥95.0 (Reb D content)	≥95.0 (Stevioside >90%)	HPLC
Rebaudioside A (%)	NS	<30.0	≥50.0	≥95.0	NS	NS	HPLC
Loss on drying (%)	≤6.0	≤6.0	≤6.0	≤6.0	≤6.0	≤6.0	Eur. Ph. 2.8.17
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	pH meter
Residual ethanol (%)	≤0.5	<0.5	<0.5	<0.5	<0.5	<0.5	CH.P.(2)-VIII-P
Residual methanol (%)	≤0.02	<0.02	<0.02	<0.02	<0.02	<0.02	CH.P.(2)-VIII-P
Total ash (%)	≤1.0	<1.0	<1.0	<1.0	<1.0	<1.0	AOAC 945.96
Lead (ppm)	≤1.0	<1.0	<1.0	<1.0	<1.0	<1.0	ICP-MS AOAC
Arsenic (ppm)	≤1.0	<1.0	<1.0	<1.0	<1.0	<1.0	ICP-MS AOAC
Cadmium (ppm)	NS	<1.0	<1.0	<1.0	<1.0	<1.0	ICP-MS AOAC
Mercury (ppm)	NS	<1.0	<1.0	<1.0	<1.0	<1.0	ICP-MS AOAC
Total plate count (CFU/g)	≤1,000	<1,000	<1,000	<1,000	<1,000	<1,000	AOAC 990.12
Yeast and mold (CFU/g)	≤200	<100	<100	<100	<100	<100	AOAC 997.02
Escherichia coli (Negative/g)	Negative/g	Negative	Negative	Negative	Negative	Negative	AOAC 991.14
Salmonella sp. (in 25 g)	Negative	Negative	Negative	Negative	Negative	Negative	AOAC 2000.07
Staphylococcus aureus	NS	Negative	Negative	Negative	Negative	Negative	FDA BAM

AOAC = Association of Official Analytical Chemists; BAM = Bacteriological Analytical Manual; CFU = colony-forming units; Eur. Ph. = European Pharmacopeia; FDA = United States Food and Drug Administration; HPLC = high performance liquid chromatography; ICP-MS = inductively-coupled plasma mass spectroscopy; MPN = most probable

Table 2.3-1 Specifications for the Steviol Glycoside Starting Materials							
Specification Parameter	**JECFA Specifications for Steviol Glycosides (JECFA, 2017)**	**Steviol Glycoside Starting Material**					**Method of Analysis**
		Stevia extract-S	**Stevia extract-R**	**Reb A**	**Reb D**	**Stevioside**	

number; NS = not specified; ppm = parts per million; Reb = rebaudioside.

Table 2.3-2 Product Specifications for HBNI's Glucosylated Steviol Glycosides						
Specification Parameter	**JECFA Specifications for Steviol Glycosides (JECFA, 2017)**	**HBNI's Glucosylated Steviol Glycosides**	**PureCircle's Glucosylated Steviol Glycosides (GRN 607)**	**GLG Life Tech Corporation's Enzyme Modified Steviol Glycosides Preparations (GRN 656)**	**PureCircle's Glucosylated Stevia Leaf Extract (GRN 662)**	**Method of Analysis**
Appearance	White to light yellow powder	White to off-white powder	White to off-white powder	White/off-white powder	White to off-white powder	Visual inspection
Total steviol glycosides (dry basis) (%)	≥95.0	≥95.0	>80	≥95.0 total steviol glycosides ≤15.0 unreacted steviol glycosides	>95.0	Adsorption chromatography
Glucosylated steviol glycosides (%)	N/A	≥80	NS	≥80% α-glucosylated steviol glycosides	NS	HPLC
Loss on drying (%)	≤6.0	≤6.0	≤6	≤4.0	≤6.0	Eur. Ph. 2.8.17
Residual ethanol (%)	≤0.5	<0.5	N/A	≤0.5	<0.30	GC
Residual methanol (%)	≤0.02	<0.02	N/A	≤0.02	<0.02	GC
Total ash (%)	≤1.0	<1.0	<1	≤1.0	<1.0	Eur. Ph. 2.4.16
Lead (ppm)	≤1.0	<1.0	<1	≤1.0	<1.0	Eur. Ph. 2.8.27
Arsenic (ppm)	≤1.0	<1.0	<1	≤1.0	<1.0	Eur. Ph. 2.8.27
Cadmium (ppm)	NS	<1.0	N/A	N/A	<1.0	Eur. Ph. 2.8.27
Mercury (ppm)	NS	<1.0	<1	N/A	<1.0	Eur. Ph. 2.8.27
Total plate count (CFU/g)	≤1,000	<1,000	<1,000	<1,000	<1,000	Eur. Ph. 2.6.12
Yeast and mold (CFU/g)	≤200	<100	<200	<100	<200	Eur. Ph. 2.6.12
Escherichia coli	Negative/g	Negative	ND	<3 MPN/g	ND	Eur. Ph. 2.6.13
Salmonella sp.	Negative	Negative in 25 g	Absent in 25 g	Negative in 25 g	Absent in 25 g	Eur. Ph. 2.6.13
Staphylococcus aureus	NS	Negative	N/A	<10 CFU/g	N/A	Eur. Ph. 2.6.13

Table 2.3-2 Product Specifications for HBNI's Glucosylated Steviol Glycosides						
Specification Parameter	**JECFA Specifications for Steviol Glycosides (JECFA, 2017)**	**HBNI's Glucosylated Steviol Glycosides**	**PureCircle's Glucosylated Steviol Glycosides (GRN 607)**	**GLG Life Tech Corporation's Enzyme Modified Steviol Glycosides Preparations (GRN 656)**	**PureCircle's Glucosylated Stevia Leaf Extract (GRN 662)**	**Method of Analysis**

CFU = colony-forming units; Eur. Ph. = European Pharmacopeia; GC = gas chromatography; GRN = Generally Recognized as Safe (GRAS) Notice; HPLC = high performance liquid chromatography; JECFA = Joint FAO/WHO Expert Committee on Food Additives; MPN = most probable number, N/A = not available, ND = not detected; ppm = parts per million.

2.4 Batch Analyses

HBNI has manufactured 5 different glucosylated steviol glycoside products, including glucosylated rebaudioside A, glucosylated rebaudioside D, glucosylated stevioside, glucosylated steviol glycosides (>50% rebaudioside A), and glucosylated steviol glycosides (<30% rebaudioside A). Three non-consecutive lots for each product were analyzed and the results of which demonstrates conformance to the established product specifications. The average and standard deviation of 3 non-consecutive lots of each glucosylated steviol glycoside product are presented in Table 2.4-1 below, and Certificates of Analysis are provided in Appendix A.

