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Office of Food Safety 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 ***Streptococcus thermophilus*** **CBT ST3**
II932.2-CBI.2.2

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 this notice of a claim that the addition of the microorganism ***Streptococcus thermophilus*** **CBT ST3** to the foods identified in this notice at the specified levels is exempt from the premarket approval requirements 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 addresses the safety of the substance for use in human food applications.

Respectfully,

Jim Lassiter, President/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-ro
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. has undertaken an independent safety evaluation of the substance in this notification:

***Streptococcus thermophilus* CBT ST3**

Intended Conditions of Use and Levels of Inclusion

The intended use of *Streptococcus thermophilus* CBT ST3 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.

Streptococcus thermophilus CBT ST3 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 bifidum* CBT BF3 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 *Streptococcus thermophilus* CBT ST3 is GRAS for its intended conditions of use as stated in this notification and, such use of *Streptococcus thermophilus* CBT ST3 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 for CBI's GRAS conclusion are available for review and copying at reasonable times at the offices of the Agent.

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

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

Trade Secrets

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

Certification

Cell Biotech Co. Ltd. has concluded that *Streptococcus thermophilus* CBT ST3 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 *Streptococcus thermophilus* CBT ST3.

Respectfully submitted,

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

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

Common name: *Streptococcus thermophilus* CBT ST3 (KCTC 11870BP)

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

Taxonomic Lineage:
Kingdom: Bacteria
Phylum: Firmicutes
Class: Bacilli
Order: Lactobacillales
Family: Streptococcaceae
Genus: *Streptococcus*
Species: *thermophilus*
Strain: ST3

Streptococcus thermophilus, also known as *Streptococcus salivarius* subsp. *thermophilus* (Anon. 1995) is a gram-positive bacterium. It is a facultative anaerobe that tests negative for cytochrome, oxidase, catalase, and is positive for alpha-hemolytic activity. *S. thermophilus* has an optimal growth temperature of 35˚-42˚C. It is classified among the lactic acid bacterium. *S. thermophilus* is frequently found in fermented milk products and is widely used throughout the world in the production of yogurt and cheese. It has a symbiotic relationship with *Lactobacillus delbrueckii* subsp. *bulgaricus*. *S. thermophilus* produces folic acid and formic acid as metabolic by-products that are utilized by *L. delbrueckii* subsp. *bulgaricus* for purine synthesis.

In the early 1900's *S. thermophilus* began to be used routinely in the dairy industry to produce yogurt. *S. thermophilus* uses sugars found in dairy to create lactic acid that produces the gel-like structure characteristic of yogurt (Delcour 2000). It is also used widely by cheese manufacturers worldwide to make reduced fat cheeses that contain similar characteristics to full fat cheeses. The exopolysaccharides made by it and *Lactococcus lactis* subsp. *cremoris* can be used to produce a reduced fat cheddar cheese with a texture and flavor nearly identical to regular cheddar cheeses (Awad 2007).

Antibiotic therapy can allow harmful bacteria such as *Clostridium difficile* to proliferate in the gut of patients and otherwise lead to a pathogenesis that creates Antibiotic Associated Diarrhea (AAD). Yogurt containing live cultures of *S.* thermophilus, *Lactobacillus acidophilus*, and *L. bulgaricus* has been shown to reduce the incidents and duration of AAD in patients on antibiotic therapy (Beniwal 2003).

CBI's *Streptococcus thermophilus* CBT ST3 has been well characterized and is deposited in an internationally recognized culture collection (*EFSA Journal* 2009). *Streptococcus thermophilus* CBT ST3 (KCTC 11870BP) was taxonomically identified based on the 16s rRNA gene sequence, phylogenetic relationship, and fermentation characteristics. The 16s rRNA sequence was deposited in GenBank under the accession number AY675258 (Cell Biotech Co. Ltd. 2018).

Identification

The organism that is the subject of notified substance, originally isolated from the traditional Korean fermented food kimchi, is identified as *Streptococcus thermophilus* and has been uniquely characterized as a distinct strain known as CBT ST3 by means of genomic typing.

Carbohydrate Utilization

Fermentative characteristics of *Streptococcus thermophilus* CBT ST3 were analyzed using API 50 CHL kit. Results are shown in Table 1.

Table 1. Fermentative characteristics of *Streptococcus thermophilus* CBT ST3 obtained with an API 50 CHL Kit (Cell Biotech 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	-
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	Arbitine	-	49	5-Ceto-Gluconate	-

Genomic Classification, Sequence, and Profile

The 16s rRNA gene sequence were aligned and compared with different *Streptococcus thermophilus* CBT ST3 was aligned and compared with those of *S. thermophilus* (ATCC 19258) and some other closely related species of the genus *Streptococcus*. Percent identity and divergence were compared between

Streptococcus species and strains in Table 2. As presented in Table 2, distinctive sequences of 16S rRNA genes were used to generate the phylogenetic tree shown in Figure 1 (Cell Biotech Co. Ltd. 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. *Streptococcus thermophilus* CBT ST3 DNA was compared using RAPD with *S. thermophilus* (ATCC 19258) 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. *Streptococcus thermophilus* CBT ST3 (KCTC 11870BP) and *Streptococcus thermophilus* (ATCC 19258) 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.

A comparison of the genetic profiles between *Streptococcus thermophilus* CBT ST3 (KCTC 11870BP) and *Streptococcus thermophilus* (ATCC 19258) showed that they were, in fact, different at the strain level as shown in Figure 2 (Cell Biotech Co. Ltd. 2018)

Table 2. Percent identity between *Streptococcus thermophilus* CBT ST3 and other closely related species based on 16S rRNA gene sequences.

Percent Identity

Divergence	1	2	3	4	5	6	7	8
1		99.5	99.8	99.5	99.5	98.8	83.4	84.1
2	0.1		99.6	99.6	99.6	99.2	83.5	84.3
3	0.2	0.3		99.5	99.5	98.8	83.6	84.4
4	0.2	0.2	0.5		99.2	98.7	83.4	84.1
5	0.5	0.4	0.5	0.5		99.5	83.6	84.5
6	0.5	0.4	0.7	0.6	0.1		83.3	84.2
7	12.6	12.4	12.3	12.5	12.3	12.2		95.2
8	12.0	11.8	11.7	11.9	11.6	11.6	3.7	

1. *S. thermophilus* (KCTC 11870BP)
2. *S. thermophilus*^{T} (ATCC 19258)
3. *S. thermophilus* T1
4. *S. thermophilus*^{T} (ATCC 19987)
5. *S. vestibularis* F0396
6. *S. vestibularis*^{T} (ATCC 15697)
7. *Enterococcus faecalis*^{T} (JCM 8904)
8. *E. faecium*^{T} (ATCC 19434)

Figure 3. Phylogenetic relationship between *Streptococcus thermophilus* CBT ST3 and its related species based on the 16s rRNA gene sequence analysis (Cell Biotech Co. Ltd. 2018).

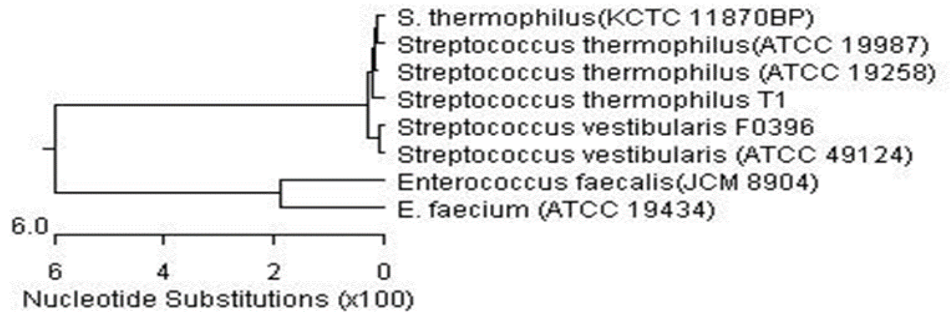
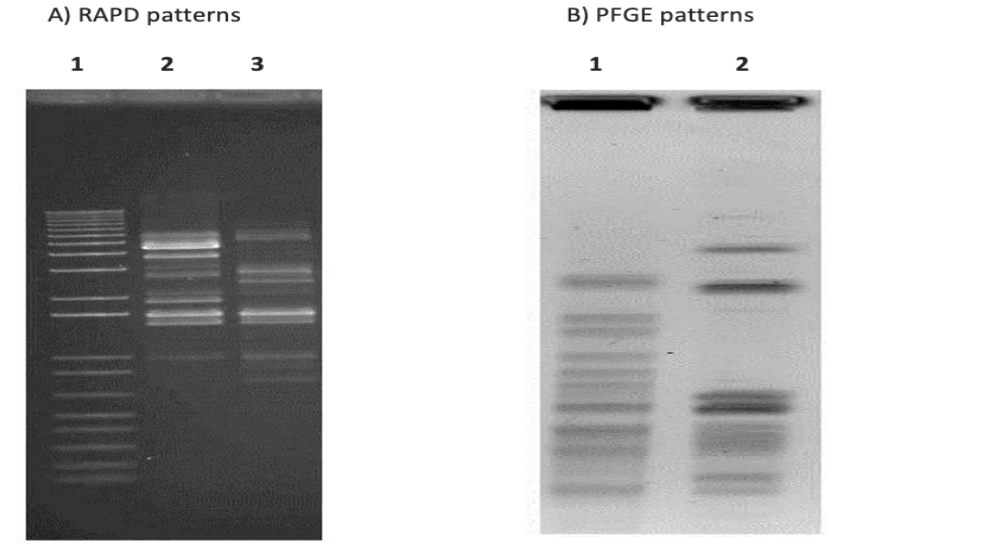


Figure 4. RAPD and PFGE patterns for *Streptococcus thermophilus* CBT ST3 and *S. thermophilus* (ATCC 19258)(Cell Biotech Co. Ltd., 2018).



Lane 1: 1kbp DNA ladder

Lane 2: *S. thermophilus*^{T}(ATCC 19258)
Lane 3: *S. thermophilus* CBT ST3 (KCTC 11870BP)

Lane 1: *S. thermophilus*^{T}(ATCC 19258)

Lane 2: *S. thermophilus* CBT ST3 (KCTC 11870BP)

Manufacturing

Components

All components employed in the manufacture of *Streptococcus thermophilus* CBT ST3 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**
Lactose	[63-42-3]	21 CFR §182.1
Soy Peptone	[73049-73-7]	21 CFR §184.1553
Yeast Extract Powder	[8013-01-1]	21 CFR §184.1983
Skim Milk	[999999-99-4]	21 CFR §131.110
Potassium Phosphate, Dibasic	[7758-11-4]	21 CFR §182.6285
Magnesium Sulfate	[10034-99-8]	21 CFR §184.1443
L-Ascorbic acid	[50-81-7]	21 CFR §182.8013
Monosodium L-Glutamate	[6106-04-3]	21 CFR §182.1
Polysorbate 80	[9005-65-6]	21 CFR §178.3400
Protease	[9001-92-7]	21 CFR §182.1
Coating Ingredient	**CAS No.**	**Reference**
Trehalose	[6138-23-4]	FEMA No. 4600 (FEMA GRAS Publication No. 24)
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
Corn Starch	[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
Potassium Phosphate, Dibasic	[7758-11-4]	21 CFR §182.6285
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 using 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 at approximately every two hours. Once the endpoint is reached, bacterial morphology is inspected by microscopy and the organisms are separated 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.

