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Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
United States Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

5/9/2022

RE: GRAS Notification of ***Bifidobacterium longum*** **CBT BG7**
II965.1-CBI.1.4

To Whom It Concerns,

In accordance with 21 CFR, Part 170, Subpart E, we as the agent [REJIMUS, INC., 600 W. Santa Ana Blvd. Ste 1100, Santa Ana, CA 92701], respectfully provides notice of a claim that the addition of the microorganism ***Bifidobacterium longum*** **CBT BG7** to the foods identified in this notice at the specified levels is exempt from the premarket approval requirement of the Federal Food, Drug and Cosmetic Act because the notifier [**Cell Biotech Co. Ltd.**, 50, Agibong-ro, 409 Beon-gil, Wolgot-myeon, Gimpo, Republic of Korea] has determined that the intended uses are generally recognized as safe (GRAS). The attached documents contain the specific information and data that address the safety of the substance for use in human food applications.

Respectfully,

[redacted]

Jim Lassiter, COO
REJIMUS, INC.
jim@rejimus.com

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PART 1 – SIGNED STATEMENTS AND CERTIFICATION

Cell Biotech Co. Ltd. submits this notification of a conclusion of GRAS through its agent, REJIMUS, INC. in accordance with 21 CFR §170.30.

Name and Address of Notifier and Agent

Agent:

Jim Lassiter
President/COO
REJIMUS, INC.
600 W. Santa Ana Blvd., Suite 1100
Santa Ana, CA 92701
Tel: +1 (949) 485-2112
www.rejimus.com

Notifier:

Cell Biotech Co. Ltd.
50, Agibong-ro, 409 Beon-gil
Wolgot-myeon, Gimpo
Republic of Korea
Tel: +82 31 987 6205

Name and Address of Manufacturer:

Cell Biotech Co. Ltd.
397 Aegibong-rol
Wolgot-myeon, Gimpo-si, Gyeonggi-do 415-872
Republic of Korea
Tel: +82 31 987 8107

Name of the GRAS Substance

Cell Biotech Co. Ltd. (herein referred to as CBI) has undertaken an independent safety evaluation of the substance in this notification:

***Bifidobacterium longum* CBT BG7**

Intended Conditions of Use and Levels of Inclusion

The intended use of *Bifidobacterium longum* CBT BG7 is a food ingredient for inclusion in dairy products where standards of identity do not preclude such use. The intended addition level to these foods is up to 1×10^{11} CFU per serving.

Bifidobacterium longum CBT BG7 will not be added to meat and poultry products (including soups and soup mixes containing meat or poultry), and will not be included in foods that are marketed towards infants and young children, inclusive of infant formula. *Bifidobacterium longum* CBT BG7 is not intended for addition to standardized foods unless it is permitted by the applicable standard of identity.

Basis for GRAS Conclusion

The statutory basis for conclusion of GRAS status is through scientific procedures in accordance with 21 CFR §170.30(a) and (b).

Premarket Approval Exemption

We have concluded that the intended use of *Bifidobacterium longum* CBT BG7 is GRAS for its intended conditions of use as stated in this notification and, such use of *Bifidobacterium longum* CBT BG7 is not subject to the premarket approval requirements of the *Federal Food, Drug, and Cosmetic Act.*

Availability of Information

The data and information that serve as the basis of GRAS conclusion are available for review and copying at reasonable times at the offices of the Agent.

Should FDA have any questions of additional requests for information regarding this notification, the Agent shall provide further clarification and/or information at:

Attn: Jim Lassiter
REJIMUS, INC.
600 W. Santa Ana Blvd., Suite 1100
Santa Ana, CA 92701
Email: jim@rejimus.com

Trade Secrets

The notification does not contain trade secrets and the data are not exempt from disclosure under the Freedom of Information Act, 5 U.S.C. Part 552.

Authorization for FDA to share information with FSIS

As Agent for the Notifier, we authorize FDA to send any information deemed necessary to FSIS. The notice does not contain trade secrets and the data are not exempt from disclosure under the *Freedom of Information Act*, 5 U.S.C. 552.

Certification

Cell Biotech Co. Ltd. has concluded that *Bifidobacterium longum* CBT BG7 is generally recognized as safe for use in dairy products based on scientific procedures and supported by a history of use in accordance with 21 CFR Part 170, Subpart E. As their Agent, REJIMUS, INC. takes responsibility for all communications on this matter. To the best of our knowledge, this GRAS Notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to

us and pertinent to the evaluation of the safety and GRAS status of the use of *Bifidobacterium longum* CBT BG7.

Respectfully submitted,

Jim Lassiter, COO
REJIMUS, INC.
jim@rejimus.com

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

Common Name: *Bifidobacterium longum* CBT BG7 (KCTC 12200BP)

Taxonomic Lineage (Accessed from the Integrated Taxonomic Information System [http:www.itis.gov]):

Kingdom: Bacteria
Subkingdom: Posibacteria
Phylum: Actinobacteria
Class: Actinobacteridae
Order: Bifidobacteriales
Family: Bifidobacteriaceae
Genus: *Bifidobacterium*
Species: *longum*
Strain: CBT BG7

Bifidobacterium longum is a species of the genus *Bifidobacterium* and the class Actinobacteridae that can be isolated from human feces (Ventura et al. 2007). *Bifidobacterium* spp. are gram-positive, non-motile, non-spore forming, anaerobic rods with variable appearance (Candela et al. 2007). The gram staining morphology of *Bifidobacterium* can vary as long, slender rods, in clusters, pairs or even independently. *Bifidobacterium* are studied as other Lactic Acid Bacteria (LAB) since they are found predominantly in the gastric and intestinal mucosa. Nursing newborns may have a bifidobacteria population of more than 95% with this population decreasing as humans age (Toure et al. 2003). It is estimated that, on average, approximately 4% of the bacterial population of the adult human colon are bifidobacteria (Turroni et al. 2014).

This particular strain of *Bifidobacterium longum* CBT BG7 is known under the commercial name as LAB2PRO™ as a high stability lactic acid bacterium.

Identification

The organism that makes is the subject of the notification, originally isolated from human feces or fermented food is identified as *Bifidobacterium longum* and has been uniquely characterized as a distinct strain known as CBT BG7 by means of genomic typing. The strain was deposited in the Korean Collection for Type Cultures (KCTC), accession number KCTC 12200BP.

Carbohydrate Utilization

Fermentative characteristics of *Bifidobacterium longum* CBT BG7 were analyzed using API 50 CHL kit. Results are shown in Table 1.

Table 1. Fermentative Characteristics of *Bifidobacterium longum* CBT BG7 obtained with an API 50 CHL Kit. (Cellbiotech R&D Center (2018))

No	Carbohydrates	Utilized	No	Carbohydrates	Utilized
0	Control	-	25	Esculine	+
1	Glycerol	-	26	Salicine	+
2	Erythritol	-	27	Cellobiose	-
3	D-Arabinose	-	28	Maltose	+
4	L-Arabinose	+	29	Lactose	+
5	Ribose	+	30	Melibiose	+
6	D-Xylose	+	31	Saccharose	+
7	L-Xylose	-	32	Trehalose	-
8	Adonitol	-	33	Inuline	-
9	β-Methyl-xyloside	-	34	Melezitose	-
10	Galactose	+	35	D-Raffinose	+
11	D-Glucose	+	36	Amidon	-
12	D-Fructose	+	37	Glycogene	-
13	D-Mannose	+	38	Xylitol	-
14	L-Sorbose	-	39	β-Gentiobiose	-
15	Rhamnose	-	40	D-Turanose	w
16	Dulcitol	-	41	D-Lyxose	-
17	Inositol	-	42	D-Tagatose	-
18	Mannitol	+	43	D-Fucose	-
19	Sorbitol	+	44	L-Fucose	-
20	α-Methyl-D-mannoside	-	45	D-Arabitol	-
21	α-Methyl-D-glucoside	+	46	L-Arabitol	-
22	N-Acetyl glucosamine	-	47	Gluconate	-
23	Amygdaline	-	48	2-Ceto-gluconate	-
24	Arbutine	+	49	5-Ceto-gluconate	w

Genomic Classification, Sequence, and Profile

The 16S rRNA gene sequence were aligned and compared with different *Bifidobacterium* strains: *B. longum* (KCTC 12200BP), *B. longum* (ATCC 15707), *B. infantis* (ATCC 15697), *B. breve* (ATCC 15700), *B. bifidum* (DSM 20456T), *B. lactis* (DSM 10140), and *B. catenulatum* (KCTC 3221). Percent identity and divergence were compared between *Bifidobacterium* species and strains in Table 2. As presented in Table 2, distinctive sequences of 16S rRNA genes were used to generate the phylogenic tree shown in Figure 1 (Cellbiotech R&D Center 2018).