Table 2.4-1 Summary of the Product Analysis for 3 Non-Consecutive Lots of HBNI's Glucosylated Steviol Glycosides						
Specification Parameter	**Specification Limit**	**Glucosylated Reb A (AGG)[a]**	**Glucosylated Reb D (PGG)[a]**	**Glucosylated Stevioside (SGG)[a]**	**Glucosylated Steviol Glycosides (>50% Reb A) (LGG)[a]**	**Glucosylated Steviol Glycosides (<30% Reb A) (RGG)[a]**
Appearance	White to off-white powder	White powder	White powder	White powder	White powder	White powder
Total steviol glycosides (dry basis) (%)	≥95	95.5±0.9	98.8±0.6	98.8±0.7	96.7±0.6	96.4±1.4
Glucosylated steviol glycosides (%)	≥80	92.9±1.6	94.6±0.9	92.7±0.7	92.6±0.9	93.7±1.9
Loss on drying (%)	≤6	2.4±0.2	3.8±0.05	3.3±0.1	3.3±0.1	2.7±0.0
Residual ethanol (ppm)	<5,000	13±5.0	693±343	585±31	38±4.5	10.3±0.9
Residual methanol (ppm)	<200	2.3±1.2	4±0.8	4±0.8	4±0.0	1.5±0.5
Total ash (%)	<1	0.3±0.1	0.1±0.0	0.1±0.0	0.3±0.05	0.3±0.04
Lead (ppm)	<1	0.13±0.04	0.13±0.05	0.13±0.05	0.13±0.05	0.13
Arsenic (ppm)	<1	0.06±0.01	0.07±0.02	0.05±0.0	0.05±0.0	0.07±0.02
Cadmium (ppm)	<1	<0.05	<0.05	<0.05	<0.05	<0.05
Mercury (ppm)	<1	<0.05	<0.05	<0.05	<0.05	<0.05
Total plate count (CFU/g)	<1,000	<10±0	87±12	32±8	40±4	107±28
Yeast and mold (CFU/g)	<100	23±2	47±12	52±6	55±11	27±8
Escherichia coli	Negative	Negative	Negative	Negative	Negative	Negative
Salmonella sp.	Negative in 25 g	Negative	Negative	Negative	Negative	Negative
Staphylococcus aureus	Negative	Negative	Negative	Negative	Negative	Negative

CFU = colony-forming units; ppm = parts per million; Reb = rebaudioside.
[a] Results are the average and standard deviation of 3 non-consecutive lots of each product.

2.5 Stability of Glucosylated Steviol Glycosides

The stability of steviol glycosides has been reviewed by various scientific bodies, such as JECFA, European Food Safety Authority (EFSA), and Food Standards Australia New Zealand (FSANZ), and has been discussed in the published scientific literature (Chang and Cook, 1983; Kroyer, 1999). JECFA evaluated the data on the stability of steviol glycosides mimicking their use in foods and noted that these compounds do not undergo browning or caramelization when heated and are reasonably stable under elevated temperatures used in food processing. JECFA specifically concluded that high-purity steviol glycosides (90 to 94% purity) are stable for at least 180 days when stored at temperatures up to 24°C in acidic conditions (pH 2 to 4); at higher temperatures and pH (80°C and pH 3 and 4) however, 8% and 4% decomposition were observed in steviol glycoside solutions, respectively. Likewise, at temperatures greater than 100°C, greater levels of decomposition were observed (10% and 40% at pH 4 and 3, respectively). Overall, JECFA concluded that the stability of steviol glycosides is pH- and temperature-dependent.

The stability of enzyme-modified steviol glycosides or glucosylated steviol glycosides have been evaluated in various product-specific studies as discussed in GRN 607 and GRN 662 (U.S. FDA, 2016a,c). In a long-term storage stability study, a glucosylated steviol glycoside preparation (≥80% steviol glycosides) was maintained in original packaging at 40°C and 75% relative humidity for 144 weeks (GRN 607 – U.S. FDA, 2016a). Minimal changes in total steviol glycoside content (both steviol glycosides and glucosylated steviol glycosides) were detected at various timepoints throughout the storage period. The pH stability of glucosylated steviol glycosides was also assessed at temperatures ranging from 5 to 37°C and pH 2 to 8 for 34 weeks, and the results of this study demonstrated that glucosylated steviol glycoside degradation was pH-, temperature-, and time-dependent. Degradation rates of less than 3% were observed after 26 weeks of storage at pH 2, 3, 5, and 6 and at 5°C; at higher temperatures (25 and 37°C) and pH 2, approximately 10% and 50% degradation, respectively, was observed. No significant degradation was observed at pH 3 to 8 over 34 weeks, irrespective of the storage temperature. The storage and pH stability of a glucosylated stevia leaf extract (containing primarily glucosylated rebaudioside A) were discussed in GRN 662 (U.S. FDA, 2016c). In the storage stability study, 1 lot of glucosylated stevia leaf extract was stored at 40°C and 75% relative humidity for 4 weeks. The total steviol glycoside content was not changed over the storage period. In the pH stability study, the same lot of glucosylated stevia leaf extract was stored over a pH range of 2 to 8 and temperatures of 5, 25, 37, and 56°C for 7 weeks. Total steviol glycoside content was measured as the sum of glucosylated rebaudioside A and rebaudioside A. The results of this study were consistent with the results for glucosylated steviol glycosides reported in the stability studies within GRN 607 and the overall conclusions of JECFA on the stability of

steviol glycosides in that the stability of these substances are pH-, temperature-, and time-dependent. Therefore, the results of the stability studies cited within GRN 607 and 662 provide evidence that the stability of glucosylated steviol glycosides are similar to steviol glycosides due to similarities in chemical structure.

In order to provide further support to these conclusions, HBNI conducted an accelerated stability and a temperature and pH stability study on the glucosylated steviol glycosides. These studies are briefly described below. In general, the results of these studies are consistent with the results of the stability studies cited within GRN 607 and 662 and provide further evidence that the stability of glucosylated steviol glycosides is similar to steviol glycosides, and that JECFA's conclusions regarding the stability of steviol glycosides can be extended to support the stability of HBNI's glucosylated steviol glycosides.

2.5.1 Accelerated Stability of Glucosylated Steviol Glycosides

In the accelerated stability study, powder samples of glucosylated rebaudioside A (Lot No. AGG-180541), glucosylated stevia extract (≥95% stevioside) (Lot No. RGG-180520), and glucosylated stevia extract (≥95% rebaudioside A) (Lot No. LGG-180501) were to be stored in aluminum bags for up to 6 months at 40±2°C and 75±5% relative humidity. The total steviol glycoside content will be measured at baseline (0 weeks), 2 weeks, 4 weeks, 2 months, 3 months, and 6 months. Data up to 4 weeks are currently available (Table 2.5.1-1). The results at 4 weeks indicate no significant change in total steviol glycoside content, consistent with the results of other storage stability studies with glucosylated steviol glycosides as described in previous GRAS Notices (GRN 607 and 662).