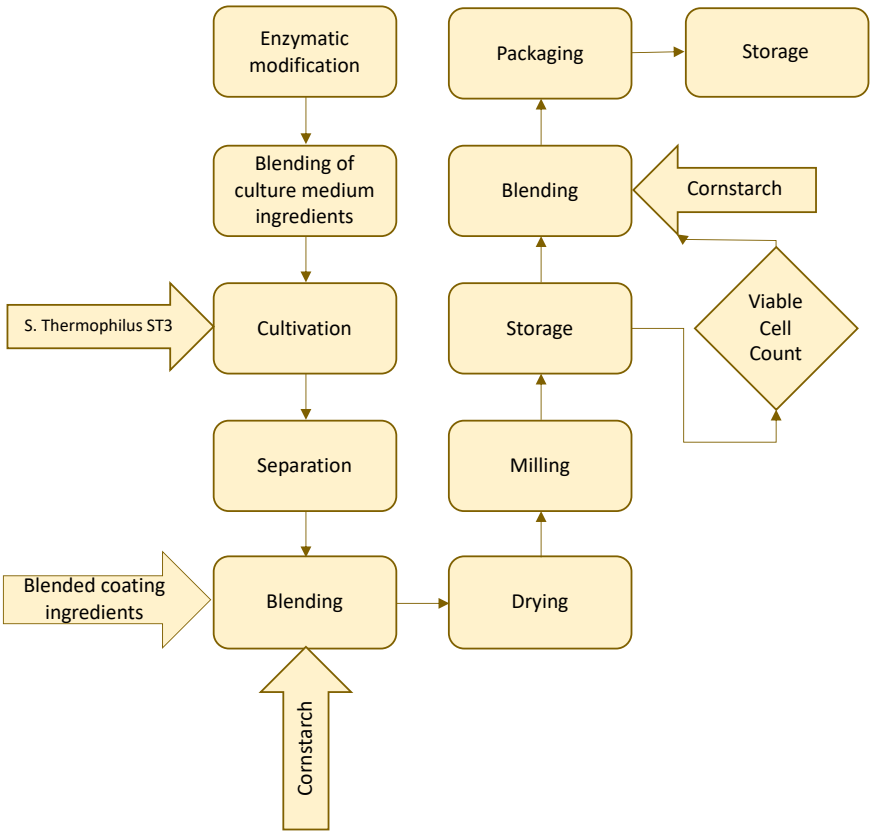
Standardization

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 *Streptococcus thermophilus* CBT ST3 have been established as shown in Table 4. Test results of 3 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. *Streptococcus thermophilus* CBT ST3 food grade specifications and conforming test results.

Parameter	Limits	Method	Batch 40S	Batch 28R	Batch 03S
Appearance	Light brown powder	Visual	Light brown powder	Light brown powder	Light brown powder
Viable Cell Count	$\geq 1.0 \times 10^{11}$ CFU/g	In-house method	Conforms	Conforms	Conforms
Coliforms	Absent in 10 g	In-house method	Conforms	Conforms	Conforms

Stability Data

In order to determine the stability of *Streptococcus thermophilus* CBT ST3, 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 *Streptococcus thermophilus* CBT ST3. 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 *Streptococcus thermophilus* CBT ST3 at 5 ± 3 °C.

Strain	Batch No.	Test	Time Point				
			Initial	3 Months	6 Months	9 Months	12 Months
Streptococcus thermophilus CBT ST3	ST3 82Q	VCC (CFU/g)	6.84×10^{11}	5.84×10^{11}	5.16×10^{11}	4.31×10^{11}	3.77×10^{11}
		Survival Rate (%)	100.0	85.4	80.7	71.5	65.0
	ST3 85Q	VCC (CFU/g)	7.06×10^{11}	6.58×10^{11}	5.19×10^{11}	4.68×10^{11}	4.11×10^{11}
		Survival Rate (%)	100.0	86.6	68.3	61.5	54.1
	ST3 101Q	VCC (CFU/g)	6.88×10^{11}	5.69×10^{11}	4.96×10^{11}	4.42×10^{11}	3.94×10^{11}
		Survival Rate (%)	100.0	82.7	72.1	64.2	57.2
	Average Survival Rate (%)		100.0	84.9	73.7	65.7	58.8

Technical Effects

This substance will be used to provide as a dietary source of *Streptococcus thermophilus* CBT ST3 as a food ingredient to dairy products.

PART 3 – DIETARY EXPOSURE

Intended Use and All Sources in the Diet

The intended use of ***Streptococcus** thermophilus* CBT ST3 as food ingredient for inclusion in dairy products to provide at least 1×10^{11} CFU per serving.

The consensus of 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 of a general content 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 1.0×10^{11} CFU per serving in dairy products would result in intakes in all users of 8.94×10^{10} CFU and 1.85×10^{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 2.05×10^{11} per person per day.

Table 7. EDIs of *Streptococcus thermophilus* CBT ST3 from proposed uses in dairy products across all users based on 2017-2018 NHANES.

Group	% (n)	Dairy intake g/day		Dairy, serving/day		*Streptococcus thermophilus* CBT ST3, 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 *Streptococcus thermophilus* CBT ST3, the suggested three daily servings would result in a cumulative exposure of 2.68×10^{11} CFU per day ($8.94\times10^{10} \times 3$). 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 *Streptococcus thermophilus* CBT ST3. 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 90th 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 *Streptococcus thermophilus* CBT ST3**.**

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 *Streptococcus thermophilus* CBT ST3 is included. The metabolic by-products from *Streptococcus thermophilus* CBT ST3 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. *Streptococcus thermophilus* CBT ST3 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.
- 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.
- 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.
- 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 *Streptococcus thermophilus* CBT ST3 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 fermented with *Lactobacilli* and specifically *Streptococcus thermophilus* 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 same article as Nout 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 1983).

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).

Additionally, in March 2012 a notification was published for Cultured [dairy sources, sugars, wheat, malt, and fruit- and vegetable-based sources] fermented by [*Streptococcus thermophilus*, *Bacillus coagulans*, *Lactobacillus acidophilus*, *Lactobacillus paracasei* subsp *paracasei*, *Lactobacillus plantarum*, *Lactobacillus sakei*, *Lactobacillus bulgaricus* and *Proprionibacterium freudenreichii*, subsp. *Shermanii* or mixtures of these strains]. (GRAS 378)

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 *Streptococcus thermophilus* CBT ST3 as the test strain. Observed MIC values for *Streptococcus thermophilus* CBT ST3 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 8 bacterial susceptibility to antimicrobials of human and veterinary importance published by the European Food Safety Authority (EFSA), as shown in Table 8 and therefore susceptible to AMP, VAN, GEN, KAN, STM, ERM, CLM, TET, and CP.

Table 8. Antibiotic sensitivity of *Streptococcus thermophilus* CBT ST3 (Cellbiotech R&D Center (2018)).

Strain	**Minimum Inhibitory Concentrations (μg/mL) of Antibiotics**								
	AMP	VAN	GEN	KAN	STM	ERM	CLM	TET	CP
***S. thermophilus* CBT ST3**	0.5	< 0.5	< 8	< 32	< 16	< 1	< 1	< 0.5	< 0.5
EFSA Cut-off Value	4	N.R.	32	64	64	1	1	4	4

Current Marketplace Availability of *Streptococcus thermophilus* CBT ST3

While the conclusion of general recognition of safety (GRAS) is based upon scientific procedures, there is a history of use of *Streptococcus thermophilus* CBT ST3 in foreign countries and in multiple food products.

In vitro Toxicity Studies

Hemolysis Assay

The Cell Biotech R&D Center tested *Streptococcus thermophilus* CBT ST3 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 *Streptococcus thermophilus* CBT ST3 were investigated using male and female Sprague-Dawley rats. The pathogenicity of *Streptococcus thermophilus* CBT ST3 was examined after treating the rats with 10^{11} CFU/kg doses or 0.85% saline (control) intragastrically. 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 9. In addition, results indicate no significant differences in net body weight gain (Figure 4), gross pathological findings (Table 10), feed and water consumption (Figure 5), organ weight (Table 11), and body temperature (Table 12) among the different treatment groups and between the treated and control rats.

Table 10. Mortality of male and female rats orally administered 10^{11} CFU/kg *Streptococcus thermophilus* CBT ST3.

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 ST3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	$>10^{11}$ CFU/kg
	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Female	CBT ST3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	$>10^{11}$ 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 *Streptococcus thermophilus* CBT ST3 and control for 14 days. Values are mean ± SE (Cellbiotech R&D Center 2018).

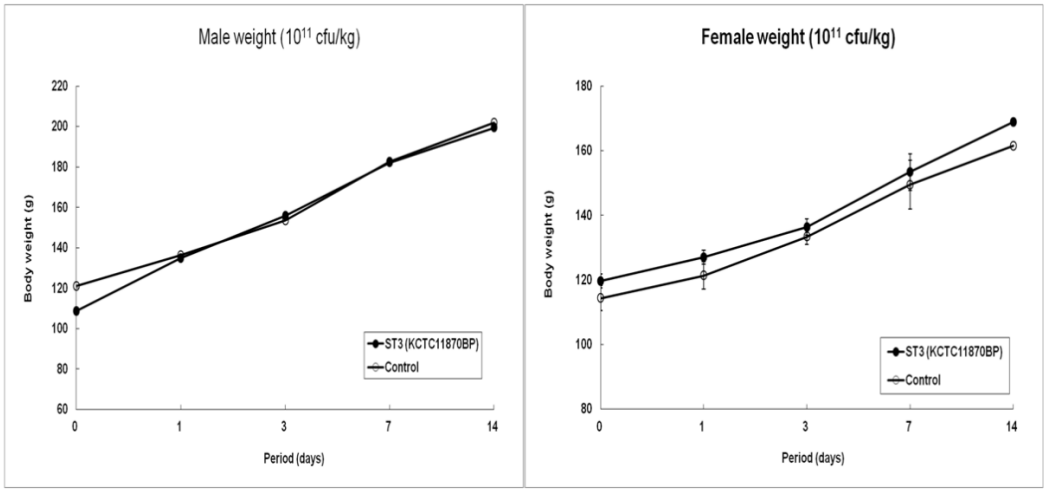


Table 11. Clinical findings of male and female rats orally administered with 10^{11} CFU/kg *Streptococcus thermophilus* CBT ST3 (Cellbiotech R&D Center 2018).