Random Amplified Polymorphic DNA (RAPD) is a method used to obtain a molecular "fingerprint" from random DNA segments of genomic DNA that have been amplified using a single primer of an arbitrary nucleotide sequence. *Bifidobacterium longum* CBT BG7 DNA was compared using RAPD with *Bifidobacterium longum* ATCC 15707 strain. Both strains were amplified through PCR, ribotyping and pulsed-field gel electrophoresis (PFGE) in order to compare the RAPD patterns and genotypes between both species (Figure 2). Fragment yields presented difference between strains. DNA fragments were amplified with (GTG) primer (5' – GTGGTGGTGGTGGTG – 3') using genomic DNA as a template and analyzed in 0.8% agarose gel (Syngene, UK).

Pulse Field Gel Electrophoresis (PFGE) digests the genomic DNA with rare-cutting restriction enzymes. Separation of the macrofragments occurs via a continuously reorienting electric field. *Bifidobacterium longum* CBT BG7 (KCTC 12200BP) and *B. longum* (ATCC 15707) strains were cultivated to OD_{600}=4 and treated with proteinase K and multiple restriction enzymes. DNA fragments from digestion were analyzed on agarose gel.

Table 2. Percent identity between *Bifidobacterium longum* CBT BG7 and other closely related species based on 16S rRNA gene sequences. (Cellbiotech R&D Center 2018)

Percent Identity

Divergence

	1	2	3	4	5	6	7
1		99.1	99.1	98.0	92.9	90.8	93.2
2	0.5		98.8	95.8	93.4	90.6	93.7
3	0.9	0.9		96.8	93.4	90.8	93.0
4	3.0	3.1	2.3		92.9	91.4	93.1
5	5.0	5.1	4.6	4.6		89.3	94.1
6	6.7	7.0	6.9	6.3	7.6		90.9
7	4.9	5.0	5.2	5.1	4.9	6.7	

1 ***B. longum*** **(KCTC 12200BP)**
2 *B. longum* ATCC 15707
3 *B. infantis* ATCC 15697
4 *B. breve* ATCC 15700
5 *B. bifidum* DSM 20456T
6 *B. cantenulatum* KCTC 3221

Figure 1. Phylogenetic association between *Bifidobacterium longum* CBT BG7 and closely related species Bifidobacterium spp. based on 16S rRNA gene sequence. (Cellbiotech R&D Center 2018).

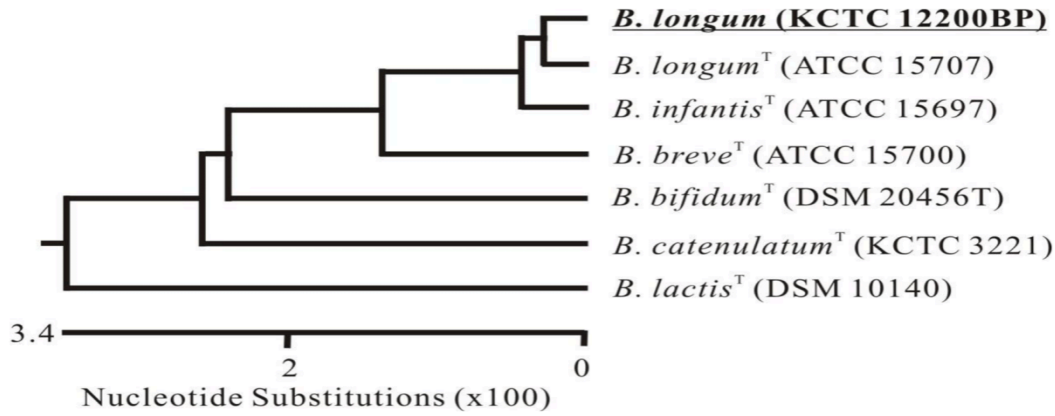
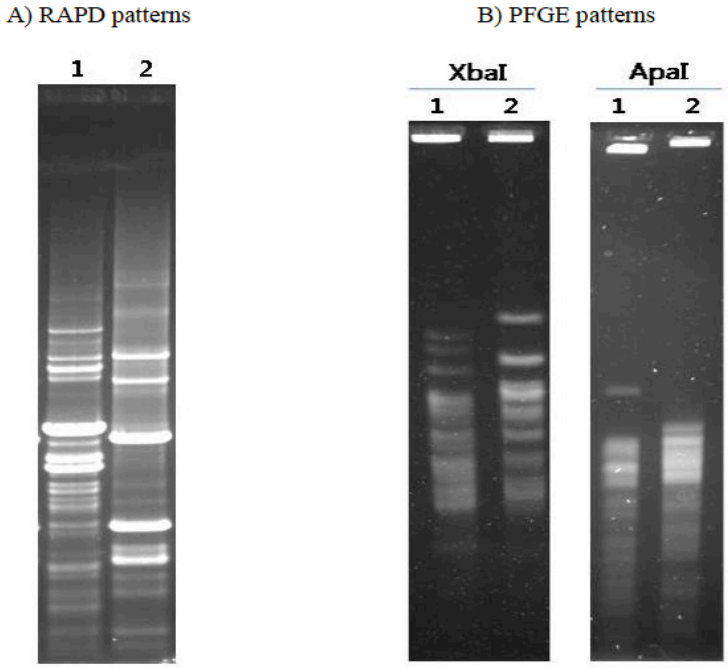


Figure 2. Comparison of DNA profiles using RAPD (A) and PFGE (B). *Bifidobacterium longum* ATCC 15707 – Lane 1; Bifidobacterium longum CBT BG7 – Lane 2. (Cellbiotech R&D Center 2018)



Manufacturing

Components

All components employed in the manufacture of *Bifidobacterium longum* CBT BG7 are suitably used for one or more effects described within FDA's Substances Added to Food Inventory as identified in Table 3.

Table 3. Identification of the ingredients used in the manufacturing process.