Table 2.5.1-1 Interim Results of Accelerated Storage Stability of Glucosylated Steviol Glycosides (Lot Nos. AGG-180541, RGG-180520, and LGG-180501) at 40°C and 75% Relative Humidity

Parameter	Week		
	0	2	4
Lot No. AGG-180541			
Loss on Drying (%)	2.55	2.45	2.58
Total Unreacted Steviol Glycosides (%)	2.22	2.12	2.30
Glucosylated Steviol Glycosides (%)	94.69	94.36	93.74
Total Steviol Glycosides (%)	**96.91**	**96.48**	**96.04**
Lot No. RGG-180520			
Loss on Drying (%)	2.68	2.76	2.82
Total Unreacted Steviol Glycosides (%)	1.94	1.65	1.87

Table 2.5.1-1 Interim Results of Accelerated Storage Stability of Glucosylated Steviol Glycosides (Lot Nos. AGG-180541, RGG-180520, and LGG-180501) at 40°C and 75% Relative Humidity			
Parameter	**Week**		
	0	**2**	**4**
Glucosylated Steviol Glycosides (%)	96.44	95.74	95.23
Total Steviol Glycosides (%)	**98.38**	**97.39**	**97.10**
Lot No. LGG-180501			
Loss on Drying (%)	3.10	3.03	3.10
Total Unreacted Steviol Glycosides (%)	4.47	3.93	4.24
Glucosylated Steviol Glycosides (%)	91.85	91.59	91.67
Total Steviol Glycosides (%)	**96.32**	**95.52**	**95.91**

RH = relative humidity.

2.5.2 Temperature and pH Stability of Glucosylated Steviol Glycosides

In the temperature and pH stability study, solutions of glucosylated rebaudioside A (Lot No. AGG-180541) and glucosylated stevia extract (≥95% stevioside) (Lot No. RGG-180520) were prepared at concentrations of approximately 3.5% in 100 mL buffer solution (mixture of 0.1 M sodium dihydrogen phosphate, 0.1 M phosphoric acid, and 0.1 M sodium hydrogen phosphate) and stored in amber glass vials. Glucosylated rebaudioside A (Lot No. AGG-180541) was tested at different pH (2.65, 3.25, 5.5, 7.0, 8.0) and temperatures (25, 50, 80°C) over 4 days. Glucosylated stevia extract (≥95% stevioside) (Lot No. RGG-180520) was tested at pH 3.0, 5.5, 7.0, and 8.0 over temperature ranges of 22 to 25°C, 37 to 40°C, and 50 to 55°C over 4 days. In addition, the same lot of glucosylated rebaudioside A was tested at pH 3.0, 5.5, 7.0, and 8.0 at 80°C for 4 hours. Total steviol glycosides were measured at baseline and Days 2 and 4, and were calculated as the sum of total steviol glycosides and glucosylated steviol glycosides. The total steviol glycoside content was approximately 95.7%, 96.9%, 97.3%, and 96.4% at pH 3, 5.5, 7, and 8, respectively, following storage at 80°C for 4 hours. Over the 4 day storage period, the samples were generally stable at pH 3.0 to 8.0 at all temperatures tested. The least amount of degradation over 4 days (less than 1.5%) was observed under the following conditions: pH 5.0, 7.0, and 8.0 at 22°C, pH 7.0 and 8.0 at 37°C. Some samples showed slightly higher levels of degradation, for example, after 4 days at 55°C the samples degraded by 19.3%, 16.1%, 12.6%, and 10.5% at pH 3.0, 5.0, 7.0, and 8.0, respectively. The results of the stability tests are summarized below in Tables 2.5.2-1 to 2.5.2-3. Overall, the results of these studies demonstrate that the stability of HBNI's glucosylated steviol glycosides is consistent with the results of previous stability studies on glucosylated steviol glycosides as discussed in GRNs 607 and 662.

Table 2.5.2-1 pH and Temperature Stability of Glucosylated Rebaudioside A (Lot No. AGG-180541)					
pH	**Total Steviol Glycosides (%)**				
	Day 0 (baseline)	**Day 1**	**Day 2**	**Day 3**	**Day 4**
25°C					
2.65	96.9	89.90	90.21	91.05	90.94
3.25	96.9	92.78	93.01	92.76	93.43
5.5	96.9	90.42	91.54	92.08	91.04
7.0	96.9	96.20	94.62	95.16	95.16
8.0	96.9	93.31	95.57	90.23	103.13
50°C					
2.65	96.9	90.71	93.13	95.47	91.70
3.25	96.9	92.70	94.14	92.70	92.56
5.5	96.9	91.15	90.76	92.31	92.59
7.0	96.9	94.45	94.33	94.05	94.14
8.0	96.9	92.38	94.50	88.85	94.47
80°C					
2.65	96.9	85.99	78.25	75.66	78.28
3.25	96.9	92.05	86.64	83.54	87.34
5.5	96.9	91.57	89.40	89.71	91.23
7.0	96.9	94.25	38.33[a]	92.97	99.69
8.0	96.9	94.16	92.89	91.93	92.24

[a] Low steviol glycoside content likely due to low sample dry weight (1.353 g) compared to dry weights for other samples (~3 to 3.3 g).

Table 2.5.2-2 pH and Temperature Stability of Glucosylated Stevia Extract (≥95% Stevioside) (Lot No. RGG-180520)						
pH	**Total Steviol Glycosides (%)[a]**					
	Day 0 (baseline)	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
22–25°C						
3.0	98.38	95.86	95.30	95.98	94.46	96.80
5.5	98.38	95.60	95.04	96.06	94.68	95.41
7.0	98.38	96.34	95.88	96.64	95.23	96.66
8.0	98.38	96.17	96.67	95.71	96.69	94.60
37–40°C						
3.0	98.38	95.15	94.97	94.70	95.56	96.31
5.5	98.38	97.12	96.42	96.28	97.10	96.63
7.0	98.38	96.65	96.33	96.18	96.10	96.72
8.0	98.38	95.04	95.64	96.17	95.43	96.69
50–55°C						
3.0	98.38	95.90	98.50	95.39	95.77	95.36
5.5	98.38	96.61	96.50	96.95	96.14	95.87
7.0	98.38	94.86	94.22	95.93	96.80	95.07
8.0	98.38	96.41	96.69	95.62	95.88	95.58

[a] Results are the average of 3 samples at each time point.

Table 2.5.2-3 Stability of Glucosylated Stevia Extract (≥95% Stevioside) (Lot No. RGG-180520) at 80°C and pH 3.0, 5.5, 7.0, and 8.0			
pH	**Total Steviol Glycosides (%)[a]**		
	0 Hours	**2 Hours**	**4 Hours**
3.0	98.38	96.23	95.72
5.5	98.38	97.53	96.86
7.0	98.38	97.51	97.27
8.0	98.38	98.43	96.40

[a] Results are the average of 3 samples at each time point.