Sex	LAB Strain	Clinical Signs	Hours after treatment				Days after treatment				
			1	2	5	6	1	3	5	7	14
Male	CBT ST3	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 ST3	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 *Streptococcus thermophilus* CBT ST3 and control for 14 days (Cellbiotech R&D Center 2018).

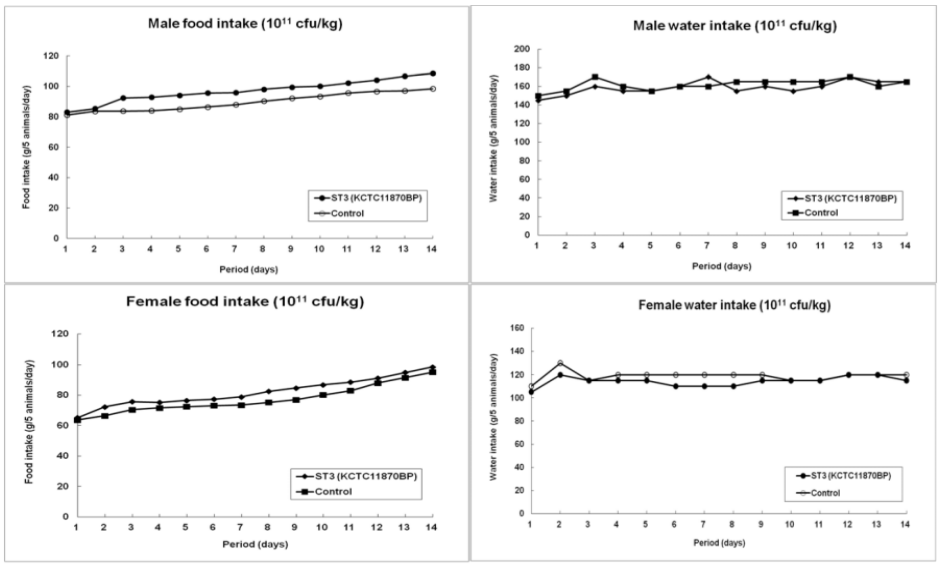


Table 12. Absolute organ weights (g) of male and female orally administered with 10^{11} CFU/kg *Streptococcus thermophilus* CBT ST3 (Cellbiotech R&D Center 2018).

Sex	**Parameters**	**Lab**	**CBT ST3**	**Control**
		No. of Animals	5	5
Male	Body weight (g)		199.41 ± 7.72	201.83 ± 9.46
	Liver (g)		7.73 ± 0.70	8.32 ± 0.55
	Spleen (g)		0.72 ± 0.07	0.62 ± 0.07
	Kidney (g)	Right	0.71 ± 0.05	0.61 ± 0.05
		Left	0.35 ± 0.04	0.34 ± 0.07
Female	Body weight (g)		168.83 ± 4.05	161.49 ± 8.01
	Liver (g)		6.55 ± 0.94	5.92 ± 0.75
	Spleen (g)		0.56 ± 0.04	0.56 ± 0.05
	Kidney (g)	Right	0.54 ± 0.02	0.55 ± 0.03
		Left	0.30 ± 0.07	0.37 ± 0.07

Table 13. Body temperature changes in male and female orally treated with 10^{11} CFU/kg *Streptococcus thermophilus* CBT ST3 (Cellbiotech R&D Center 2018).

Day	No.	Male body temperature		Female body temperature	
		CBT ST3 (˚C)	Control (˚C)	CBT ST3 (˚C)	Control (˚C)
Pre-treatment	Ave	34.28	34.52	35.86	35.16
	SEM	0.67	0.25	0.29	0.32
Day 1	Ave	34.66	34.94	35.86	34.98
	SEM	0.55	0.64	0.85	.38
Day 2	Ave	34.98	34.80	36.16	35.60
	SEM	0.19	0.32	0.47	0.62
Day 3	Ave	34.78	34.70	35.38	34.50
	SEM	0.81	0.45	0.45	0.63
Day 4	Ave	34.96	34.88	34.80	35.06
	SEM	0.50	0.44	0.45	0.27

Human Studies

Study 1

Lee (2014) conducted a randomized, double-blind, placebo-controlled clinical study on the effects of co-administration of a microbial mixture, including *S. thermophilus*, with herbal medicine on obesity, metabolic endotoxemia and dybiosis. Fifty female patients, ages 19-65 years, were enrolled in the study and given either the microbial mixture + Bofutsushosan (an Asian herbal medicine comprised of 18 components) or a placebo and the Bofutsushosan. The microbial mixture capsule contained five billion viable cells. All fifty patients tolerated the microbial mixture with no reported negative issues.

Study 2

Kwak (2014) studied the effects of short term microbial therapy with six bacterial species, including *S. thermophilus*, 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 3

Forty participants aged 60 years or older were randomly assigned to take one capsule containing six bacterial strains (2.5×10^8 viable cells). Following a two-week period the study participants were evaluated. While there were no overall changes in body mass index, weight, or overall health, the study demonstrated that multi-organism mixture have a positive effect in alleviating constipation, and the study participants tolerated the microorganisms well. (Yeun 2014).

Study 4

Forty-nine patients suffering from Irritable Bowel Syndrome (IBS) were enrolled in a randomized, double-blind, placebo-controlled study to determine the effect of a multispecies microbial therapy on IBS symptoms and gut microbiota. One capsule twice daily containing a total of 5×10^9 viable microbial cell strains, including *S. thermophilus* (KCTC 11870BP), was given to twenty-five study participants for 4 weeks. The treatment was effective in symptom relief and no adverse reactions from the microbial therapy were reported (Yoon 2014).

Study 5

Yoon (2015) conducted a study on the effect of administering a multispecies microbiological mixture with six organisms, including *Streptococcus thermophilus* CBT ST3, on the changes in fecal microbiota and symptoms of irritable bowel syndrome. The study used 81 volunteers, and studied the effects of capsules containing 5×10^9 viable microbiological cells taken over a period of four weeks.

The study concluded that while the overall composition of gut microflora did not significantly change, the concentration of most of the microbial strains increased in the intestinal flaura group, and adequate irritable bowel symptom relief was higher in this group than those on placebo. None of the patients in the microbiological study arm reported adverse effects.

Study 6

Han (2016) conducted a study using 50 patients with diarrhea predominant irritable bowel syndrome to determine the effects of an uncoated vs. dual coated seven-species, including *S. thermophilus*, capsule containing 5×10^9 viable bacterial cells taken as two capsules twice a day for 4 weeks.

There was an absence of reported adverse effects from the 46 patients who completed this study.

CONCLUSION

The scientific data, information, methods, and principles described in this notification provide the basis for conclusion that *Bifidobacterium breve* CBT BR3 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 breve* 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 *Streptococcus thermophilus* 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 *Streptococcus thermophilus*, other species of *Lactobacillus*, as well as members of other genera of lactic acid-producing bacteria, intended for inclusion as food ingredients. The applicable GRAS notices, referenced are within Part 6 of this notice, incorporate myriad studies demonstrating the safety of ingestion of substances closely related to *Streptococcus thermophilus* CBT ST3.

Streptococcus thermophilus CBT ST3 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. *Streptococcus thermophilus* CBT ST3's potential for antibiotic resistance was tested in accordance with EFSA guidelines where *Lactobacillus* strains are intrinsically resistant to vancomycin.

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 *Streptococcus thermophilus* CBT ST3 at the 90th percentile of high-level consumers of products of the intended inclusion food is 5.55×10^{11} CFU per day of *Streptococcus thermophilus* CBT ST3. The 90th 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.

SUPPORTING DATA AND INFORMATION

Generally Unavailable

Cell Biotech R&D Center (2018) Identification. Molecular Typing and Safety Assessment of *Streptococcus thermophilus* CBT ST3 KCTC11870BP

Generally Available

Anon (1995) Validation of the Publication of New Names and New Combinations Previously Effectively Published Outside the IJSB: List No. 54. *International Journal of Systematic Bacteriology*. 45(3):619-620.
Awad S, Hassan AN, Muthukumarappan K (2005) Application of Exopolysaccharide-Producing Cultures in Reduced-Fat Cheddar Cheese *Journal of Dairy Science* 88:4204-4213.
Beniwal RS, Arena VC, Thomas L, Narla S, Imperiale TF, Chaudhry RA, Ahmad UA (2003) A Randomized Trial of Yogurt for Prevention of Antibiotic-Associated Diarrhea *Dig Dis Sci* 48:2077-2082.
Delcour J, Ferain T, Hols P (2000) Advances in the genetics of thermophilic lactic acid bacteria *Food Biotechnology* 11:497-504.
Han K, Wang J, Seo J, Kim H (2016) Efficacy of double-coated probiotics for irritable bowel syndrome: A randomized double-blind controlled study *J Gastroenterology* 52:432-443.
Hesseltine CW (1983) Future of Fermented Foods *Nutr Rev* 41(10):293-301.
Hill C, Guarner F, Ried G, Gibson G, Merenstein D, Pot B, Morelli L, Berni Canani R, Flint H, Salminen S, Calder P, Sanders M (2014) The International Scientific Association for Probiotics and Prebiotics Consensus Statement on the Scope and Appropriate Use of the Term Probiotic. *Nat Rev Gastroenterol Hepatol* 11:506-514
Kwak D, Jun D, Seo J, Chung W, Park S, Lee K, Khalid-Saeed W, Lee H, Lee O, Yoon B, Choi H (2014) Short term probiotic therapy alleviates small intestinal bacterial overgrowth, but does not improve intestinal impermeability in chronic liver disease. *European Journal of Gastroenterology and Hepatology* 26:1353-1359.
Lee SJ, Bose S, Seo J, Chung W, Lim C, Kim H (2014) The effects of co-administration of probiotics with herbal medicine on obesity, metabolic endotoxemia and dysbiosis: A randomized double-blind controlled clinical trial *Clinical Nutrition* 33:973-981.
National Dairy Council (2010) NHANES Average Daily Servings of Dairy Foods *National Dairy Council*
Nout MJR (1992) *Applications of Biotechnology to Fermented Foods: Report of an Ad Hoc Panel of the Board on Science and Technology for International Development* Washington DC: National Academies Press
Scientific Opinion on the substantiation of health claims related to non-characterized microorganisms pursuant to Article 13(1) of Regulation *EFSA Journal* (2009) 7:1247.

Steinkraus KH (1992). Lactic Acid Fermentations. Applications of Biotechnology to Traditional Fermented Foods: Report of an Ad Hoc Panel of the Board on Science and Technology for International Development. Washington, DC: National Academies Press.

World Health Organization, Food and Agriculture Organization of the United Nations (2011) Milk and Milk Products, Second Edition *Codex Alimentarius* http://www.fao.org/docrep/015/i2085e/i2085e00.pdf.

Yeun Y, Lee J (2014) Effect of a Double-coated probiotic formulation on Functional Constipation in the Elderly: a Randomized, Double Blind, Controlled Study. *Arch Pharm Res* 38:1345-1350.