Fermentation Medium Ingredient	CAS No.	Reference
Fructose	[9010-10-0]	21 CFR §184.1866
Soy Peptone	[73049-73-7]	21 CFR §184.1553
Yeast Extract Powder	[8013-01-1]	21 CFR §184.1983
Potassium Phosphate, Dibasic	[7758-11-4]	21 CFR §182.1073
Sodium acetate	[127-09-3]	21 CFR §182.70
Magnesium Sulfate	[10034-99-8]	21 CFR §184.1443
L-Cysteine Monohydrochloride	[7048-04-6]	21 CFR §182.1272
L-Ascorbic Acid	[50-81-7]	21 CFR §182.8013
Monosodium L-Glutamate	[142-47-2]	21 CFR §182.1
Coating Ingredient	**CAS No.**	**Reference**
Trehalose	[6138-23-4]	FEMA No. 4600 (FEMA GRAS Publication No. 24)
L-Arginine	[74-79-3]	21 CFR §172.320
Potassium Phosphate, Dibasic	[7758-11-4]	21 CFR §182.6285
Potassium Phosphate, Monobasic	[7778-7-0]	21 CFR §175.105
Xanthan Gum	[11138-66-2]	21 CFR §172.695
Cornstarch	[977050-21-3]	21 CFR §182.70 / 21 CFR §182.90
Sodium Carboxymethylcellulose	[9004-32-4]	21 CFR §182.1745
Sodium Chloride	[7647-14-5]	21 CFR §182.1
Excipient	**CAS No.**	**Reference**
Cornstarch	[977050-21-3]	21 CFR §182.70 / 21 CFR §182.90

Process Description and Flow Chart

The flowchart for the manufacturing process through packaging is shown at Figure 3 below.

Preparation of culture medium

All fermentation medium ingredients are blended together. The mixture is then sterilized with saturated steam.

Cultivation
Stock organism is prepared and tested for microbiological contaminants. The stock organism is then inoculated into the prepared medium where it is allowed to propagate. During fermentation, the process is monitored by testing for pH and for change in optical density approximately every two hours. Once the endpoint is reached, bacterial morphology is inspected by microscopy and the organisms are separated via filtration from the culture medium.

Preparation of coating materials
Coating ingredients are added to water, mixed, and sterilized with saturated steam.

Blending
The concentrated organisms, coating mixture, and cornstarch are blended together and then dispensed into trays for freezing.

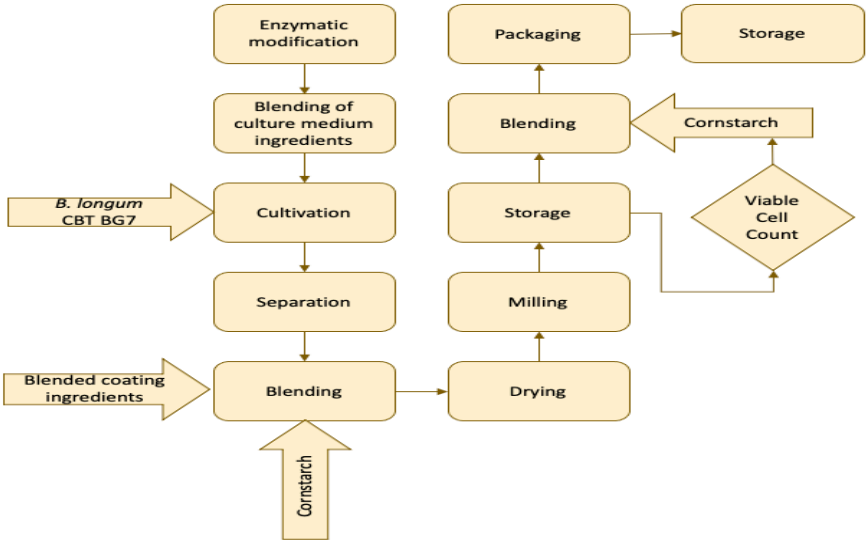
Drying
Trays containing the blended product are initially quick-frozen and then freeze dried.

Milling
Freeze-dried material is removed from the drying trays, milled, placed in polyethylene bags, passed through a metal detector, and stored as semi-finished product.

Standardization
The semi-finished product is tested for viable cell count and blended with a corresponding amount of cornstarch to ensure standardized potency.

Packaging
The standardized product is then packaged, passed through a metal detector again, sampled by QC for testing, and stored in a low -temperature warehouse.

Figure 3. Manufacturing process flow chart.



Specifications

Food grade specifications for *Bifidobacterium longum* CBT BG7 have been established as shown in Table 4. Test results of three production batches are additionally presented in demonstration of the ability to consistently produce the notified substance in conformance with these specifications. Consistency of conformance to specifications is further evidenced by stability study results.

Table 4. *Bifidobacterium longum* CBT BG7 food grade specifications and conforming test results.

Parameter	Limits	Method	Batch 25R	Batch 58R	Batch 67R
Appearance	Light yellow powder	Visual	Light brown powder	Light brown powder	Light brown powder
Viable Cell Count	$\geq 1.0 \times 10^{11}$ CFU/g	USP <2022> or equivalent	Conforms	Conforms	Conforms
Coliforms	Absent in 10g	USP <2023> or equivalent	Conforms	Conforms	Conforms

Stability Data

In order to determine the stability of *Bifidobacterium longum* CBT BG7, the food ingredient was placed in a stability study by Cell Biotech Co. Ltd.

A 12-month stability study was conducted at 5 ± 3 °C using 3 different batches of *Bifidobacterium longum* CBT BG7. At each time point, samples were analyzed in triplicate using 3 different analysts; the results of viable cell count assays are averaged and summarized in Table 5. Coliform testing was additionally performed by each analyst at all time points, the results of which are negative for all samples. Appearance test was performed by each analyst at all time points, the results of which were of a light brown powder.

Table 5. Viable cell count and percent survival rate of *Bifidobacterium longum* CBT BG7 at 5 ± 3 °C.

Strain	Batch No.	Test	Time Point				
			Initial	3 Months	6 Months	9 Months	12 Months
***Bifidobacterium longum* CBT BG7**	25R	VCC (CFU/g)	5.35×10^{11}	4.75×10^{11}	4.41×10^{11}	4.23×10^{11}	3.91×10^{11}
		Survival Rate (%)	100.0	88.7	82.4	79.1	73.1
	58R	VCC (CFU/g)	7.10×10^{11}	5.80×10^{11}	5.92×10^{11}	5.29×10^{11}	4.76×10^{11}
		Survival Rate (%)	100.0	81.6	83.3	74.5	67.0
	67R	VCC (CFU/g)	1.15×10^{12}	9.77×10^{11}	9.20×10^{11}	8.63×10^{11}	8.07×10^{11}
		Survival Rate (%)	100.0	85.0	80.0	75.1	70.2
	Average Survival Rate (%)		100.0	85.1	81.9	76.2	70.1

Technical Effects

This substance will be used to provide as a dietary source of *Bifidobacterium longum* CBT BG7 as a food ingredient to dairy products.

PART 3 – DIETARY EXPOSURE

Intended Use and All Sources in the Diet

The intended use of *Bifidobacterium longum* CBT BG7 is as a food ingredient for inclusion in dairy products to provide at least 1×10^{11} CFU per serving.

The consensus of an international scientific expert panel categorized live microorganisms for human use as defined in Table 6. The panel suggested a minimum level of 1×10^{9} CFU of LAB per serving to be the minimum criteria in support a claim of "contains live and active cultures." (Hill 2014)

Table 6. Categories of live microorganisms for human use (Hill et al. 2014).