Part 3. Dietary Exposure (21 CFR § 170.235)

3.1 Proposed Uses and Use Levels of Glucosylated Steviol Glycosides

HBNI's glucosylated steviol glycosides have a relative sweetening potency of approximately 120 to 150 times that of sucrose and are intended for use as a general purpose sweetening agents in accordance with cGMP. A number of high-intensity sweeteners have been approved by the FDA as general purpose sweeteners without their uses being restricted to specific foods or use levels (*e.g.*, acesulfame-potassium, aspartame, sucralose). Hence, the foods to which high-intensity sweeteners are added and the use levels are controlled by technological properties (*e.g.*, sweetness potency).

The sweetness potency of HBNI's glucosylated steviol glycosides, such as the glucosylated rebaudioside A, glucosylated rebaudioside D, glucosylated stevioside, and the glucosylated mixture of various steviol glycosides, was determined to be 150, 150, 130, and 120 times sweeter than 5% of sucrose, respectively. Considering that glucosylated steviol glycosides are characterized by a sweetness profile that is, for the most part, comparable to that of other glucosylated steviol glycoside preparations (GRN 337, 375, 448, 452, 656, 662 – U.S. FDA, 2011a,b, 2013a,b, 2016b,c), the uses and use levels of HBNI's glucosylated steviol glycosides are likely to reflect those currently permitted for glucosylated steviol glycoside sweeteners produced in accordance with cGMP in the U.S.

3.2 Estimated Daily Intakes of Glucosylated Steviol Glycosides

The estimates of the daily consumption of several steviol glycoside preparations have been determined previously through the use of post-market data analysis as described in numerous GRAS Notices for steviol glycosides submitted to the FDA. For example, the most recent GRAS Notice for a glucosylated steviol glycoside preparation reviewed by the FDA employed this approach to estimate intakes (GRN 662 – U.S. FDA, 2011a). Briefly, this method makes use of the post-market surveillance data for other high-intensity sweeteners as provided in Renwick (2008), where potential dietary exposure to rebaudioside A was approximated by assuming full replacement of the approved intense sweeteners with the novel sweetener (in this case, glucosylated steviol glycosides). This method results in intake estimates that are conservative yet realistic. Specifically, the intakes mirror the actual post-market intakes of high-intensity sweeteners; however, complete substitution of all other sweeteners in the marketplace with the new sweetener is highly unlikely. The average and high-end dietary intakes of rebaudioside A (expressed as sucrose equivalents) were determined by Renwick (2008) in various population

groups, such as non-diabetic and diabetic adults and children, and values were adjusted using the sweetness intensity of rebaudioside A relative to sucrose (approximately 200).

The same methodology as applied by Renwick (2008) was used herein to estimate the dietary intake of glucosylated steviol glycosides. Since HBNI's glucosylated steviol glycosides are reported to be 120 to 150 times as sweet as sucrose, the intake values for intense sweeteners were adjusted accordingly to derive an estimated intake range for glucosylated steviol glycosides. The estimated intake ranges were then converted to steviol equivalents based upon the estimated average molecular weight for glucosylated steviol glycosides of 1,479.58 g/mol. The results for estimated intakes are presented in Table 3.2-1. Overall, the predicted intakes of glucosylated steviol glycosides, expressed as steviol equivalents, for all population groups are below the current acceptable daily intake (ADI) for steviol glycosides of 0 to 4 mg/kg body weight as steviol (JECFA, 2007). JECFA reviewed several intakes models for estimating dietary exposure to steviol glycosides, including the methodology described by Renwick (2008). Although the intake estimates presented by Renwick (2008) were lower than those identified using other methodologies, including those considering substitution of all sweeteners used in or as food (up to approximately 6 mg/kg body weight/day, expressed as steviol equivalents), JECFA noted that alternate methods were highly conservative and that actual exposures to steviol glycosides (expressed as steviol equivalents) would be 20 to 30% of the estimates resulting from the conservative methods (1 to 2 mg/kg body weight/day, expressed as steviol equivalents). Moreover, JECFA noted that the lower range was further confirmed by intake estimates based on post-market surveillance. More recently, JECFA reassessed the dietary exposure to steviol glycosides using sugar/intense sweetener substitution methods (FAO, 2016). The Committee assumed the most conservative sucrose equivalence of 200 and applied conversion factors ranging from 0.2 to 0.7 to account for the different molecular weights of the different individual steviol glycosides, including mixtures of steviol glycosides. The Committee determined consumption estimates ranging from 0.4 to 7.2 mg/kg body weight/day, expressed as steviol equivalents, based on the substitution of various sugar/intense sweetener consumption data from various global jurisdictions (such as the U.S. and Australia) with steviol glycosides. Based on their findings, the Committee noted that the described sugar substitution methods were "*generally overestimates of dietary exposure, as not all sugar in food products would be replaced by intense sweeteners, and a number of intense sweeteners are used in the marketplace*". Therefore, dietary exposure to glucosylated steviol glycosides is estimated to be consistent with the current consumption estimates for steviol glycosides and are within the established ADI of 0 to 4 mg/kg body weight, expressed as steviol equivalents.

Table 3.2-1 Estimated Consumption of Glucosylated Steviol Glycosides Using the Methodology Described by Renwick (2008)						
Population Group	**Intakes of intense sweeteners (expressed as sucrose equivalents) (mg/kg bw/day)**		**Consumption Estimates**			
			Glucosylated Steviol Glycosides[a] (mg/kg bw/day)		**Glucosylated Steviol Glycosides as Steviol Equivalents[b] (mg/kg bw/day)**	
	Average Consumer	**High Consumer**	**Average Consumer**	**High Consumer**	**Average Consumer**	**High Consumer**
Non-diabetic adults	255	675	1.70–2.13	4.50–5.63	0.37–0.46	0.97–1.21
Diabetic adults	280	897	1.87–2.33	5.98–7.48	0.40–0.50	1.29–1.61
Non-diabetic children	425	990	2.83–3.54	6.60–8.25	0.61–0.76	1.42–1.78
Diabetic children	672	908	4.48–5.60	6.05–7.57	0.96–1.21	1.30–1.63

bw = body weight.
a Glucosylated steviol glycosides are approximately 120–150 times as sweet as sucrose.
b Calculated based on the molecular weights of steviol (318.45 g/mol) and average weight of glucosylated steviol glycosides of 1,479.58 g/mol (steviol conversion factor of 0.21).

Part 4. Self-Limiting Levels of Use (21 CFR § 170.240)

The glucosylated steviol glycosides are intended for use as a general purpose sweetener, similar to other glucosylated steviol glycoside products currently on the U.S. market. The levels and foods to which the glucosylated steviol glycosides are added are self-limiting due to their organoleptic properties.