Yoon J, Sohn W, Lee O, Lee S, Lee K, Jun D, Lee H, Yoon B, Choi H, Chung W, Seo J (2014) Effect of multispecies probiotics on irritable bowel syndrome: A randomized, double-blind, placebo-controlled trial *Journal of Gastroenterology and Hepatology* 29:52-59.

Yoon H, Park Y, Lee D, Seo J, Shin C, Kim N (2015) Effect of administering a multispecies probiotic mixture on the changes in fecal microflora microbiota and symptoms of irritable bowel syndrome: A randomized, double-blind, placebo-controlled trial *J Clin Biochem Nutr* 57:129-134.

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Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Determination of Cell Biotech Co. Ltd. *Streptococcus thermophilus* CBT ST3

February 25, 2021

Cell Biotech Co. Ltd. intends to market ***Streptococcus thermophilus*** **CBT ST3** as an ingredient in dairy products. ***Streptococcus thermophilus*** **CBT ST3** 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 ***Streptococcus thermophilus*** **CBT ST3** 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 ***Streptococcus thermophilus*** **CBT ST3** 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. ***Streptococcus thermophilus*** **CBT ST3**, 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. ***Streptococcus thermophilus*** **CBT ST3** 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 ***Streptococcus thermophilus* CBT ST3** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature:___  Date:_22 March 2021_

Steven Dentali, Ph.D.
Dentali Botanical Sciences

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The individual endorsement pages follow hereunder.

ENDORSEMENT BY JEANNE MOLDENHAUER, M. SC.

I, Jeanne Moldenhauer, hereby affirm that ***Streptococcus thermophilus* CBT ST3** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature: [redacted] Date: 6 APR 21

Jeanne Moldenhauer, M. Sc.
Excellent Pharma Consulting

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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
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The individual endorsement pages follow hereunder.

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

I, Mary Mulry, hereby affirm that ***Streptococcus thermophilus* CBT ST3** 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

Form Approved: OMB No. 0910-0342; Expiration Date: 07/31/2022
(See last page for OMB Statement)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
001087	May 12, 2022
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	Position or Title
Myung-jun Chung	CEO

Organization *(if applicable)*: Cell Biotech Co. Ltd.

Mailing Address *(number and street)*: 50 Agibong-ro, 409 Beon-gil

City	State or Province	Zip Code/Postal Code	Country
Wolgot-myeon, Gimpo	Gyeonggi-do		Korea, Republic of

Telephone Number	Fax Number	E-Mail Address
+82 31 987 6205		ceo@cellbiotech.com

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

Name of Contact Person	Position or Title
Jim Lassiter	COO

Organization *(if applicable)*: REJIMUS, INC.

Mailing Address *(number and street)*: 600 W Santa Ana Blvd Suite 1100

City	State or Province	Zip Code/Postal Code	Country
Santa Ana	California	92701	United States of America

Telephone Number	Fax Number	E-Mail Address
9492290072		jim@rejimus.com

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

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

Streptococcus thermophilus CBT ST3

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 33

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 Streptococcus thermophilus CBT ST3 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 Streptococcus thermophilus CBT ST3
(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 12:23:52 -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
	GRASNotice_II932.2-CBI.2.2_Streptococcus_thermophilus_CBT_ST3_2022-05-09.pdf	Administrative
	Cell_Biotech_Co_Ltd_Streptococcus_thermophilus_CBT_ST3_2018.pdf	GRAS Notice
	Yoon_2015.pdf	GRAS Notice
	Yoon_2014.pdf	GRAS Notice
	Yeun_2014.pdf	GRAS Notice
	WHO_2011.pdf	GRAS Notice
	Steinkraus_1992.pdf	GRAS Notice
	EFSA_2009.pdf	GRAS Notice

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Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Nout_1992.pdf	GRAS Notice
	National_Dairy_Council_NHANES_2010.pdf	GRAS Notice
	Lee_2014.pdf	GRAS Notice
	Kwak_2014.pdf	GRAS Notice
	Hill_2014.pdf	GRAS Notice
	Hesseltine_1981.pdf	GRAS Notice
	Han_2016.pdf	GRAS Notice
	Delcour_2000.pdf	GRAS Notice
	Beniwal_2003.pdf	GRAS Notice

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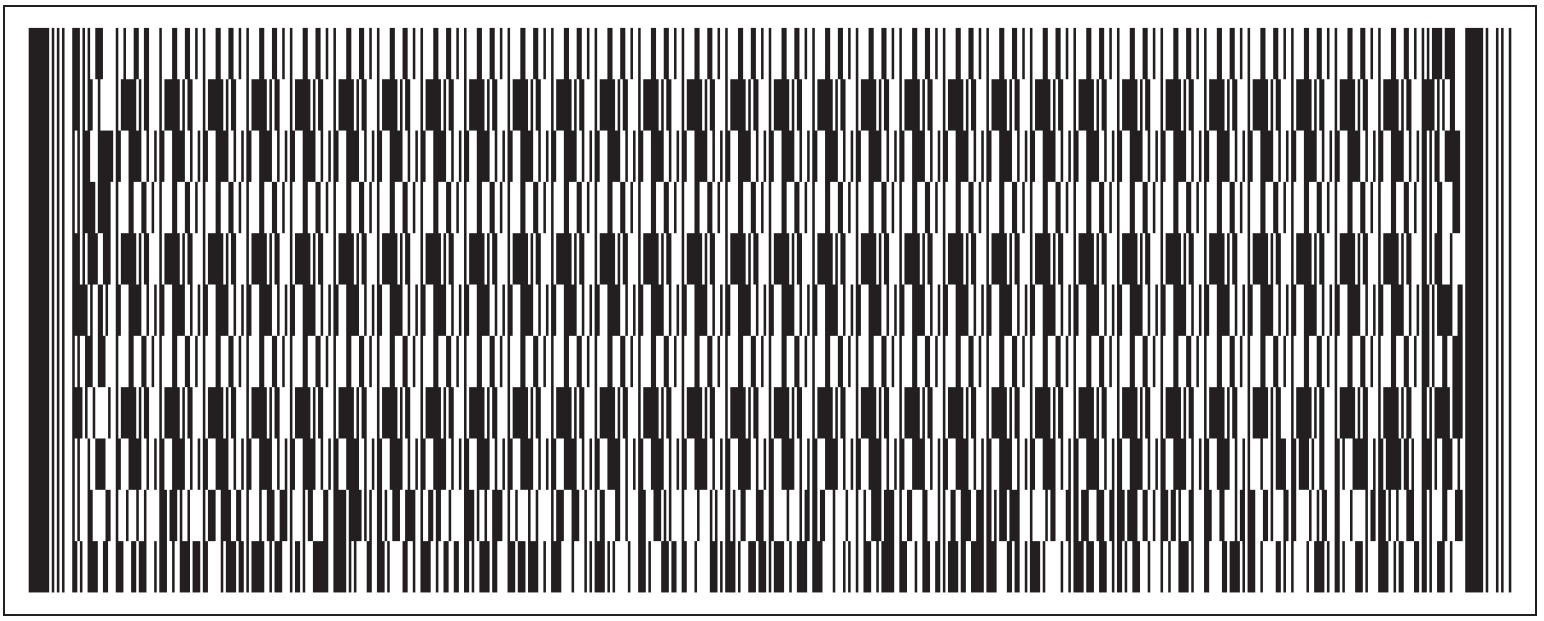
Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Awad_2005.pdf	GRAS Notice
	Anonymous_1995.pdf	GRAS Notice



Viebrock, Lauren

From: Joel Villareal <joel@rejimus.com>
Sent: Friday, May 26, 2023 8:25 PM
To: Viebrock, Lauren
Cc: Jim Lassiter; Kenneth Cairns; Brandon M. Griffin; Kent Phan; Livia Consedine
Subject: [EXTERNAL] FW: GRN 001087 Questions
Attachments: II932.2-CBI.7.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr. VieBrock,

In response to the document "2023_05_12 Questions GRN 1087" for the request for more information for GRN 001087 (*Streptococcus thermophilus* CBT ST3) and in accordance with the below correspondence, attached you will find responses to the questions/comments (II932.2-CBI.7) with the respective attachments included therein.

Please note that there are still three (3) questions that will require additional time to address additional questions from the Agency regarding GRNs 1078-1082 as a result of the meeting with FDA on 5/10/23. The responses to the additional questions for GRN 1078-1082 would likely be identical to the questions raised for GRN 1087. Currently, we are awaiting for these questions from the Agency.

The responses to the remaining questions and any additional documents will be promptly provided to the Agency for review once we received the additional questions. Please let us know if this suffices for this response.

Thank you for sending your feedback and if there any other questions/concerns, please let us know.

Kind Regards

Joel Villareal | Regulatory Manager
Quality Development Services
joel@rejimus.com

REJIMUS

REJIMUS INC.
600 W. Santa Ana Blvd. Suite 1100 & 1110
Santa Ana, CA 92701
Main: 949.485.2112 | Fax: 949.200.8546
www.rejimus.com

From: Joel Villareal <joel@rejimus.com>
Date: Thursday, May 18, 2023 at 10:10 AM
To: Lauren.Viebrock@fda.hhs.gov <Lauren.Viebrock@fda.hhs.gov>
Cc: Jim Lassiter <jim@rejimus.com>, Brandon M. Griffin <brandon@rejimus.com>, Kenneth Cairns <kenneth@rejimus.com>, Kent Phan <kent@rejimus.com>, Livia Consedine <livia@rejimus.com>
Subject: FW: GRN 001087 Questions

Dear Dr. VieBrock,

Thank you for your email with the questions regarding GRN 001087, on behalf of our client Cell Biotech Co. Ltd., for *Streptococcus thermophilus* CBT ST3. We are actively working on the responses and intend to provide a response to the question/comments within 10 business days from when the questions/comments were issued on 5/12/23. Therefore, the response is expected to be provided by 5/26/23.

In the meantime, if there are any other questions, please let us know.

Kind Regards.

Joel Villareal | Regulatory Manager
Quality Development Services
joel@rejimus.com

REJIMUS INC.
600 W. Santa Ana Blvd. Suite 1100 & 1110
Santa Ana, CA 92701
Main: 949.485.2112 | Fax: 949.200.8546
www.rejimus.com

From: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>
Date: Friday, May 12, 2023 at 8:00 PM
To: Jim Lassiter <jim@rejimus.com>
Subject: GRN 001087 Questions

Dear Mr. Lassiter,

During our review of GRAS Notice No. 001087, we noted questions that need to be addressed. Please find the questions attached to this email.

We respectfully request a response within **10 business days**. If you are unable to complete the response within that time frame, please contact me to discuss further options.

If you have questions or need further clarification, please feel free to contact me. Thank you in advance for your attention to our comments.