Description	Claim	Criteria*	Minimum level of evidence required to make claim	Comments
Not probiotic				
Live or active cultures	"Contains live and active cultures"	Any food fermentation microbe(s) Proof of viability at a minimum level reflective of typical levels seen in fermented foods, suggested to be 1×10^{9} CFU per serving[73]	No product-specific efficacy studies needed	The terms 'live' or 'active' do not imply probiotic activity Fermented foods containing live cultures might also qualify as a 'probiotic' if they meet the criteria for that category (e.g. evidence that yogurt can improve lactose digestion in lactose maldigesters would qualify it as a 'probiotic'[74,75])
Probiotic				
Probiotic in food or supplement without health claim	"Contains probiotics"	A member(s) of a safe[76,77] species, which is supported by sufficient evidence of a general beneficial effect in humans OR a safe microbe(s) with a property (e.g. a structure, activity or end product) for which there is sufficient evidence for a general beneficial effect in humans Proof of viability at the appropriate level used in supporting human studies[73]	Well-conducted human studies (e.g. these could involve RCT(s), observational studies, systematic reviews or meta-analyses supporting the observed general beneficial effect for the taxonomical category concerned) The evidence does not have to be generated for the specific strain included in the product	Extrapolation of evidence must be based on reasonable expectations that the strain(s) incorporated in the product would have similar general beneficial effects in humans This evidence could be based on taxonomical or functional comparisons
Probiotic in food or supplement with a specific health claim	Specific health claim, such as "helps to reinforce the body's natural defences in children" or "helps reduce the risk of antibiotic-associated diarrhoea"	Defined probiotic strain(s) Proof of delivery of viable strain(s) at efficacious dose at end of shelf-life[73]	Convincing evidence needed for specific strain(s) or strain combination in the specified health indication Such evidence includes well-conducted studies in humans, including: positive meta-analyses on specific strain(s) or strain combinations, as per principles outlined by Cochrane,[78] PASSCLAIM,[79] or GRADE;[80] well-conducted RCT(s) OR strong evidence from large observational studies[81]	Well-designed observational studies are useful to detect the effect of foods on health in 'real life', that is, outside the controlled environment of an RCT (e.g. data on health benefits by dietary fibre are mostly observational) Sample sizes must be large enough to manage confounding factors
Probiotic drug	Specific indication for treatment or prevention of disease, such as "useful for the prevention of relapse of ulcerative colitis"	A defined strain(s) of live microbe Proof of delivery of viable probiotic at efficacious dose at end of shelf-life Risk–benefit assessment justifies use	Appropriate trials to meet regulatory standards for drugs	What constitutes a drug claim varies among countries

*Unless otherwise indicated, all criteria indicated must be met. Abbreviations: CFU, colony forming unit; GRADE, Grades of Recommendation Assessment, Development and Evaluation; PASSCLAIM, Process for the Assessment of Scientific Support for Claims on Food; RCT, randomized controlled trial.

Consumption Data

Based on the food consumption data reported in the most recent National Health and Nutrition Examination Survey (NHANES 2017-2018) dataset compiled by the U.S. Department of Health and Human Services, National Center for Health Statistics, and the Nutrition Coordinating Center, the EDIs of dairy products were determined by several age groups.

The intended use of at least 1.0 x 10^{11} CFU per serving in dairy products would result in intakes in all users of 8.94 x 10^{10} CFU and 1.85 x 10^{11} CFU per person per day in the mean and 90th percentile, respectively (Table 7). A maximum exposure would occur in male adults with a 90th percentile EDI of 2.05 x 10^{11} per person per day.

Table 7. EDIs of *Bifidobacterium longum* CBT BG7 from proposed uses in dairy products across all users based on 2017-2018 NHANES.

Group	% (n)	Dairy intake g/day		Dairy, serving/day		*Bifidobacterium longum* CBT BG7, cfu/day	
		Mean	90th percentile	Mean	90th percentile	Mean	90th percentile
Children, 3-11	74.04 (739)	360.44	456.85	0.97	1.87	9.74×10^{10}	1.87×10^{11}
Females, 12-19	42.44 (191)	186.02	362.90	0.76	1.49	7.62×10^{10}	1.49×10^{11}
Males, 12-19	54.73 (243)	265.10	477.28	1.09	1.96	1.09×10^{11}	1.96×10^{11}
Females, 20 and up	38.21(826)	179.05	360.87	0.73	1.48	7.34×10^{10}	1.48×10^{11}
Males, 20 and up	44.06(871)	222.93	499.63	0.91	2.05	9.13×10^{10}	2.05×10^{11}
All users	47.61(3161)	218.16	452.44	0.89	1.85	8.94×10^{10}	1.85×10^{11}

Assuming all servings of the intended dairy products consumed contain *Bifidobacterium longum* CBT BG7, the suggested three daily servings would result in a cumulative exposure of 2.68 × 10^{11} CFU per day ($8.94\times10^{10}\times3$). The estimated 90th percentile of consumers of dairy products at this level of recommended consumption adjusted for the findings of the per capita data would potentially be exposed to up to 5.55 × 10^{11} CFU per day *Bifidobacterium longum* CBT BG7. The LD_{50} identified is the uppermost safety point that has been studied to date. The study presented by CBI R&D Center (2018) demonstrated that > 10^{11} CFU/kg was still safe for the rats at that dosage. In point of fact, no true LD_{50} nor NOAEL has ever been determined for this organism. This is due to the fact that an amount of organism greater than this cannot feasibly be administered to the rats.

The LD_{50} of greater than 10^{11} CFU/kg from the animal studies from the Cell Biotech R&D Center corresponds to the human equivalent dose of 9.6×10^{11} CFU in a 60 kg human (using the animal-specific body surface area-based conversion factor presented in the Center for Drug Evaluation and Research's Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers 2005). Therefore, even if the general population consumers of dairy products were to meet these guidelines, the recommended levels of the cumulative exposure of 2.68×10^{11} CFU per day and the cumulative exposure at an estimated 90^{th} percentile of 5.55×10^{11} CFU per day is less than the LD_{50} levels of greater than 10^{11} CFU/kg (or 9.6×10^{11}) of *Bifidobacterium longum* CBT BG7**.**

Substances Expected to Be Formed in Food

Under the intended conditions of use, there are no substances expected to be formed in the foods in which *Bifidobacterium longum* CBT BG7 is included. The metabolic by-products from *Bifidobacterium longum* CBT BG7 do not go beyond the expected fermentation products from any of the other LAB microorganisms. These include lactic acid, carbon dioxide, and the ATP necessary for the cell. *Bifidobacterium longum* CBT BG7 is not known to secrete any exotoxins or any other substances that are classified as harmful to humans. Additionally, the number of viable organisms will decline during a product's shelf life to further minimize the exposure to any of the metabolic by-products.

Substances Naturally Present or Due to Manufacturing

Any remaining ingredients used to produce the fermentation media should have little to no presence in the overall finished output and therefore, the EDIs for these ingredients were not determined or calculated.

The coating ingredients and excipients used in the manufacturing process are listed in FDA's Substances Added to Food Inventory for various uses:

- Trehalose is listed as a flavoring agent or adjuvant.
- L-arginine is listed as a nutrient supplement.
- Xanthan gum is listed as an anticaking agent or free-flow agent, color or coloring adjunct, drying agent, emulsifier or emulsifier salt, formulation aid, processing aid, solvent or vehicle, stabilizer or thickener, surface-finishing agent, or texturizer.
- Potassium phosphate, dibasic is listed as an emulsifier or emulsifier salt, nutrient supplement, pH control agent, sequestrant, or stabilizer or thickener.
- Potassium phosphate, monobasic is listed as malting or fermenting aid, nutrient supplement, pH control agent, or stabilizer or thickener.
- Cornstarch is listed as an anticaking agent or free-flow agent, drying agent, flavoring agent or adjuvant, formulation aid, humectant, non-nutritive sweetener, nutritive sweetener, solvent or vehicle, stabilizer or thickener, or texturizer.

- Sodium carboxymethylcellulose is listed as an anticaking agent or free-flow agent, drying agent, emulsifier or emulsifier salt, formulation aid, processing aid, humectant, stabilizer or thickener, or texturizer.

- Sodium chloride is listed as an anticaking agent or free-flow agent, antimicrobial agent, color or coloring adjunct, emulsifier or emulsifier salt, firming agent, flavoring agent or adjuvant, formulation aid, nutrient supplement, solvent or vehicle, stabilizer or thickener.

PART 4 – SELF-LIMITING LEVELS OF USE

There is no recognized self-limiting level of use for this organism. Issues of palatability of the substance are not present at the levels of inclusion identified.