Part 5. Experience Based on Common Use in Foods before 1958 (21 CFR § 170.245)

Not applicable as the ingredient has not been in use in foods before 1958.

Part 6. Narrative (21 CFR § 170.250)

Glucosylated steviol glycosides (also known as enzyme-modified steviol glycosides) have been the subject of numerous GRAS Notices that have been filed by the FDA without objection under GRN 337, 375, 448, 452, 607, 656, and 662 (U.S. FDA, 2011a,b, 2013a,b, 2016a-c). The Agency has consistently raised "no questions" regarding the GRAS status of these materials when used as a general purpose sweetener in various food and beverage products. In addition, glucosyl steviol glycosides (Flavor Extract Manufacturers Association of the United States [FEMA] No. 4728) and glucosylated stevia extract (FEMA No. 4845) when used as a flavor

enhancer and flavoring agent have received GRAS status by the FEMA Expert Panel (Mamett *et al.,* 2013; Leffingwell and Leffingwell, 2014). Glucosylated steviol glycosides are authorized for use in Japan, Malaysia, and Korea.

The primary basis for the safety conclusions on glucosylated steviol glycosides is that these substances are subjected to hydrolysis by intestinal glucose hydrolases, thus yielding the corresponding steviol glycosides, as determined in several *in vitro* metabolism studies (Koyama *et al.,* 2003 – reviewed in GRN 337). The resulting steviol glycosides then pass through the small intestine unchanged to the colon and are completely metabolized by the intestinal microbiota to yield the aglycone steviol. This metabolic pathway for the digestion of steviol glycosides is well established and has been extensively described in detail in GRAS Notices for other steviol glycoside preparations (*e.g.*, GRN 619, 626, 667 – U.S. FDA, 2016d-f). Thus, considering that glucosylated steviol glycosides and steviol glycosides share a common metabolic fate, the publicly available safety information for steviol glycosides is relevant in the assessment of glucosylated steviol glycosides and may be used to support their safety. The key safety information for steviol glycosides includes metabolic and pharmacokinetic studies in rodents and humans, toxicological studies (short-term, subchronic and long-term) in rodents, reproductive and developmental toxicity studies in rabbits and rats, and *in vitro* and *in vivo* studies evaluating mutagenicity and genotoxicity. Several published clinical studies show that steviol glycosides do not affect glucose metabolism in healthy subjects or in subjects with impaired glucose tolerance/insulin resistance and no effects on blood pressure have been reported. Based on this information JECFA established an ADI of 0 to 4 mg/kg body weight expressed as steviol equivalents. The safety of steviol glycosides has also been reviewed on multiple occasions by qualified scientific experts under the GRAS procedure, and these GRAS conclusions have been filed without objection by the U.S. FDA under the voluntary GRAS Notification procedure. Furthermore, several scientific committees and regulatory agencies, including JECFA, the European Commission's Scientific Committee on Food, EFSA, FSANZ, and Health Canada, have reviewed the safety of steviol glycosides and have not raised any safety concerns. JECFA, FSANZ, and Health Canada have recently extended their safety conclusions to include all steviol glycosides present in the *Stevia rebaudiana* Bertoni leaf.

The enzymes used in the glucosylation reaction (CGTase and α-amylase) are derived from non-genetically modified and non-pathogenic strains of *Bacillus licheniformis* and *Bacillus subtilis*, respectively. The uses of these enzymes in the glucosylation of steviol glycosides to produce glucosylated steviol glycosides have been previously described in GRAS Notifications filed without objection by the Agency under GRN 337, 375, 448, 452, and 656 (U.S. FDA, 2011a,b, 2013a,b, 2016b), and these enzymes are GRAS when used in accordance with 21 CFR § 184.1012 and 184.1148, respectively (U.S. FDA, 2018). Furthermore, the safety of CGTase and

α-amylase was evaluated using the Pariza and Johnson (2001) decision tree for evaluating the safety of microbially-derived food enzymes and was concluded to be "accepted" for use in food processing based on the fact that the final products meet the JECFA specifications. The enzymes are inactivated *via* a heat treatment step and are subsequently removed from the final product *via* a series of filtration and purification steps. Thus, the use of CGTase and α-amylase derived from *Bacillus licheniformis* and *Bacillus subtilis* in the glucosylation of steviol glycosides are not anticipated to pose any safety concerns.

In a recent publication, the FDA outlined their regulatory approach to steviol glycosides (Perrier et al., 2018). This approach involved a description of the identity and composition of the steviol glycosides preparation, method of manufacture and specifications, intended use and technical effect, dietary exposure using the methodology described by Renwick (2008), and a discussion on the safety of steviol glycosides. Perrier *et al.* (2018) indicated that the use of a purified steviol glycoside can be supported by an existing GRAS notification if the products share similar identity, manufacturing process, specifications, intended use, and dietary exposure. Thus, the FDA's regulatory approach has been adapted by HBNI, and the necessary data and information to support the safety evaluation of steviol glycosides, including glucosylated steviol glycosides, has been provided herein. The information has been independently reviewed by an Expert Panel who unanimously concluded that HBNI's glucosylated steviol glycosides, as described herein, is GRAS under its intended conditions of use as a general purpose sweetener in foods and beverages. A summary of the conclusions of the Expert Panel is provided in Appendix B.

Part 7. List of Supporting Data and Information (21 CFR § 170.255)

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Table of CFR Sections Referenced (Title 21—Food and Drugs)		
Part	**Section §**	**Section Title**
170— Food additives	170.30	Eligibility for classification as generally recognized as safe (GRAS)
184—Direct Food Substances Affirmed as Generally Recognized as Safe	184.1012	α-Amylase enzyme preparation from Bacillus stearothermophilus
	184.1148	Bacterially-derived carbohydrase enzyme preparation

CERTIFICATE OF ANALYSIS

Certificate No. 2018060403

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	AGG-S1	Date of Manufacture	:	May 3，2018
Lot No.	:	180541	Date of Certificate	:	Jun. 4, 2018
Expiry Date	:	May 2，2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to off white fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	96.9%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	94.7%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	2.6%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.3%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.06ppm
Residual Ethanol	GC	5,000ppm Max.	6ppm
Residual Methanol	GC	200ppm Max.	1ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	< 10cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	20cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

* Means HBNI can provide CoC (Certificate of Compliance) for those items if necessary.
HBNI will test randomly every year.