Regards,
Lauren

Lauren VieBrock, Ph.D.
Regulatory Review Scientist/Microbiology Reviewer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Tel: 301-796-7454
lauren.viebrock@fda.hhs.gov

REJIMUS
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5/26/2023

Lauren VieBrock, PhD
Regulatory Review Scientist/Microbiology Reviewer
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
United States Food and Drug Administration
lauren.viebrock@fda.hhs.gov

RE: First Response to FDA Questions/Comments Regarding GRN 001087
II932.2-CBI.7

Dear Dr. VieBrock,

REJIMUS, INC. received your email dated 5/12/23 regarding additional FDA questions/comments to GRN 001087. This is a first response to address the majority of the questions presented. Additional questions from FDA related to GRNs 001078 – 001082 are intended to be provided by the Agency as a result of the meeting held between FDA and REJIMUS on 5/10/23. We have not yet received these questions and the answers to these are likely identical to questions raised concerning GRN 001087. Unfortunately, a follow-up response will be necessary and is expected to be promptly provided to you once we received those additional questions surrounding the intended maximum use level as well as the target level over the shelf life of food.

Should you have any questions or concerns with this additional information or have additional requests based on the information provided so far, please let us know, and we will be sure to address that promptly for the Agency.

Sincerely,

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

TABLE OF CONTENTS

FDA QUESTIONS/COMMENTS REGARDING GRN 001087

Question 1

Please confirm that *Streptococcus thermophilus* strain KCTC 11870BP is non-pathogenic and non-toxigenic. Please provide generally available and generally accepted data and information to support these statements.

Response

Based on the results of the toxicity studies, there were no signs of the mortality or adverse effects of the animals at levels of 1 x 10^{11} CFU/kg. In addition, according to the Pathogenicity Island Database (http://www.paidb.re.kr/about_paidb.php?m=h), there are no pathogenicity islands (PAI) observed in the genome of this strain. Therefore, it can be affirmed that Streptococcus thermophilus strain KCTC 11870BP is non-pathogenic and non-toxigenic.

Question 2

In Table 8, the EFSA cutoff value for vancomycin (page 19) states "nr." Please define this abbreviation.

Response

The notation "nr" in Table 8 refers to "not required" according to EFSA.

Question 3

Please confirm that the fermentation stage is monitored for contamination and if observed there are protocols in place to address it.

Response

Prior to inoculation of the organism into the prepared sterilized medium, the stock of the strain is checked for purity. As a process inspection in the cultivation of the organism, a bacterial morphology under microscopy is performed.

The fermentation process is conducted in a contained, sterile environment. The broth storage tank and its components used in the fermentation process are steam sterilized prior to use. During the fermentation process, the bottom valve of the broth storage tank is opened, and the cultivated broth is transferred to a separator that is cleaned via Clean-in-place (CIP) procedures.

The contamination control program utilized during the manufacturing process includes the testing for contamination of stock organism(s), and all equipment used in the fermentation as well as the manufacturing processes, which are conducted through controlled cleaning programs. The finished ingredient testing is performed to verify purity and potency in accordance with the approved specification.

Question 4

Please state whether any of the raw materials used in the manufacturing process are major allergens or are derived from major allergens and are expected to be present in the final ingredient.

Response

Aside from soy peptone and skim milk used only in the fermentation medium, the product that is the subject of this GRAS determination does not have any other raw materials used in the manufacturing process that represent any of the major food allergens required to be listed in accordance with the Food Allergen Labeling and Consumer Protection Act, identified as milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans and sesame. These major allergens are not expected to be present in the final ingredient.

Question 5

Please define "coating ingredient" as stated in the manufacturing process.

Response

The inclusion of these materials occurs toward the end of the fermentation process. The intent of the inclusion is to encapsulate the microorganism comprising the finished ingredient for delivery in its dried and final form.

Question 6

In Figure 3, the flow chart for the manufacturing process includes "enzymatic modification", however, this step is not described in the notice. Please provide additional information (i.e., identity, source, intended use, inactivation and/or removal) on enzyme.

Response

a. *The enzyme used in the enzymatic modification step is a protease (Alcalase) with the enzyme commission number 3.4.21.62.*

b. *The intended use of the enzyme during the manufacturing process is for protein hydrolysis.*

c. *The source of the enzyme is from the microorganism, Bacillus licheniformis.*

d. *The microorganism, Bacillus licheniformis, where the enzyme is produced is a non-pathogenic strain and is not genetically engineered. In addition, protease enzymes using the non-pathogenic strain of Bacillus licheniformis are considered GRAS according to 21 CFR§184.1027 "Mixed carbohydrase and protease enzyme product."*

e. *After fermentation is complete, all components of the fermentation media, including the enzyme, are removed from the strain through the separator.*

Question 7

Table 3 includes a list of raw materials used during the manufacturing process (page 11). The CAS numbers provided for yeast extract powder, skim milk, monobasic potassium phosphate, corn starch, and sodium carboxymethyl cellulose do not appear to correspond to the correct substances. Please provide the correct CAS numbers for these substances. In addition, we note that the correct names for the ingredients designated by CAS numbers 6106-04-3, and 10034-99-8 are monosodium L-glutamate monohydrate and magnesium sulfate heptahydrate, respectively. Please confirm the names of these ingredients.

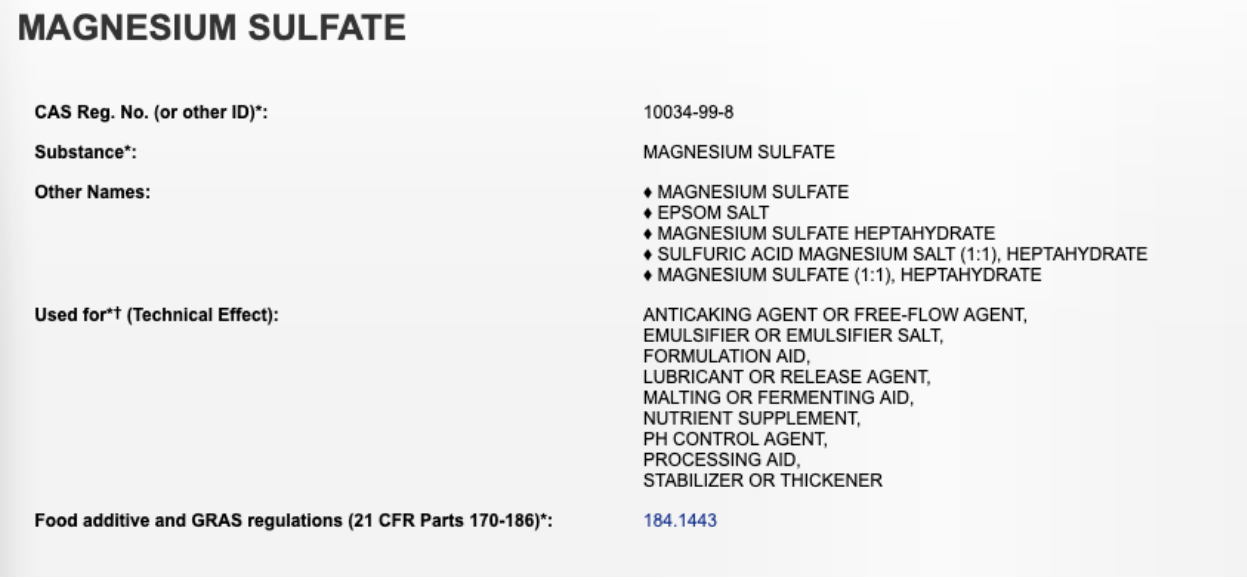
Response

The CAS numbers for the following raw materials have been corrected.

Ingredient	CAS No.
Yeast Extract Powder	[8013-01-2]
Corn Starch	[977050-51-3]
Skim Milk	[999999-99-4]
Monobasic potassium phosphate	[7778-77-0]
Sodium carboxymethyl cellulose	[9004-32-4]

The CAS number has been corrected for Monosodium L-glutamate as CAS No. 142-47-2.

According to the U.S. Food and Drug Administration Substances Added to Food database (screenshot below), Magnesium sulfate has an identified CAS Number of 10034-99-8 as shown in the screenshot below. It is acknowledged that Magnesium sulfate heptahydrate does have the same CAS number.



MAGNESIUM SULFATE

CAS Reg. No. (or other ID)*:	10034-99-8
Substance*:	MAGNESIUM SULFATE
Other Names:	♦ MAGNESIUM SULFATE ♦ EPSOM SALT ♦ MAGNESIUM SULFATE HEPTAHYDRATE ♦ SULFURIC ACID MAGNESIUM SALT (1:1), HEPTAHYDRATE ♦ MAGNESIUM SULFATE (1:1), HEPTAHYDRATE
Used for*† (Technical Effect):	ANTICAKING AGENT OR FREE-FLOW AGENT, EMULSIFIER OR EMULSIFIER SALT, FORMULATION AID, LUBRICANT OR RELEASE AGENT, MALTING OR FERMENTING AID, NUTRIENT SUPPLEMENT, PH CONTROL AGENT, PROCESSING AID, STABILIZER OR THICKENER
Food additive and GRAS regulations (21 CFR Parts 170-186)*:	184.1443

Question 8

Table 4 does not include specifications for heavy metals (page 13). We note that we typically request that, at a minimum, a limit for lead be included in the specifications for fermentation-derived ingredients. Please include a limit for lead in the specifications for *S. thermophilus* strain KCTC 11870BP and provide analytical results from a minimum of three non-consecutive batches to demonstrate that the ingredient can be manufactured that to meet this specification limit. Please note that the limit for lead should be as low as possible and be reflective of the results of the batch analyses. In addition, please specify the analytical method that is used to test for lead.

Response

Heavy metals are being performed as identified in the Certificate of Analysis. These include results for Lead, Arsenic, Cadmium, and Mercury in three non-consecutive batches. The limit for Lead is $\leq$ 1.0 mg/kg. Attached is the Certificate of Analysis of the three non-consecutive batches. The analytical method used for testing for lead is through ICP performed under Korean FDA Food Code, VIII. Food Analytical Method, 9.1 Heavy Metal.

Attachment: II932.2-CBI.7-A1

Question 9

Please state whether all analytical methods used to analyze the batches for conformance with the stated specifications (including lead) have been validated for that particular purpose.

Response

All analytical methods used in the testing of the batches (including lead) are tested based on the compendial methods and are, therefore, validated for their respective purpose.

Question 10

On page 14, the notifier states *S. thermophilus* strain KCTC 11870BP is intended to be added to dairy products at concentrations needed to provide at least 1 x 10^{11} CFU per serving. According to the stability study (Table 5, page 14), the survival rate decreases ~40% during 12-months of storage. Considering the loss during storage, please provide narrative how the notifier ensures that 1 × 10^{11} CFU per serving remains viable over the product shelf life.

Response

In Progress

Additional questions related to GRN 1078 – 1082 will be provided from the Agency as a result of the FDA meeting on 5/10/23 regarding the clarification of the intended maximum use level as well as the target level over the shelf life of food. These additional questions will be applicable to this response and will be addressed in the follow-up response.