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

As the conclusion of general recognition of safety is through scientific procedures, this Part is not applicable. Information about the current international marketplace availability of products containing *Bifidobacterium longum* CBT BG7 as an ingredient is discussed as part of the scientific procedures upon which the general recognition of safety is based. Nevertheless, the historical use of foods with *Bifidobacterium longum* is discussed in Part 6.

PART 6 – NARRATIVE

Introduction

Fermented foods have a long history of consumption in the human population, with some of the earliest records of such in Southeast Asia and Africa (Nout 1992). Prevalence of fermented foods is much higher in some parts of the world outside the U.S., such as in Sudan where it seems the majority of foods are prepared and preserved by fermentation (Dirar 1992).

Used as an inexpensive means throughout the world, lactic acid-producing bacteria (LAB) are one major group of microorganisms used to process milk, meat, and various plant material like vegetables, cereals, and legumes into fermented foods that undergo flavor and nutritive profile changes from their original forms as well as gain the benefit of improved stability (Steinkraus 1992). By preventing the formation of pathogenic and spoilage organisms, fermented foods have an increased shelf life and decreased potential for causing food poisoning (Hesseltine 1981).

In the United States, LAB in general are permitted for use in several standardized foods. A variety of cheeses, whose requirements are found within 21 CFR Part 133—Cheeses and Related Cheese Products, include the use of these and other types of bacterial cultures. LAB are also used in the production of Sour Cream [§131.160], are optional ingredients for use in Bread, Rolls, and Buns [§136.110(c)(10)], and may be used as characterizing microbial organisms or as microbial cultures to produce aroma and flavor in the production of Acidified Milk [§131.111] and Cultured Milk [§131.112].

History of GRAS Notices

There is a history of successfully notified GRAS substances intended for inclusion in foods dating back to 2002 (GRAS No. 49).

GRAS notices of food ingredient substances containing the same species as *Bifidobacterium longum* CBT BG7 to which FDA has no questions are presented below in Table 8. These GRAS notices reference and address a large body of established scientific procedures evidencing the safe and common use of various strains of *Bifidobacterium longum* and its subspecies. GRAS notices of *Bifidobacterium* organisms of species other than *longum* which FDA has no questions are presented below in Table 9.

Table 8. GRAS notices containing *Bifidobacterium longum* receiving reply from FDA that it had no questions (GRAS Notices Inventory Database).

GRAS No.	Date of Closure	Substance
877	26-Dec-2019	*Bifidobacterium longum* BB536
758	20-Aug-2018	*Lactobacillus helveticus* strain R0052, *Bifidobacterium longum* subsp. *infantis* strain R0033, and *Bifidobacterium bifidum* strain R0071
268	08-Jul-2009	*Bifidobacterium longum* strain BB536

Table 9. GRAS notices of *Bifidobacterium* organisms of species other than *longum* receiving reply from FDA of no questions (GRAS Notices Inventory Database)

GRAS No.	Date of Closure	Substance
872	9-Dec-2019	*Bifidobacterium animalis* subsp. *lactis* UABla-12
856	09-Dec-2019	*Bifidobacterium animalis* subsp. *lactis* strain BB012
855	05-Feb-2020	*Bifidobacterium animalis* subsp. *lactis* strain R0421
814	25-Jun-2019	*Bifidobacterium bifidum* BGN4
813	21-Jun-2019	*Bifidobacterium bifidum* BORI
455	30-Sep-2013	*Bifidobacterium breve* M-16V
454	27-Sep-2013	*Bifidobacterium breve* M-16V
453	27-Sep-2013	*Bifidobacterium breve* M-16V
445	10-Apr-2013	*Bifidobacterium animalis* subsp. *lactis* strains HN019, Bi-07, BI-04 and B420

GRAS No.	Date of Closure	Substance
377	29-Sep-2011	*Bifidobacterium animalis* subsp. *lactis* strain Bf-6

Approved Use

The status of *Bifidobacterium longum* in Canada involves the accepted use of the microorganism in food products. Specific claims may be made about these products when the level of use is a minimum of 1×10^9 CFU per serving.

In a December 12th, 2019 update to their Qualified Presumption of Safety list, the European Food Safety Authority confirmed *Bifidobacterium* spp. (including *Bifidobacterium longum*) presence in an inventory of recommended biological agents intentionally added to food or feed based on review of latest applicable literature.

Antibiotic Resistance

Determination of the minimal inhibitory concentration (MIC) of select antibiotics [ampicillin (AMP), gentamycin (GEN), kanamycin (KAN), streptomycin (STM), erythromycin (ERM), clindamycin (CLM), tetracycline (TET), and chloramphenicol (CP)] was performed in accordance with ISO 10932:2010 using *Bifidobacterium longum* CBT BG7 as the test strain. Observed MIC values for *Bifidobacterium longum* CBT BG7 were determined to be lower than the cut-off values prescribed by 2012 Guidance on the assessment of bacterial susceptibility to antimicrobials of human and veterinary importance published by the European Food Safety Authority (EFSA), as shown in Table 10 and therefore susceptible to AMP, GEN, KAN, STM, ERM, CLM, TET, and CP. Most *Bifidobacterium* species are reported to be resistant to aminoglycosides, because of the lack of a cytochrome-mediated drug transport system and the particular resistance to kanamycin is well known and testing for such in *Bifidobacterium longum* is not required by EFSA guidance (EFSA 2012).

Table 10. Antibiotic sensitivity of *Bifidobacterium longum* CBT BG7.

Strain	Minimum Inhibitory Concentrations (μg/mL) of Antibiotics								
	AMP	VAN	GEN	KAN	STM	ERM	CLM	TET	CP
***B. longum* CBT BG7**	<0.5	<0.5	<16	<256	<32	<0.5	<0.12	<8	<2
EFSA Cut-off Value	2	2	64	NR	128	1	1	8	4

Current Marketplace Availability of *Bifidobacterium longum* CBT BG7

While the conclusion of general recognition of safety (GRAS) is based upon scientific procedures, there is a history of use of *Bifidobacterium longum* CBT BG7 in foreign countries and in multiple food products.

In vitro Toxicity Studies

Hemolysis Assay

The Cell Biotech R&D Center tested *Bifidobacterium longum* CBT BG7 for its hemolytic activity by inoculating microorganism in MRS agar supplemented with 5% horse blood and incubated under anaerobic conditions. The test showed no hemolytic activity.

Animal Studies

The pathogenicity and acute toxicity of *Bifidobacterium longum* CBT BG7 were investigated using male and female Sprague-Dawley rats (5 of each sex in each group). The animals were intragastrically administered either 0.85% saline solution or 1×10^{11} CFU/kg *Bifidobacterium longum* CBT BG7 and observed for the ensuing 14 days. The net body weight gain, gross pathological findings, feed and water consumption, organ weight, and body temperature were monitored and recorded for two (2) weeks.

This investigation revealed no mortalities or obvious adverse clinical signs in rats administered with the live bacterial cells at the investigated dose level as shown on Table 11. In addition, results indicate no significant differences in net body weight gain (Figure 4), gross pathological findings (Table 12), feed and water consumption (Figure 5), organ weight (Table 13), and body temperature (Table 14) among the different treatment groups and between the treated and control rats.