Approval: (b) (6) **Date: 2018.06.04**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060405

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	AGG-S1	Date of Manufacture	:	May 6，2018
Lot No.	:	180544	Date of Certificate	:	Jun. 4, 2018
Expiry Date	:	May 5，2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to off white fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	97.5%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	93.2%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	2.2%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.2%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.2ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.08ppm
Residual Ethanol	GC	5,000ppm Max.	16ppm
Residual Methanol	GC	200ppm Max.	4ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	< 10cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	25cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

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Approval: (b) (6) **Date: 2018.06.04**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060406

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	AGG-S1	Date of Manufacture	:	May 8，2018
Lot No.	:	180546	Date of Certificate	:	Jun. 4, 2018
Expiry Date	:	May 7，2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to off white fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	95.2%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	90.8%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	2.5%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.4%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.05ppm
Residual Ethanol	GC	5,000ppm Max.	17ppm
Residual Methanol	GC	200ppm Max.	2ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	20cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	25cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

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Approval: (b) (6) **Date: 2018.06.04**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018052301

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	LGG-S1	Date of Manufacture	:	May 1, 2018
Lot No.	:	180501	Date of Certificate	:	May 6, 2018
Expiry Date	:	Apr. 30, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to off white fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	96.3%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	91.8%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	3.1%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.4%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.05ppm
Residual Ethanol	GC	5,000ppm Max.	32ppm
Residual Methanol	GC	200ppm Max.	4ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	40cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	70cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

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Approval: (b) (6) **Date: 2018.05.23**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060411

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	LGG-S1	Date of Manufacture	:	May 4, 2018
Lot No.	:	180504	Date of Certificate	:	May 10, 2018
Expiry Date	:	May 3, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to off white fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	97.6%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	93.8%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	3.3%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.3%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.2ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.05ppm
Residual Ethanol	GC	5,000ppm Max.	41ppm
Residual Methanol	GC	200ppm Max.	4ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	35cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	50cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

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HBNI will test randomly every year.

Approval: (b) (6) **Date: 2018.06.04**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060412

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	LGG-S1	Date of Manufacture	:	May 6, 2018
Lot No.	:	180506	Date of Certificate	:	May 10, 2018
Expiry Date	:	May 5, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to off white fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	96.2%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	92.3%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	3.4%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.3%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
Residual Ethanol	GC	5,000ppm Max.	42ppm
Residual Methanol	GC	200ppm Max.	4ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	45cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	45cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

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Approval: (b) (6) **Date: 2018.06.04**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060402

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	PGG-S3	Date of Manufacture	:	May 5, 2018
Lot No.	:	180517	Date of Certificate	:	Jun. 4, 2018
Expiry Date	:	May 4, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	99.6%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	95.8%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	3.8%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.1%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.2ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
Residual Ethanol	GC	5,000ppm Max.	1,170ppm
Residual Methanol	GC	200ppm Max.	3ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	100cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	60cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

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Approval: (b) (6) **Date: 2018.06.04**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060407

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	PGG-S3	Date of Manufacture	:	May 12, 2018
Lot No.	:	180524	Date of Certificate	:	Jun. 4, 2018
Expiry Date	:	May 11, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	98.4%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	93.7%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	3.8%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.1%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.07ppm
Residual Ethanol	GC	5,000ppm Max.	530ppm
Residual Methanol	GC	200ppm Max.	4ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	90cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	50cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

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Approval: (b) (6) **Date: 2018.06.04**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060408

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	PGG-S3	Date of Manufacture	:	May 15, 2018
Lot No.	:	180527	Date of Certificate	:	Jun. 4, 2018
Expiry Date	:	May 14, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	98.3%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	94.4%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	3.7%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.1%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.05ppm
Residual Ethanol	GC	5,000ppm Max.	380ppm
Residual Methanol	GC	200ppm Max.	5ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	70cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	30cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060404

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	RGG-S1	Date of Manufacture	:	May 2, 2018
Lot No.	:	180520	Date of Certificate	:	Jun. 4, 2018
Expiry Date	:	May 1, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to light yellow fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	98.4%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	96.4%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	2.7%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.5%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.05ppm
Residual Ethanol	GC	5,000ppm Max.	11ppm
Residual Methanol	GC	200ppm Max.	1ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	145cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	30cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

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Approval: (b) (6) **Date: 2018.06.04**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060413

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	RGG-S1	Date of Manufacture	:	May 7, 2018
Lot No.	:	180525	Date of Certificate	:	Jun. 4, 2018
Expiry Date	:	May 6, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to light yellow fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	95.8%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	92.6%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	2.7%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.3%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
Residual Ethanol	GC	5,000ppm Max.	9ppm
Residual Methanol	GC	200ppm Max.	Absent
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	95cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	35cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

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HBNI will test randomly every year.

Approval: (b) (6) **Date: 2018.06.04**

Haigen-BGG
Natural Ingredients

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060414

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	RGG-S1	Date of Manufacture	:	May 10, 2018
Lot No.	:	180528	Date of Certificate	:	Jun. 4, 2018
Expiry Date	:	May 9, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to light yellow fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	95.1%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	92.0%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	2.7%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.2%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.2ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.05ppm
Residual Ethanol	GC	5,000ppm Max.	11ppm
Residual Methanol	GC	200ppm Max.	2ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	80cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	15cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

* Means HBNI can provide CoC (Certificate of Compliance) for those items if necessary.
HBNI will test randomly every year.

Approval: (b) (6) **Date: 2018.06.04**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060409

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	SGG-S3	Date of Manufacture	:	May 2, 2018
Lot No.	:	180514	Date of Certificate	:	May 10, 2018
Expiry Date	:	May 1, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to off white fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	98.8%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	92.9%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	3.3%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.1%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.05ppm
Residual Ethanol	GC	5,000ppm Max.	624ppm
Residual Methanol	GC	200ppm Max.	5ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	35cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	45cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

* Means HBNI can provide CoC (Certificate of Compliance) for those items if necessary.
HBNI will test randomly every year.

Approval: (b) (6) **Date: 2018.06.04**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018052316

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	SGG-S3	Date of Manufacture	:	May 4, 2018
Lot No.	:	180516	Date of Certificate	:	May 10, 2018
Expiry Date	:	May 3, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to off white fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	99.6%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	93.5%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	3.2%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.1%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.1ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.06ppm
Residual Ethanol	GC	5,000ppm Max.	584ppm
Residual Methanol	GC	200ppm Max.	3ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	20cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	50cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

* Means HBNI can provide CoC (Certificate of Compliance) for those items if necessary.
HBNI will test randomly every year.