Question 11

Please provide food subcategories included in the estimation of consumption of "dairy products" in Table 7 (page 16). In addition, please specify a serving size for each food subcategory and provide the reference that was used as the basis for determining the serving size.

Response

In Progress

Additional questions related to GRN 1078 – 1082 will be provided from the Agency as a result of the FDA meeting on 5/10/23 regarding the clarification of the intended maximum use level as well as the target level over the shelf life of food. These additional questions will be applicable to this response and will be addressed in the follow-up response.

Question 12

Please clarify what population is represented by "all users" in the dietary exposure estimate (Table 7, page 16). If the dietary exposure estimate is not for the U.S. population aged 2 years and older, please provide mean and 90th percentile eaters-only dietary exposure estimates for U.S. population aged 2 years and older.

Response

In Progress

Additional questions related to GRN 1078 – 1082 will be provided from the Agency as a result of the FDA meeting on 5/10/23 regarding the clarification of the intended maximum use level as well as the target level over the shelf life of food. These additional questions will be applicable to this response and will be addressed in the follow-up response.

Question 13

On page 16, the notifier states, "three daily servings would result in a cumulative exposure of 2.68×10^{11} CFU per day ($8.94 \times 10^{10} \times 3$)". Further, the notifier states, "the recommended levels of the cumulative exposure of 2.68×10^{11} CFU per day and the cumulative exposure at an estimated 90th percentile of 5.55×10^{11} CFU per day". Please note that the cumulative dietary exposure should consider background sources, and all current and proposed uses of *S. thermophilus* strain KCTC 11870BP. For the administrative record, please confirm that the term "cumulative" was incorrectly used in the statements mentioned above.

Further, on page 16 the notifier states, "The estimated 90th percentile of consumers of dairy products at this level of recommended consumption adjusted for the findings of the per capita data". We consider that the data in Table 7 (page 16) represents estimates for "users" (eaters) only, i.e., individuals consuming the proposed dairy products at least once during the survey period. Please note that "per capita" estimates would include eaters and non-eaters. For the administrative record, please confirm that the estimates in Table 7 are for the eaters-only population and explain what is meant by "the findings of the per capita data".

Response

Currently, Streptococcus thermophilus strain KCTC 11870BP is considered a novel ingredient in food and there are no current uses of this strain. As dairy products are the only proposed food, the dietary exposure of the ingredient is only based on the dairy products. Therefore, the term "cumulative" was inappropriately used.

The estimates used in the Table 7 is confirmed as eaters-only population. Therefore, the appropriate term was "findings from the eaters-only population" and not "findings of the per capita data."

Conclusion

We sincerely appreciate this opportunity to clarify the additional questions submitted so far as part of this review and we look forward to a positive assessment of these responses and the notification itself. Should the agency have any additional questions or requests on the above responses or the prior responses, please let us know at your earliest convenience and we will do everything we can to address those promptly. We look forward to completing the follow up response to the Agency addressing the remaining items that are identified herein as "in progress" promptly.

Attachments

II932.2-CBI.7-A1	Certificate of Analysis

Attachment
II932.2-CBI.7-A1

CELL BIOTECH

Certificate of Analysis

Product Name : ***Streptococcus thermophilus***

Place of Production: KOREA

Batch(Lot) No. : ST3 82Q

Issued Date: 10 Oct. 2016

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 06 Oct. 2016

Exp. Date: 05 Oct. 2017

Manufacturing origin country: KOREA
Shipping Origin country: KOREA

ITEMS	SPECIFICATION	RESULTS
Appearance	Light brown powder	Light brown powder
Initial viable cell	$\geq 1.0 \times 10^{11}$ CFU/g	Passes test
Coliforms	Absent	Passes test
Yeast & Mold	≤ 10 CFU/g	Passes test
E. coli	Absent in 1g	Passes test
S. aureus	Absent in 1g	Passes test
Salmonella	Absent in 25g	Passes test
L. monocytogene	Absent in 10g	Passes test
Lead (Pb)	≤ 1.0 mg/kg	Passes test
Cadmium (Cd)	≤ 0.3 mg/kg	Passes test
Mercury (Hg)	≤ 0.1 mg/kg	Passes test
Arsenic (As)	≤ 0.1 mg/kg	Passes test

Remark : *Be kept in an airtight container and stored at a temperature not exceeding 5 ℃.*

Director, Head of Quality Management Division

CELL BIOTECH

Certificate of Analysis

Product Name : ***Streptococcus thermophilus***

Place of Production: KOREA

Batch(Lot) No. : ST3 85Q

Issued Date: 12 Oct. 2016

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 08 Oct. 2016

Exp. Date: 07 Oct. 2017

Manufacturing origin country: KOREA
Shipping Origin country: KOREA

ITEMS	SPECIFICATION	RESULTS
Appearance	Light brown powder	Light brown powder
Initial viable cell	$\geq 1.0 \times 10^{11}$ CFU/g	Passes test
Coliforms	Absent	Passes test
Yeast & Mold	≤ 10 CFU/g	Passes test
E. coli	Absent in 1g	Passes test
S. aureus	Absent in 1g	Passes test
Salmonella	Absent in 25g	Passes test
L. monocytogene	Absent in 10g	Passes test
Lead (Pb)	≤ 1.0 mg/kg	Passes test
Cadmium (Cd)	≤ 0.3 mg/kg	Passes test
Mercury (Hg)	≤ 0.1 mg/kg	Passes test
Arsenic (As)	≤ 0.1 mg/kg	Passes test

Remark : *Be kept in an airtight container and stored at a temperature not exceeding 5 ℃.*

Director, Head of Quality Management Division

CELL BIOTECH

Certificate of Analysis

Product Name : ***Streptococcus thermophilus***

Place of Production: KOREA

Batch(Lot) No. : ST3 101Q

Issued Date: 15 Dec. 2016

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 11 Dec. 2016

Exp. Date: 10 Dec. 2017

Manufacturing origin country: KOREA
Shipping Origin country: KOREA

ITEMS	SPECIFICATION	RESULTS
Appearance	Light brown powder	Light brown powder
Initial viable cell	$\geq 1.0 \times 10^{11}$ CFU/g	Passes test
Coliforms	Absent	Passes test
Yeast & Mold	≤ 10 CFU/g	Passes test
E. coli	Absent in 1g	Passes test
S. aureus	Absent in 1g	Passes test
Salmonella	Absent in 25g	Passes test
L. monocytogene	Absent in 10g	Passes test
Lead (Pb)	≤ 1.0 mg/kg	Passes test
Cadmium (Cd)	≤ 0.3 mg/kg	Passes test
Mercury (Hg)	≤ 0.1 mg/kg	Passes test
Arsenic (As)	≤ 0.1 mg/kg	Passes test

Remark : *Be kept in an airtight container and stored at a temperature not exceeding 5 ℃.*

Director, Head of Quality Management Division

Viebrock, Lauren

From: Joel Villareal <joel@rejimus.com>
Sent: Friday, June 23, 2023 6:48 PM
To: Viebrock, Lauren
Cc: Jim Lassiter; Kenneth Cairns; Brandon M. Griffin; Kent Phan; Livia Consedine
Subject: [EXTERNAL] Re: GRN 001087 Questions
Attachments: II932.2-CBI.8.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr. VieBrock,

In response to the document "2023_05_12 Questions GRN 1087" for the request for more information for GRN 001087 (*Streptococcus thermophilus* CBT ST3) and in accordance with the below correspondence, attached you will find responses to the remaining questions (II932.2-CBI.8).

Thank you for sending your feedback and if there any other questions/concerns, please let us know.

Best Regards.

Joel Villareal | Regulatory Director
Quality Development Services
joel@rejimus.com

REJIMUS

REJIMUS INC.
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From: Joel Villareal <joel@rejimus.com>
Date: Wednesday, June 14, 2023 at 5:48 PM
To: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>

Cc: Jim Lassiter <jim@rejimus.com>, Kenneth Cairns <kenneth@rejimus.com>, Brandon M. Griffin <brandon@rejimus.com>, Kent Phan <kent@rejimus.com>, Livia Consedine <livia@rejimus.com>
Subject: Re: GRN 001087 Questions

Dear Dr. VieBrock,

As an update, this email is to inform you that we received the additional questions for GRNs 1078 to 1082 as a result of the FDA meeting held on 5/10/23. These questions will assist in the completing the responses for the three remaining questions for GRN 1087 mentioned from the previous correspondence. Therefore, we anticipate to provide a response to these remaining three (3) questions by Friday, 6/23/23, if this is acceptable to you.

If there are any other questions, please let us know.

Kind Regards.

Joel Villareal | Regulatory Director
Quality Development Services
joel@rejimus.com

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From: Joel Villareal <joel@rejimus.com>
Date: Friday, May 26, 2023 at 5:25 PM
To: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>
Cc: Jim Lassiter <jim@rejimus.com>, Kenneth Cairns <kenneth@rejimus.com>, Brandon M. Griffin <brandon@rejimus.com>, Kent Phan <kent@rejimus.com>, Livia Consedine <livia@rejimus.com>
Subject: FW: GRN 001087 Questions

Dear Dr. VieBrock,

In response to the document "2023_05_12 Questions GRN 1087" for the request for more information for GRN 001087 (*Streptococcus thermophilus* CBT ST3) and in accordance with the below correspondence, attached you will find responses to the questions/comments (II932.2-CBI.7) with the respective attachments included therein.

Please note that there are still three (3) questions that will require additional time to address additional questions from the Agency regarding GRNs 1078-1082 as a result of the meeting with FDA on 5/10/23. The responses to the additional

questions for GRN 1078-1082 would likely be identical to the questions raised for GRN 1087. Currently, we are awaiting for these questions from the Agency.

The responses to the remaining questions and any additional documents will be promptly provided to the Agency for review once we received the additional questions. Please let us know if this suffices for this response.

Thank you for sending your feedback and if there any other questions/concerns, please let us know.

Kind Regards

Joel Villareal | Regulatory Manager
Quality Development Services
joel@rejimus.com

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From: Joel Villareal <joel@rejimus.com>
Date: Thursday, May 18, 2023 at 10:10 AM
To: Lauren.Viebrock@fda.hhs.gov <Lauren.Viebrock@fda.hhs.gov>
Cc: Jim Lassiter <jim@rejimus.com>, Brandon M. Griffin <brandon@rejimus.com>, Kenneth Cairns <kenneth@rejimus.com>, Kent Phan <kent@rejimus.com>, Livia Consedine <livia@rejimus.com>
Subject: FW: GRN 001087 Questions

Dear Dr. VieBrock,

Thank you for your email with the questions regarding GRN 001087, on behalf of our client Cell Biotech Co. Ltd., for *Streptococcus thermophilus* CBT ST3. We are actively working on the responses and intend to provide a response to the question/comments within 10 business days from when the questions/comments were issued on 5/12/23. Therefore, the response is expected to be provided by 5/26/23.