Table 11. Mortality of male and female rats orally administered with 1×10^{11} CFU/kg *Bifidobacterium longum* CBT BG7 (Cellbiotech R&D Center 2018)

Sex	Group	Days After Administration														Final Mortality (%)	LD_{50}
		1	2	3	4	5	6	7	8	9	10	11	12	13	14		
Male	CBT BG7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	> 1×10^{11} CFU/kg
	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Female	CBT BG7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	> 1×10^{11} CFU/kg
	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Figure 4. Body weight curves for male and female rats given 10^{11} CFU/kg *Bifidobacterium longum* CBT BG7 and control for 14 days. Values are mean ± SE. (Cellbiotech R&D Center 2018)

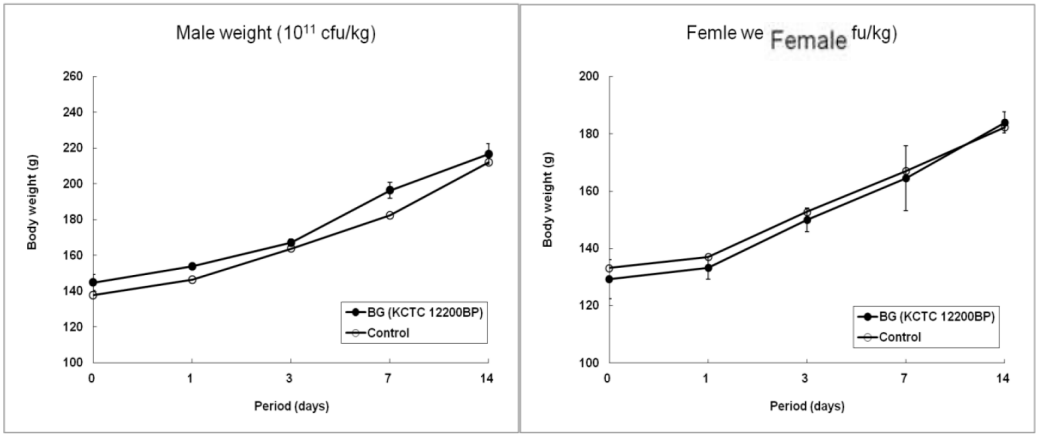

Male weight (10^{11} cfu/kg)
Body weight (g)
260
240
220
200
180
160
140
120
100
0
1
3
7
14
Period (days)
BG (KCTC 12200BP)
Control
Femle we Female fu/kg)
Body weight (g)
200
180
160
140
120
100
0
1
3
7
14
Period (days)
BG (KCTC 12200BP)
Control

Table 12. Clinical findings of male and female rats orally administered with 10^{11} CFU/kg *Bifidobacterium longum* CBT BG7 (Cellbiotech R&D Center 2018).

Sex	LAB Strain	Clinical Signs	Hours after treatment				Days after treatment				
			1	2	5	6	1	3	5	7	14
Male	CBT BG7	NAD	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
	Control	NAD	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
Female	CBT BG7	NAD	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
	Control	NAD	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5

NAD: No abnormality detected

Figure 5. Food and water consumption of male and female rats given 10^{11} CFU/kg *Bifidobacterium longum* CBT BG7 and control for 14 days. (Cellbiotech R&D Center 2018).

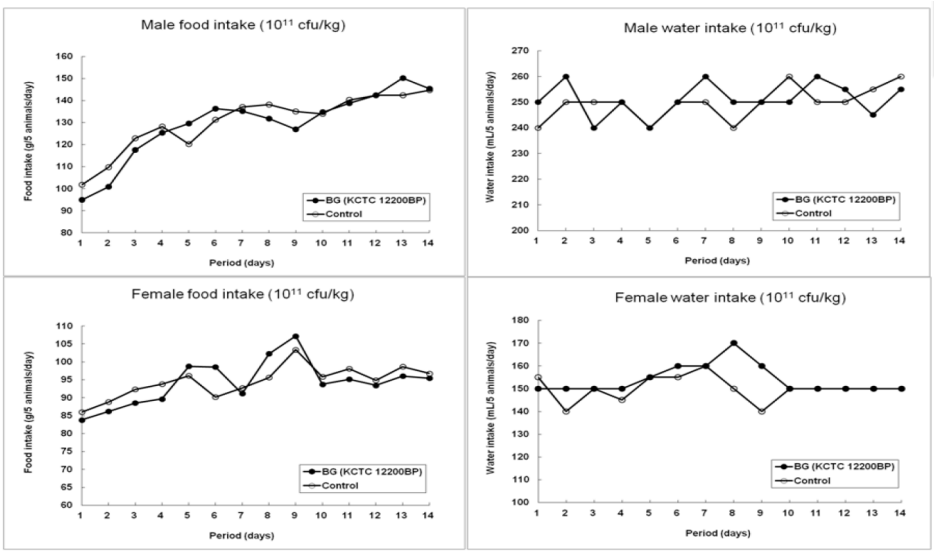


Table 13. Absolute organ weights (g) of male and female orally administered with 10^{11} CFU/kg *Bifidobacterium longum* CBT BG7 (Cellbiotech R&D Center 2018)

Sex	Parameters	Lab	CBT BG7	Control
		No. of Animals	5	5
Male	Body weight (g)		216.59 ± 11.30	211.90 ± 5.66
	Liver (g)		7.27 ± 0.89	7.20 ± 0.70
	Spleen (g)		0.82 ± 0.03	0.79 ± 0.05
	Kidney (g)	Right	0.87 ± 0.07	0.81 ± 0.09
		Left	0.41 ± 0.03	0.30 ± 0.06
Female	Body weight (g)		184.01 ± 4.87	182.32 ± 4.33
	Liver (g)		5.60 ± 0.66	5.32 ± 0.53
	Spleen (g)		0.62 ± 0.05	0.63 ± 0.05
	Kidney (g)	Right	0.64 ± 0.04	0.66 ± 0.05
		Left	0.38 ± 0.06	0.32 ± 0.04

Table 14. Body temperature changes in male and female orally treated with 10^{11} CFU/kg *Bifidobacterium longum* CBT BG7 ((Cellbiotech R&D Center (2018))

Day	No.	Male body temperature		Female body temperature	
		CBT BG7 (˚C)	Control (˚C)	CBT BG7 (˚C)	Control (˚C)
Pre-treatment	Ave	35.24	34.40	34.68	35.16
	SEM	0.41	0.24	0.72	0.70
Day 1	Ave	35.08	34.70	34.88	35.08
	SEM	1.36	0.92	0.58	0.66
Day 2	Ave	35.54	34.90	35.20	35.12
	SEM	0.56	0.56	0.67	0.83
Day 3	Ave	35.82	35.10	35.18	35.36
	SEM	0.41	0.69	0.49	0.32
Day 4	Ave	35.40	34.10	35.22	35.30
	SEM	0.72	0.60	0.26	0.30

Human Studies

Study 1

Kwak et al. (2014) studied the effects of short-term microbial therapy with six bacterial species, including *B. bifidum*, and reported that it alleviated small intestine bacterial overgrowth, but did not improve intestinal permeability in patients with chronic liver disease. Fifty-three patients were given either microbial therapy or a placebo. Those given the microbial therapy tolerated it well.

Study 2

In a study conducted by Yeun and Lee (2014), forty participants aged 60 years or older were randomly assigned to take a capsule containing six double coated (with proteins and polysaccharides) bacterial strains (2.5×10^8 viable cells), including *Bifidobacterium longum* CBT BG7, or the same uncoated organisms, twice daily to assess to assess efficacy in treating functional constipation. Following the 2-week treatment period, all patients showed significant increases in the quantity of fecal bacteria with some few improvements in symptoms and no overall changes in body mass index, weight, or overall health. No adverse effects were reported in either treatment group.

Study 3

Yoon et al. (2014) conducted a randomized, double-blind, placebo-controlled trial enrolled forty-nine patients suffering from irritable bowel syndrome (IBS) to determine the effect of multispecies microorganisms on this condition. Twenty-five patients were given a capsule containing 5×10^9 viable cells of six bacterial strains in equal measure, including *Bifidobacterium longum* CBT BG7*,* twice daily for four weeks. All of the active arm participants in the study appeared to tolerate the microbial capsules well with no adverse events reported. Significantly more patients experienced global relief of IBS symptoms in the microbial group than in the placebo group.