Approval: (b) (6) **Date: 2018.05.23**

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CERTIFICATE OF ANALYSIS

Certificate No. 2018060410

Product	:	Alpha-glucosylated Steviol Glycosides			
Product No.	:	SGG-S3	Date of Manufacture	:	May 9, 2018
Lot No.	:	180523	Date of Certificate	:	May 10, 2018
Expiry Date	:	May 8, 2020	Specification No.	:	(A0)000

Analysis Items	Test Method	Specifications	Results
Appearance	Visual inspection	White to off white fine powder	White powder
Total Steviol Glycosides	Adsorption chromatography	95.0% Min.	98.0%
Alpha-glucosylated Steviol Glycosides	HPLC	80.0% Min.	91.8%
Loss on drying	Eur. Ph. 2.8.17	6.0% Max.	3.5%
Ash	Eur. Ph. 2.4.16	1.0% Max.	0.1%
*Lead	Eur. Ph. 2.4.27	1 ppm Max.	0.2ppm
*Cadmium	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Mercury	Eur. Ph. 2.4.27	1 ppm Max.	<0.05ppm
*Arsenic	Eur. Ph. 2.4.27	1 ppm Max.	0.05ppm
Residual Ethanol	GC	5,000ppm Max.	549ppm
Residual Methanol	GC	200ppm Max.	4ppm
Total plate count	Eur. Ph. 2.6.12	< 1,000 cfu/g	40cfu/g
Yeast & Mold	Eur. Ph. 2.6.12	< 100 cfu/g	60cfu/g
E. Coli	Eur. Ph. 2.6.13	Negative/g	Negative
Salmonella	Eur. Ph. 2.6.13	Negative/10g	Negative
Staphylococcus Aureus	Eur. Ph. 2.6.13	Negative/g	Negative

* Means HBNI can provide CoC (Certificate of Compliance) for those items if necessary.
HBNI will test randomly every year.

Approval: (b) (6) **Date: 2018.06.04**

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Summary and Conclusions of the Expert Panel on the Generally Recognized as Safe (GRAS) Status of High-Purity Glucosylated Steviol Glycosides (≥80% Glucosylated Steviol Glycosides) for Use as a General Purpose Sweetener

Haigen-BGG Natural Ingredients (HBNI) Limited manufactures high-purity glucosylated steviol glycosides consisting of ≥80% glucosylated steviol glycosides and intends to market this material as a general purpose sweetener in the United States (U.S.), consistent with the uses of other glucosylated steviol glycoside products currently on the U.S. market. Glucosylated steviol glycosides are generated from a starting material of steviol glycosides that are extracted from the leaves of the *Stevia rebaudiana* Bertoni plant and meeting the purity criteria for steviol glycosides established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). This starting material is subjected to a glucosylation reaction using cyclomaltodextrin glucanotransferase (CGTase) derived from a non-genetically modified *Bacillus licheniformis* or α-amylase derived from *Bacillus subtilis* in the presence of a source of glucose (*i.e.,* tapioca starch). The resulting glucosylated steviol glycosides consist of steviol glycosides with up to 3 additional glucose units attached by stereospecific and regiospecific 1,4-α-D-glycosidic bonds. The final product consists of ≥80% glucosylated steviol glycosides and ≥95% steviol glycosides, thus meeting the purity criteria for steviol glycosides established by JECFA. All raw materials, processing aids, and purification equipment used to manufacture HBNI's glucosylated steviol glycosides are food-grade and comply with applicable U.S. federal regulations or are GRAS for their respective uses. Further, the manufacturing process generally complies with the methodology described in the Chemical and Technical Assessment for steviol glycosides (FAO, 2016). The analytical data from 3 non-consecutive batches of the glucosylated steviol glycosides establish that the manufacturing process generates a consistent high-purity material that does not contain any chemical or microbiological contaminants.

The uses of HBNI's glucosylated steviol glycosides are consistent with the current uses of other related high-intensity sweeteners that are currently on the U.S. market. The estimated intakes of glucosylated steviol glycosides were calculated for adults and children using a post-market surveillance approach (Renwick, 2008) where data for other high-intensity sweeteners were adjusted for the relative sweetness intensity of glucosylated steviol glycosides (*i.e.,* 120 to 150 times sweeter than sucrose). The results are summarized in the table below. The results indicate that the maximum estimated intake of glucosylated steviol glycosides of 0.81 mg/kg body weight/day is well below the acceptable daily intake (ADI) for steviol glycosides of 0 to 4 mg/kg body weight, when expressed as steviol. This dietary intake assessment approach was noted by JECFA to be conservative and to likely overestimate dietary exposure (FAO, 2016).

Table 1 Estimated Consumption of Glucosylated Steviol Glycosides Using the Renwick (2008) Methodology

Population Group	Intakes of intense sweeteners (expressed as sucrose equivalents) (mg/kg bw/day)		Consumption estimates			
			Glucosylated Steviol Glycosides[a] (mg/kg bw/day)		Glucosylated Steviol Glycosides as steviol equivalents[b] (mg/kg bw/day)	
	Average Consumer	High Consumer	Average Consumer	High Consumer	Average Consumer	High Consumer
Non-diabetic Adults	255	675	0.85	2.25	0.21	0.55
Diabetic Adults	280	897	0.93	2.99	0.23	0.74
Non-diabetic Children	425	990	1.42	3.30	0.35	0.81
Diabetic Children	672	908	2.24	3.03	0.55	0.74

bw = body weight
[a] Glucosylated steviol glycosides are approximately 120 to 150 times as sweet as sucrose.
[b] Calculated based on the molecular weights of steviol (318.45 g/mol) and average weight of glucosylated steviol glycosides of 1,479.58 g/mol (steviol conversion factor of 0.21).

Publicly available data and information relevant to the safety of glucosylated steviol glycosides for use as a general purpose sweetener were reviewed and summarized in a dossier [titled "Glucosylated Steviol Glycosides (>80% Glucosylated Steviol Glycosides) As Generally Recognized As Safe (GRAS) For Use As A General Purpose Sweetener" dated 12 October 2018] for independent review by the Expert Panel. Seven GRAS notices for different glucosylated steviol glycoside preparations (also known as enzyme-modified steviol glycosides) for use as general purpose sweeteners have been submitted to the offices of the U.S. Food and Drug Administration (U.S. FDA) and filed on the FDA's GRAS Notices inventory without objection (*e.g.,* GRN 337, 375, 448, 452, 607, 656, 662; U.S. FDA, 2011a,b, 2013a,b, 2016a-c). Likewise, glucosyl steviol glycosides (FEMA No. 4728) and glucosylated stevia extract (FEMA No. 4845) when used as a flavor enhancer and flavoring agent have received GRAS status by the FEMA Expert Panel (Mamett et al., 2013; Leffingwell and Leffingwell, 2014). Enzyme-modified steviol glycosides (*i.e.,* glucosylated steviol glycosides) have an established history of safe use in Japan where they have been consumed for over 25 years. Furthermore, enzymatically-modified stevia is consumed to a significant degree (*ca.* 780 tons) in South Korea and in 2016 it was ranked as the 7th most consumed food additive in South Korea. Glucosylated steviol glycosides are also authorized for use in Malaysia.