In the meantime, if there are any other questions, please let us know.

Kind Regards.

Joel Villareal | Regulatory Manager
Quality Development Services
joel@rejimus.com

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From: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>
Date: Friday, May 12, 2023 at 8:00 PM
To: Jim Lassiter <jim@rejimus.com>
Subject: GRN 001087 Questions

Dear Mr. Lassiter,

During our review of GRAS Notice No. 001087, we noted questions that need to be addressed. Please find the questions attached to this email.

We respectfully request a response within **10 business days**. If you are unable to complete the response within that time frame, please contact me to discuss further options.

If you have questions or need further clarification, please feel free to contact me. Thank you in advance for your attention to our comments.

Regards,
Lauren

Lauren VieBrock, Ph.D.
Regulatory Review Scientist/Microbiology Reviewer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
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Tel: 301-796-7454
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6/23/2023

Lauren VieBrock, PhD
Regulatory Review Scientist/Microbiology Reviewer
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
United States Food and Drug Administration
lauren.viebrock@fda.hhs.gov

RE: Second Response to FDA Questions/Comments Regarding GRN 001087
II932.2-CBI.8

Dear Dr. VieBrock,

REJIMUS, INC. received your email dated 5/12/23 regarding additional FDA questions/comments to GRN 001087. A first response was submitted on 5/26/23 to address the majority of the questions. This is a second response to address the remaining questions presented.

Should you have any questions or concerns with this additional information based on the information provided so far, please let us know, and we will be sure to address that promptly for the Agency.

Sincerely,

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

TABLE OF CONTENTS

FDA QUESTIONS/COMMENTS REGARDING GRN 001087

Question 10

On page 14, the notifier states *S. thermophilus* strain KCTC 11870BP is intended to be added to dairy products at concentrations needed to provide at least 1 x 10^{11} CFU per serving. According to the stability study (Table 5, page 14), the survival rate decreases ~40% during 12-months of storage. Considering the loss during storage, please provide narrative how the notifier ensures that 1 × 10^{11} CFU per serving remains viable over the product shelf life.

Response

After additional review and re-consideration by the Sponsor relative to the available safety information included in this notification as well as the prior notices cited, and current products in the marketplace as well as published clinical studies, on of S. thermophilus KCTC 11870BP, the intended maximum use levels have been updated to up to 1 x 10^9 CFU/serving of the ingredient.

With respect to the updated intended maximum use level of up to 1 x 10^9 CFU/serving, there should not be a concern over the viability of the ingredient over a 12-months shelf-life owing to the original stability study performed at 10^{11} CFU/serving level. Even at an approximate 40% decrease in the survival rate over the identified storage period (12 months), the ingredient is capable of meeting the updated intended maximum level of use. Furthering this, the Sponsor intends to market the ingredient as a bulk ingredient only. The producer of the milk product is responsible for determinations regarding inclusion of this microorganism, but the limits of inclusion, as established in this notification, remain at not higher than 1 x 10^9 CFU/serving.

Question 11

Please provide food subcategories included in the estimation of consumption of "dairy products" in Table 7 (page 16). In addition, please specify a serving size for each food subcategory and provide the reference that was used as the basis for determining the serving size.

Response

Below is a table of food subcategories used in the estimation of consumption with the respective food code from NHANES as well as the respective serving size. As mentioned previously, the producer of the milk product is responsible for determinations regarding inclusion of this microorganism, but the limits of inclusion as established in this notification remain at not higher than 1 x 10^9 CFU/serving. The food serving size for the food subcategories of milk is based on the reference amounts customarily consumed (RACC).

Food Code	***Food Subcategories***	***Serving Size***	***Food Serving***
11100000	*Milk, NFS*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11111000	*Milk, whole*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11111100	*Milk, low sodium, whole*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11111150	*Milk, calcium fortified, whole*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11111160	*Milk, calcium fortified, low fat (1%)*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11111170	*Milk, calcium fortified, fat free (skim)*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11112110	*Milk, reduced fat (2%)*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11112210	*Milk, low fat (1%)*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11113000	*Milk, fat free (skim)*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11114300	*Milk, lactose free, low fat (1%)*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11114320	*Milk, lactose free, fat free (skim)*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11114330	*Milk, lactose free, reduced fat (2%)*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*
11114350	*Milk, lactose free, whole*	*Up to 1 x 10^9 CFU/serving*	*8 fl oz or 240mL*

Based on clinical studies provided in the GRAS notification, intended levels of previous GRAS notifications, updated literature search, and current products in the marketplace outside the United States, the serving size of 1 x 10^9 CFU/serving is reasonable to be safe for consumption.

Question 12

Please clarify what population is represented by "all users" in the dietary exposure estimate (Table 7, page 16). If the dietary exposure estimate is not for the U.S. population aged 2 years and older, please provide mean and 90th percentile eaters-only dietary exposure estimates for U.S. population aged 2 years and older.

Response

Based on the intended food uses and the intended maximum use level of up to 1 x 10^9 CFU/serving, the estimated dietary exposure, based suggested three daily servings, is shown below:

Population Group	***Age Group***	***Eaters only (CFU/day)***	
		Mean	***90th Percentile***
Total Population (eaters-only)	*2 years old and older*	*2.68×10^9*	*5.55×10^9*

Conclusion

We sincerely appreciate this opportunity to clarify the additional questions submitted as part of this review and we look forward to a positive assessment of these responses and the notification itself. Should the agency have any additional questions or requests on the above responses or the prior responses, please let us know at your earliest convenience and we will do everything we can to address those promptly.

Viebrock, Lauren

From: Highbarger, Lane A
Sent: Tuesday, October 10, 2023 2:00 PM
To: Overbey, Katie; Viebrock, Lauren
Subject: FW: [EXTERNAL] FW: Wash step in GRNs 1078-1088

Follow Up Flag: Follow up
Flag Status: Flagged

Hi Katie and Lauren,

There is one last amendment for the Cell Biotech notices. Please find a revised manufacturing protocol below. The cell mass is separated by centrifugation and not filtration.

Stiffy and I will be sharing our NQLs after they are completer.

Thank you.

~Lane

From: Joel Villareal <joel@rejimus.com>
Sent: Friday, October 6, 2023 7:53 PM
To: Highbarger, Lane A <Lane.Highbarger@fda.hhs.gov>
Cc: Jim Lassiter <jim@rejimus.com>; Brandon M. Griffin <brandon@rejimus.com>; Kenneth Cairns <kenneth@rejimus.com>; Livia Consedine <livia@rejimus.com>; Kent Phan <kent@rejimus.com>
Subject: [EXTERNAL] FW: Wash step in GRNs 1078-1088

Dear Dr. Highbarger,

Thank you for your email. Below is the response to the following question.

Request:
Is there a wash step in the purification process in GRNs 1078-1088 after the microorganisms are separated by filtration?

Response:
There is no wash step in the purification process after the microorganisms are separated.

The Sponsor has brought to our attention a translation issue concerning the separation process. As a clarification, microorganisms are separated not by filtration, but by using a centrifugation method. During this process, the microorganisms are spun down and concentrated. Following this step, all fermentation medium is removed and the microorganisms are transferred into the blending process. Please note that this process applies to all notified microorganisms from Cell Biotech Co. Ltd.

If there are any questions regarding this response, please let us know and we will be sure to address that promptly.

Sincerely,

Joel Villareal | Regulatory Director
Quality Development Services
joel@rejimus.com

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From: Highbarger, Lane A <Lane.Highbarger@fda.hhs.gov>
Date: Wednesday, October 4, 2023 at 6:25 AM
To: Jim Lassiter <jim@rejimus.com>
Subject: Wash step in GRNs 1078-1088

Hi Jim,

We have one additional quick question, is there a wash step in the purification process in GRNs 1078-1088 after the microorganisms are separated by filtration?

I am grouping all the Cell Biotech Co. Ltd. notices in this one question due to the similarity in manufacturing.

Thank you.

~Lane

Viebrock, Lauren

From: Joel Villareal <joel@rejimus.com>
Sent: Tuesday, October 17, 2023 7:17 PM
To: Viebrock, Lauren
Cc: Jim Lassiter; Brandon M. Griffin; Kenneth Cairns; Jonathan Fink; Kent Phan; Livia Consedine
Subject: [EXTERNAL] FW: GRN 001087 Questions
Attachments: II932.2-CBI.9.pdf

Dear Dr. VieBrock,

In response to the document "2023_10_13 Questions for GRN 1087" for the request for more information for GRN 001087 (*Streptococcus thermophilus* CBT ST3), attached you will find responses to the questions (II932.2-CBI.9) with the respective attachments included therein.

Thank you for sending your feedback and if there any other questions/concerns regarding this response, please let us know.

Sincerely,

Joel Villareal | Regulatory Director
Quality Development Services
joel@rejimus.com

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From: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>
Date: Friday, October 13, 2023 at 12:39 PM
To: jim@rejimus.com <jim@rejimus.com>
Subject: GRN 001087 Questions

Dear Mr. Lassiter,

During our review of GRAS Notice No. 001087, we noted additional questions to be addressed. Please find the questions attached to this email.

We respectfully request a response within **10 business days**. If you are unable to complete the response within that time frame, please contact me to discuss further options.

If you have questions or need further clarification, please feel free to contact me. Thank you in advance for your attention to our comments.

Regards,
Lauren

Lauren VieBrock, Ph.D.
Regulatory Review Scientist/Microbiology Reviewer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
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10/17/2023

Lauren VieBrock, PhD
Regulatory Review Scientist/Microbiology Reviewer
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
United States Food and Drug Administration
lauren.viebrock@fda.hhs.gov

RE: Response to FDA Questions/Comments Regarding GRN 001087 Received on 10/13/23
II932.2-CBI.9

Dear Dr. VieBrock,

REJIMUS, INC. received your email dated 10/13/23 regarding additional FDA questions/comments to GRN 001087. This is a response to address the questions presented.

Should you have any questions or concerns with this additional information, please let us know, and we will be sure to address that promptly for the Agency.

Sincerely,

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

TABLE OF CONTENTS

FDA QUESTIONS/COMMENTS REGARDING GRN 001087

Question 1

1. In the May 26, 2023 amendment (response to question 8), the notifier provides a requested specification limit for lead as well as the limits for arsenic, cadmium, and mercury along with the results (reported as "Passes test") from the analyses of three non-consecutive batches. We note that we typically do not see limits for lead as high as ≤1 mg/kg (the limit proposed by the notifier) for fermentation derived ingredients manufactured in accordance with good manufacturing practices. In addition, we would like to bring to your attention a relevant FDA's "Closer to Zero" initiative that focuses on reducing the levels of heavy metals in foods consumed by infants and young children.