Study 4

Yoon et al. (2015) conducted a trial on the effect of administering a six-species microbial mixture, including *Bifidobacterium longum* CBT BG7*,* on changes in fecal microbiota and symptoms of irritable bowel syndrome. Eighty-one patients completed the study with 39 of them having ingested two capsules containing 5×10^9 viable cells daily for four weeks. The study concluded that most of the intestinal flora strain fecal concentrations increased in patients and that the diarrhea symptom score was improved for the active group with no adverse effects noted.

Study 5

Bazanella et al. (2017) conducted a randomized, double-blind, placebo-controlled study to determine the first year of life effects of a formula containing *Bifidobacterium* spp. on the healthy infant intestinal microbiome. The treatment group consisted of 48 newborn infants provided with a supplemented formula containing a total of 1×10^8 CFU/g of *Bifidobacterium*, including *Bifidobacterium longum* CBT BG7 with three other *Bifidobacterium* in equal amounts, from birth to 12 months. The supplemented formula was shown to impact the early stage of microbiome development with no detectable long-term consequences.

Study 6

Hod et al. (2017 and 2018) investigated the effects of a bacterial mixture in 107 adult women diagnosed with diarrhea-dominant-IBS (IBS-D). The study was designed as a randomized double-blind, placebo-controlled, parallel-group trial with a 2-week run-in period prior to treatment and a treatment period for 8 weeks. Those subjects in the BIO-25 group were given a BIO-25 capsule containing 2.5×10^{10} CFU mixture of 11 bacteria twice daily that contained 1×10^9 CFU *Bifidobacterium longum* CBT BG7**.** A total of 54 subjects were used in the BIO-25 group and 53 subjects were used in the placebo group. Nine subjects in the placebo group and five subjects in the BIO-25 group did not complete the study. No serious adverse events were reported in either group.

Conclusion

The scientific data, information, methods, and principles described in this notification provide the basis for conclusion that *Bifidobacterium longum* CBT BG7 is generally recognized among qualified experts to be safe for inclusion in the food types described in the amounts noted. The historic safe use of *Bifidobacterium longum* in the food supply along with the evaluation of the consumption data serve as the foundation on which the safety of this uniquely identified strain is established.

Inclusion of *Bifidobacterium longum* and other lactic acid-producing bacteria is identified and sometimes mandated in FDA regulations surrounding standards of identity for select food types. FDA has also responded with no questions to numerous GRAS notices submitted for other strains of *Bifidobacterium longum*, other species of *Bifidobacterium*, as well as members of other genera of lactic acid-producing bacteria, intended for inclusion as food ingredients. The applicable GRAS notices, referenced in Table 8 and Table 9 within Part 6 of this notice, incorporate myriad studies demonstrating the safety of ingestion of substances closely related to *Bifidobacterium longum* CBT BG7**.**

Bifidobacterium longum CBT BG7 is well characterized genetically, taxonomically known as an organism lacking potential for harm, and supported by analyses conducted by Cell Biotech R&D Center (2018) in demonstration of its safety and elucidation of its genotypic and phenotypic traits. The substance's potential for pathogenicity and acute toxicity tested negative. *Bifidobacterium longum* CBT BG7's potential for antibiotic resistance was tested in accordance with EFSA guidelines where *Bifidobacterium* strains are intrinsically resistant to kanamycin.

Additional efficacy studies in humans and animals have been performed without the occurrence of observation of adverse events. An LD_{50} of greater than 10^{11} CFU/kg was established in rats which corresponds to a human equivalent amount of 9.6×10^{11} CFU in a 60kg human (using the animal-specific body surface area-based conversion factor presented in the Center for Drug Evaluation and Research's Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers [2005]). The estimated level of cumulative daily intake of *Bifidobacterium longum* CBT BG7 at the 90^{th} percentile of high-level consumers of products of the intended inclusion food is 5.55×10^{11} CFU per day of *Bifidobacterium longum* CBT BG7. The 90^{th} percentile for actual consumption of 5.55×10^{11} CFU/day is below the maximum safe starting dose of 9.6×10^{11} CFU/serving.

All data and information pertaining to the studies performed on the material, in-house documentation, and additional information were made available to the Expert Panel, and their findings reflect review of the totality of the information used in the preparation of this notice as shown on the Expert Panel Endorsement pages.

PART 7 – SUPPORTING DATA AND INFORMATION

Generally Unavailable

Cellbiotech R&D Center (2018) Identification. Molecular Typing and Safety Assessment of *Bifidobacterium longum* CBT BG7 (KCTC 12200BP).

Generally Available

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Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Determination of Cell Biotech Co. Ltd. *Bifidobacterium longum* CBT BG7

February 26, 2021

Cell Biotech Co. Ltd. intends to market ***Bifidobacterium longum* CBT BG7** as an ingredient in dairy products. ***Bifidobacterium longum* CBT BG7** is produced by growth of a certified source strain of the organism in an appropriate medium. The strain is verified prior to inoculation of the medium. The resultant microorganism is freeze-dried for use in dairy products.

The use of this microorganism in the production of food products is historic. The application of the specific strain ***Bifidobacterium longum* CBT BG7** identified in this dossier is further demonstrated in this submission as Generally Recognized as Safe through support from the application of scientific procedures evaluating the safety of the item.

At the request of Cell Biotech Co. Ltd., a panel of independent scientists (the "Expert Panel"), qualified by their relevant national experience, education and training, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and to determine whether the intended uses of ***Bifidobacterium longum* CBT BG7** as an ingredient in dairy products is safe, suitable, and would be Generally Recognized as Safe (GRAS) based on a combination of historic use and scientific procedures. The Expert Panel consisted of following experts: Steven Dentali, Ph.D. (Dentali Botanical Sciences), Mary C. Mulry, Ph.D. (Foodwise), and Ms. Jeanne Moldenhauer, M.Sc. (Excellent Pharma Consulting).

The Expert Panel, independently and collectively, evaluated the dossier inclusive of the following:

Basis for GRAS Determination	Narrative Summary
Claim Regarding GRAS Status	Determination of the Expert Panel
Manufacturing Process	Summary and Diagrams
Stability Data	Data and Presentation
Dietary Exposure	Summary of intended exposure
Basis for Determination	Discussion of studies
Public and Private Studies	Supporting studies included

In addition, the Expert Panel evaluated all other information deemed necessary and/or sufficient in order to arrive at its independent, critical evaluation of these data and information. The Expert Panel has attained a unanimous conclusion that the intended uses described herein for Cell Biotech Co. Ltd. ***Bifidobacterium longum* CBT BG7**, meeting appropriate food-grade specifications as described in the supporting dossier, as a dairy ingredient is identified as Generally Recognized as Safe (GRAS) by Self-determination for use as a food ingredient across a range of food categories identified in the dossier. Such dairy products that include Cell Biotech Co. Ltd. ***Bifidobacterium longum* CBT BG7** in accordance with the described applications and levels specified in the dossier, manufactured according to current Good

Manufacturing Practice (cGMP), are safe for human consumption. These determinations are made based on a combination of historic use of the microorganism in food products with support from scientific procedures.

The individual endorsement pages follow hereunder.

ENDORSEMENT BY STEVEN DENTALI, PH.D.