The available metabolism data on glucosylated steviol glycosides indicate that these substances are subjected to partial hydrolysis by intestinal glucose hydrolases, thus yielding the corresponding steviol glycoside. The resulting steviol glycosides then pass through the small intestine unchanged to the colon where they are metabolized by the intestinal microbiota to yield the aglycone steviol. This metabolic pathway for the digestion of steviol glycosides is well established and has been described in detail in GRAS notices for other steviol glycoside preparations (*e.g.* GRN 619, 626, 667). Thus, considering that glucosylated steviol glycosides and steviol glycosides share a common metabolic fate,

the publicly available safety information for steviol glycosides is relevant in the assessment of glucosylated steviol glycosides and may be used to support their safety. The key safety information for steviol glycosides includes metabolic and pharmacokinetic studies in rodents and humans, toxicological studies (short-term, subchronic and long-term) in rodents, reproductive and developmental toxicity studies in rabbits and rats, and *in vitro* and *in vivo* studies evaluating mutagenicity and genotoxicity. Several published clinical studies demonstrate that steviol glycosides do not affect glucose metabolism in healthy subjects or in subjects with impaired glucose tolerance/insulin resistance and no effects on blood pressure have been reported. Based on this collection of safety information JECFA established an ADI for steviol glycosides of 0 to 4 mg/kg body weight expressed as steviol equivalents. The safety of steviol glycosides has also been reviewed on multiple occasions by qualified scientific experts under the GRAS procedure, and these GRAS conclusions have been filed without objection by the U.S. FDA under the voluntary GRAS notification procedure. Furthermore, several scientific committees and regulatory agencies, including JECFA, the European Commission's Scientific Committee on Food, EFSA, FSANZ, and Health Canada, have reviewed the safety of steviol glycosides and have not reported any safety concerns. JECFA, FSANZ, and Health Canada have recently extended their safety conclusions to include all steviol glycosides present in the *Stevia rebaudiana* Bertoni leaf.

Therefore, on the basis of scientific procedures, the Expert Panel unanimously concluded that glucosylated steviol glycosides, meeting appropriate food grade specifications and produced in accordance with current good manufacturing practice (cGMP), as presented in the supporting dossier, is GRAS under its intended conditions of use as a general purpose sweetener in foods and beverages.

REFERENCES

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From: Dr. Varuzhan H. Abelyan
To: Zhang, Janet
Subject: RE: Question for GRN 000821
Date: Thursday, March 7, 2019 7:04:36 AM
Attachments: image001.png
FDA Response Letter.docx

Dear Ms Zhang,

Please find out our answers to your questions in the attached file, please.
Unfortunately was a transcriptional error in the estimates of dietary exposure within Table 1 of Appendix B. That is explained now.
The timeline for literature search also is provided.
Hope it is satisfactory.
Please, let me know if you will need some more additional information.
With the best regards
Varuzhan

_____

Varuzhan H. Abelyan, ScD
Doctor of Sciences in Biotechnology
Co-Chairman
Chief of Science & Technology
Haigen-BGG Natural Ingredients Limited

From: Zhang, Janet <Janet.Zhang@fda.hhs.gov>
Sent: Monday, March 4, 2019 23:35
To: Dr. Varuzhan H. Abelyan <v.abelyan@hbnaturalingredients.com>
Subject: Question for GRN 000821

Dear Dr. Abelyan, we have two questions regarding to GRN 000821, please provide the answers at your earliest convenient time.

- We note that the estimates of dietary exposure provided in Table 3.2-1 of the notice and Table 1 of Appendix B (GRAS Panel summary and conclusions) do not match. Please clarify.
- Please provide the timeframe or approximate date for your search of the literature regarding the safety of steviol glycosides described in your notice.

Thanks,
Janet

Jianrong (Janet) Zhang, Ph.D.
FDA/OFVM/CFSAN/OFAS/DBGNR
College Park, MD 20740
Phone: 240-402-1327
janet.zhang@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

[Date]

Commented [TVI1]: HBNI: Update to date of submission.

Jianrong (Janet) Zhang, Ph.D.
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

Dear Dr Zhang,

Re: GRAS Notice for Glucosylated Steviol Glycosides (GRN No. 000821)

Please find following our responses to your questions raised in your email sent on March 4, 2019 regarding the referenced GRAS Notice (GRN 000821).

FDA Question 1: We note that the estimates of dietary exposure provided in Table 3.2-1 of the notice and Table 1 of Appendix B (GRAS Panel summary and conclusions) do not match. Please clarify.

Notifier Response: The estimates of dietary exposure within Table 1 of Appendix B was unfortunately a transcriptional error. The correct dietary exposure estimates are those that are reported within the content of the notice and were determined based on the range of sweetness intensity of the ingredient (120 to 150 times). These were the actual values that were reviewed and evaluated by the Expert Panel as part of their review process.

FDA Question 2: Please provide the timeframe or approximate date for your search of the literature regarding the safety of steviol glycosides described in your notice.

Notifier Response: Two literature searches were performed for both glucosylated steviol glycosides and steviol glycosides. The search dates encompassed safety-related publications since these materials were last reviewed by the FDA. At the time of the search (November 2018), the last GRAS notices for steviol glycosides included GRN 662 and 759 for glucosylated steviol glycosides and steviol glycosides, respectively. Therefore, the specific search dates were May 2016 to November 2018 for glucosylated steviol glycosides and December 2017 to November 2018 for steviol glycosides.

I hope that these answers adequately address the concerns raised by the Agency. If I can be of any further assistance or provide further clarification, please do not hesitate to contact me.

Sincerely,

Varuzhan H. Abelyan
Chief of Science & Technology
Haigen-BGG Natural Ingredients Limited

CONCLUSION

We, the members of the Expert Panel, have, independently and collectively, critically evaluated the data and information summarized above and conclude that glucosylated steviol glycosides consisting of ≥80% glucosylated steviol glycosides and ≥95% steviol glycosides, meeting appropriate food-grade specifications and produced in accordance with current Good Manufacturing Practice (cGMP), is safe for use as a general purpose sweetener in conventional foods and beverages.

We further unanimously conclude that the proposed use of Haigen-BGG Natural Ingredients (HBNI) Limited's high-purity glucosylated steviol glycosides consisting of ≥80% glucosylated steviol glycosides and ≥95% steviol glycosides meeting appropriate food-grade specifications, as presented in the supporting dossier and produced consistent with cGMP is Generally Recognized as Safe (GRAS) under its intended conditions of use as a general purpose sweetener in conventional food and beverages based on scientific procedures.

It is our opinion that other qualified experts would concur with these conclusions.

(b) (6)

06 Nov 2018

Michael W. Pariza, Ph.D.
Professor Emeritus
University of Wisconsin-Madison

Date

(b) (6)

07 Nov 2018

I. Glenn Sipes, Ph.D.
Fellow of AAAS and ATS
Professor Emeritus Pharmacology
University of Arizona

Date

(b) (6)

05 November 2018

Stanley M. Tarka, Jr., Ph.D.
Fellow of ATS
The Tarka Group Inc.
The Pennsylvania State University, College of Medicine

Date