Please specify the limit of detection (LOD) and/or limit of quantitation (LOQ) for the analytical method(s) used to test for heavy metals and provide the results for heavy metals as the actual measured levels or state that the levels are below the specified LOQ or LOD. If ≤1 mg/kg is the LOQ or LOD of the analytical method used to test for lead, we recommend that the notifier use a more sensitive method to measure the actual levels of lead in the ingredient and propose a specification limit that reflects the results of the batch analyses and is as low as possible. If a new method is employed, please provide a statement that it is validated for its purpose.

Furthermore, we note that the results of the batch analyses provided for cadmium were similar to those for arsenic and mercury. For consistency with the specifications proposed for arsenic and mercury and in keeping with FDA's Closer to Zero initiative for heavy metals, please consider lowering the specification for cadmium to at least ≤ 0.1 mg/kg.

For the administrative record, please include the revised table (Table 4) for specifications including heavy metals in your response.

Response

Heavy metals are being performed as identified in the attached Certificate of Analysis. These include results for Lead, Arsenic, Cadmium, and Mercury in three non-consecutive batches. The Certificate of Analysis also provides the test results in actual measured levels and all test results met specifications regarding the level of these heavy metals. The analytical method used for testing for lead is through ICP performed under Korean FDA Food Code, VIII. Food Analytical Method, 9.1 Heavy Metal.

A limit of detection (LOD) and Limit of quantitation (LOQ) for the analytical method used to test for heavy metals is provided in the attached Certificate of Analysis. The established LOD and LOQ for Lead for this analytical method used is 0.017 ppb (0.000017 mg/kg) and 0.050 ppb (0.00005 mg/kg), respectively. Owing to the very low LOQ and LOD, the analytical method used is sensitive enough to detect or quantify a small amount of Lead in the product. In addressing the specification of Lead at ≤ 1mg/kg, the specification in the attached COAs was based on production from 2016. However, based on more current batch analysis results and in recognition of FDA's "Closer to Zero" initiative, future production batches of this ingredient will have an updated Lead specification of ≤ 10 ppb (≤ 0.01 mg/kg).

For consistency with the specifications proposed for arsenic and mercury and in keeping with FDA's Closer to Zero initiative for heavy metals, the specification for cadmium has been updated to ≤ 0.1 mg/kg.

Below is the revised Table 4 that includes all specifications for the ingredient:

Parameter	***Limits***	***Method***
Appearance	*Light brown powder*	*Visual*
Viable Cell Count	*≥ 1.0 x 10^{11} CFU/g*	*Analytical Method of Viable Cell Count (In-house test method)*
Coliforms	*Absent in 10 g*	*Korean FDA Food Code VIII. Food Analytical Method, 4.7 Coliforms*
Yeast and Mold	*≤ 10 CFU/g*	*Analytical Method of Yeast and Mold (In-house test method)*
E. coli	*Absent in 1 g*	*Korean FDA Food Code, VIII. Food Analytical Method, 4.8 E. coli*
S. aureus	*Absent in 25 g*	*Analytical Method of S. aureus (In-house test method)*
Salmonella	*Absent in 25 g*	*Analytical Method of Salmonella (In-house test method)*
L. monocytogenes	*Absent in 25 g*	*Analytical Method of L. monocytogenes (In-house test method)*
Lead	*≤ 0.01 mg/kg*	*Korean FDA Food Code, VIII. Food Analytical Method, 9.1 Heavy Metal*
Cadmium	*≤ 0.1 mg/kg*	*Korean FDA Food Code, VIII. Food Analytical Method, 9.1 Heavy Metal*
Mercury	*≤ 0.1 mg/kg*	*Korean FDA Food Code, VIII. Food Analytical Method, 9.1 Heavy Metal*
Arsenic	*≤ 0.1 mg/kg*	*Korean FDA Food Code, VIII. Food Analytical Method, 9.1 Heavy Metal*

Attachment(s) II932.2-CBI.9-A1

Question 2

2. In the amendment dated June 23, 2023 (response to Question 12 (GRN 001087)), the notifier multiplied the values of 8.94 x 10^8 CFU/person (p)/d and 1.85 x 10^9 CFU/p/d by three (i.e., by the number of suggested daily servings) to obtain the eaters-only estimate of dietary exposure at the mean and 90th percentile, respectively. We note that based on the information provided in Table 7 of GRNs 001087-001088, the values of 8.94 x 10^8 CFU/p/d and 1.85 x 10^9 CFU/p/d already account for the number of servings consumed per person day that were estimated based on food consumption data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES). Therefore, we consider that multiplying these values by three suggested daily servings was inappropriate. Please confirm that the estimated eaters-only dietary exposure to the ingredient would be 8.94 x 10^8 CFU /p/d at the mean and 1.85 x 10^9 CFU/p/d at the 90th percentile for the U.S. population aged 2 years and older and that these updated dietary exposure estimates would not affect your GRAS conclusion.

Response

We confirm for GRN 001087 that the estimated eaters-only dietary exposure of the ingredient for the U.S. population aged 2 years and older is 8.94 x 10^8 CFU/p/d at the mean and 1.85 x 10^9 CFU/p/d at the 90th percentile. As such, the updated dietary exposure estimates would not affect the GRAS conclusion for GRN 001087.

Conclusion

We sincerely appreciate this opportunity to clarify the additional questions submitted as part of this review and we look forward to a positive assessment of these responses and the notification itself. Should the agency have any additional questions or requests on the above responses, please let us know at your earliest convenience and we will do everything we can to address those promptly.

Attachments

II932.2-CBI.9-A1	Certificate of Analysis

Attachment
II932.2-CBI.9-A1

CELL BIOTECH

Certificate of Analysis

Product Name : ***Streptococcus thermophilus***

Place of Production: KOREA

Batch(Lot) No. : ST3 101Q

Issued Date: 15 Dec. 2016

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 11 Dec. 2016

Exp. Date: 10 Dec. 2017

Manufacturing origin country: KOREA
Shipping Origin country: KOREA

ITEMS	SPECIFICATION	RESULTS
Appearance	Light brown powder	Light brown powder
Initial viable cell	$\geq 1.0 \times 10^{11}$ CFU/g	Passes test
Coliforms	Absent	Passes test
Yeast & Mold	$\leq$ 10 CFU/g	Passes test
E. coli	Absent in 1g	Passes test
S. aureus	Absent in 1g	Passes test
Salmonella	Absent in 25g	Passes test
L. monocytogene	Absent in 10g	Passes test
Lead (Pb)*	$\leq$ 1.0 mg/kg	0.0021 mg/kg
Cadmium (Cd)**	$\leq$ 0.3 mg/kg	0.0012 mg/kg
Mercury (Hg)***	$\leq$ 0.1 mg/kg	0.0019 mg/kg
Arsenic (As)****	$\leq$ 0.1 mg/kg	0.0076 mg/kg

Remark : *Be kept in an airtight container and stored at a temperature not exceeding 5 ℃.*

* LOD: 0.017 ppb, LOQ: 0.050 ppb ** LOD: 0.026 ppb, LOQ: 0.080 ppb

*** LOD: 1.400 ppb, LOQ: 5.400 ppb **** LOD: 0.049 ppb, LOQ: 0.148 ppb

Director, Head of Quality Management Division

CELL BIOTECH Co., Ltd.
Headquarters : 50, Aegibong-ro 409 beon-gil, Wolgot-myeon, Gimpo-si, Gyeonggi-do, Korea
Manufacturer : 397, Aegibong-ro, Wolgot-myeon, Gimpo-si, Gyeonggi-do, Korea
| PHONE +82 31 987 8107 | FAX +82 31 987 6216 | www.cellbiotech.com

CELL BIOTECH

Certificate of Analysis

Product Name : ***Streptococcus thermophilus***

Place of Production: KOREA

Batch(Lot) No. : ST3 85Q

Issued Date: 12 Oct. 2016

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 08 Oct. 2016

Exp. Date: 07 Oct. 2017

Manufacturing origin country: KOREA
Shipping Origin country: KOREA

ITEMS	SPECIFICATION	RESULTS
Appearance	Light brown powder	Light brown powder
Initial viable cell	≥ 1.0×10^{11} CFU/g	Passes test
Coliforms	Absent	Passes test
Yeast & Mold	≤ 10 CFU/g	Passes test
E. coli	Absent in 1g	Passes test
S. aureus	Absent in 1g	Passes test
Salmonella	Absent in 25g	Passes test
L. monocytogene	Absent in 10g	Passes test
Lead (Pb)*	≤ 1.0 mg/kg	0.0007 mg/kg
Cadmium (Cd)**	≤ 0.3 mg/kg	0.0028 mg/kg
Mercury (Hg)***	≤ 0.1 mg/kg	0.0023 mg/kg
Arsenic (As)****	≤ 0.1 mg/kg	0.0056 mg/kg

Remark : *Be kept in an airtight container and stored at a temperature not exceeding 5 ℃.*

* LOD: 0.017 ppb, LOQ: 0.050 ppb ** LOD: 0.026 ppb, LOQ: 0.080 ppb

*** LOD: 1.400 ppb, LOQ: 5.400 ppb **** LOD: 0.049 ppb, LOQ: 0.148 ppb

Director, Head of Quality Management Division

CELL BIOTECH Co., Ltd.
Headquarters : 50, Aegibong-ro 409 beon-gil, Wolgot-myeon, Gimpo-si, Gyeonggi-do, Korea
Manufacturer : 397, Aegibong-ro, Wolgot-myeon, Gimpo-si, Gyeonggi-do, Korea
PHONE +82 31 987 8107 | FAX +82 31 987 6216 | www.cellbiotech.com

CELL BIOTECH

Certificate of Analysis

Product Name : ***Streptococcus thermophilus***

Place of Production: KOREA

Batch(Lot) No. : ST3 82Q

Issued Date: 10 Oct. 2016

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 06 Oct. 2016

Exp. Date: 05 Oct. 2017

Manufacturing origin country: KOREA
Shipping Origin country: KOREA

ITEMS	SPECIFICATION	RESULTS
Appearance	Light brown powder	Light brown powder
Initial viable cell	≥ 1.0×10^{11} CFU/g	Passes test
Coliforms	Absent	Passes test
Yeast & Mold	≤ 10 CFU/g	Passes test
E. coli	Absent in 1g	Passes test
S. aureus	Absent in 1g	Passes test
Salmonella	Absent in 25g	Passes test
L. monocytogene	Absent in 10g	Passes test
Lead (Pb)*	≤ 1.0 mg/kg	0.0026 mg/kg
Cadmium (Cd)**	≤ 0.3 mg/kg	0.0021 mg/kg
Mercury (Hg)***	≤ 0.1 mg/kg	0.0019 mg/kg
Arsenic (As)****	≤ 0.1 mg/kg	0.0064 mg/kg

Remark : *Be kept in an airtight container and stored at a temperature not exceeding 5 ℃.*

* LOD: 0.017 ppb, LOQ: 0.050 ppb ** LOD: 0.026 ppb, LOQ: 0.080 ppb

*** LOD: 1.400 ppb, LOQ: 5.400 ppb **** LOD: 0.049 ppb, LOQ: 0.148 ppb

[redacted]

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