I, Steven Dentali, hereby affirm that ***Bifidobacterium longum* CBT BG7** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature:_[redacted]___ Date:_____

Steven Dentali, Ph.D.
Dentali Botanical Sciences

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Public and Private Studies	Supporting studies included

In addition, the Expert Panel evaluated all other information deemed necessary and/or sufficient in order to arrive at its independent, critical evaluation of these data and information. The Expert Panel has attained a unanimous conclusion that the intended uses described herein for Cell Biotech Co. Ltd. ***Bifidobacterium longum* CBT BG7**, meeting appropriate food-grade specifications as described in the supporting dossier, as a dairy ingredient is identified as Generally Recognized as Safe (GRAS) by Self-determination for use as a food ingredient across a range of food categories identified in the dossier. Such dairy products that include Cell Biotech Co. Ltd. ***Bifidobacterium longum* CBT BG7** in accordance with the described applications and levels specified in the dossier, manufactured according to current Good

Manufacturing Practice (cGMP), are safe for human consumption. These determinations are made based on a combination of historic use of the microorganism in food products with support from scientific procedures.

The individual endorsement pages follow hereunder.

ENDORSEMENT BY JEANNE MOLDENHAUER, M. SC.

I, Jeanne Moldenhauer, hereby affirm that ***Bifidobacterium longum* CBT BG7** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature: [redacted] Date: 6APR21

Jeanne Moldenhauer, M. Sc.
Excellent Pharma Consulting

REJIMUS
Powering Innovative Compliance®

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WWW.REJIMUS.COM

Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Determination of Cell Biotech Co. Ltd. *Bifidobacterium longum* CBT BG7

February 26, 2021

Cell Biotech Co. Ltd. intends to market ***Bifidobacterium longum* CBT BG7** as an ingredient in dairy products. ***Bifidobacterium longum* CBT BG7** is produced by growth of a certified source strain of the organism in an appropriate medium. The strain is verified prior to inoculation of the medium. The resultant microorganism is freeze-dried for use in dairy products.

The use of this microorganism in the production of food products is historic. The application of the specific strain ***Bifidobacterium longum* CBT BG7** identified in this dossier is further demonstrated in this submission as Generally Recognized as Safe through support from the application of scientific procedures evaluating the safety of the item.

At the request of Cell Biotech Co. Ltd., a panel of independent scientists (the "Expert Panel"), qualified by their relevant national experience, education and training, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and to determine whether the intended uses of ***Bifidobacterium longum* CBT BG7** as an ingredient in dairy products is safe, suitable, and would be Generally Recognized as Safe (GRAS) based on a combination of historic use and scientific procedures. The Expert Panel consisted of following experts: Steven Dentali, Ph.D. (Dentali Botanical Sciences), Mary C. Mulry, Ph.D. CFS(FoodWise One LLC), and Ms. Jeanne Moldenhauer, M.Sc. (Excellent Pharma Consulting).

The Expert Panel, independently and collectively, evaluated the dossier inclusive of the following:

Basis for GRAS Determination	Narrative Summary
Claim Regarding GRAS Status	Determination of the Expert Panel
Manufacturing Process	Summary and Diagrams
Stability Data	Data and Presentation
Dietary Exposure	Summary of intended exposure
Basis for Determination	Discussion of studies
Public and Private Studies	Supporting studies included

In addition, the Expert Panel evaluated all other information deemed necessary and/or sufficient in order to arrive at its independent, critical evaluation of these data and information. The Expert Panel has attained a unanimous conclusion that the intended uses described herein for Cell Biotech Co. Ltd. ***Bifidobacterium longum* CBT BG7**, meeting appropriate food-grade specifications as described in the supporting dossier, as a dairy ingredient is identified as Generally Recognized as Safe (GRAS) by Self-determination for use as a food ingredient across a range of food categories identified in the dossier. Such dairy products that include Cell Biotech Co. Ltd. ***Bifidobacterium longum* CBT BG7** in accordance with the described applications and levels specified in the dossier, manufactured according to current Good

Manufacturing Practice (cGMP), are safe for human consumption. These determinations are made based on a combination of historic use of the microorganism in food products with support from scientific procedures.

The individual endorsement pages follow hereunder.

ENDORSEMENT BY MARY C. MULRY, PH.D. CFS

I, Mary Mulry, hereby affirm that ***Bifidobacterium longum* CBT BG7** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature: [redacted] Date: 3/18/21

Mary C. Mulry, Ph.D. CFS
FoodWise One LLC

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: 07/31/2022
(See last page for OMB Statement)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
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):* 2021-12-06

4 For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd):* _____

SECTION B INFORMATION ABOUT THE NOTIFIER

1a. Notifier	Name of Contact Person Myung-jun Chung		Position or Title CEO	
	Organization *(if applicable)* Cell Biotech Co. Ltd.			
	Mailing Address *(number and street)* 50 Agibong-ro, 409 Beon-gil			
City Wolgot-myeon, Gimpo	State or Province Gyeonggi-do	Zip Code/Postal Code	Country Korea, Republic of	
Telephone Number +82 31 987 6205	Fax Number	E-Mail Address ceo@cellbiotech.com		
1b. Agent or Attorney *(if applicable)*	Name of Contact Person Jim Lassiter		Position or Title COO	
	Organization *(if applicable)* REJIMUS, INC.			
	Mailing Address *(number and street)* 600 W Santa Ana Blvd Suite 1100			
City Santa Ana	State or Province California	Zip Code/Postal Code 92701	Country United States of America	
Telephone Number 9492290072	Fax Number	E-Mail Address jim@rejimus.com		

SECTION C GENERAL ADMINISTRATIVE INFORMATION

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

Bifidobacterium longum CBT BG7

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

1 DVD+R

3. For paper submissions only:

Number of volumes 1

Total number of pages 34

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 _____

☐ 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.

The intended use of Bifidobacterium longum CBT BG7 is a food ingredient for inclusion in dairy products where standards of identity do not preclude such use. The intended addition level to these foods is up to 1 × 10^11 CFU per serving.

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 Cell Biotech Co. Ltd.
(name of notifier)

has concluded that the intended use*(s)* of Bifidobacterium longum CBT BG7
(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. Cell Biotech Co. Ltd. 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.
(name of notifier)

50, Agibong-ro, 409 Beon-gil
(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)
Jim Lassiter Digitally signed by Jim Lassiter Date: 2022.05.09 12:13:15 -07'00'	Jim Lassiter, President/COO	05/09/2022

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)
	Form3667.pdf	Administrative
	Cell_Biotech_Co_Ltd_B_longum_CBT_BG7_2018.pdf	GRAS Notice
	Bazanella_2017.pdf	GRAS Notice
	Candela_2007.pdf	GRAS Notice
	CDER_Starting_dose_in_Initial_Clinical_Trials_and_Therapeutics_in_Adult_Healthy_Volunteers_2005.pdf	GRAS Notice
	Dirar_1992.pdf	GRAS Notice
	EFSA_2012.pdf	GRAS Notice
	EFSA_Scientific_Opinion_on_the_Update_of_the_list_of_QPS-recommended_biological_agents.pdf	GRAS Notice
	Health_Canada_Probiotics.pdf	GRAS Notice

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Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Hesseltine_1981.pdf	GRAS Notice
	Hill_2014.pdf	GRAS Notice
	Hod_2017.pdf	GRAS Notice
	Hod_2018.pdf	GRAS Notice
	Kwak_2014.pdf	GRAS Notice
	Nout_1992.pdf	GRAS Notice
	Steinkraus_1992.pdf	GRAS Notice
	Toure_2003.pdf	GRAS Notice
	Turroni_2014.pdf	GRAS Notice

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Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Ventura_2007.pdf	GRAS Notice
	Yeun_2014.pdf	GRAS Notice
	Yoon_2014.pdf	GRAS Notice
	Yoon_2015.pdf	GRAS Notice
	GRASNotice_II965.1-CBI.1.4_Bifidobacterium_longum_CBT_BG7_2022-05-09.pdf	Administrative