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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).

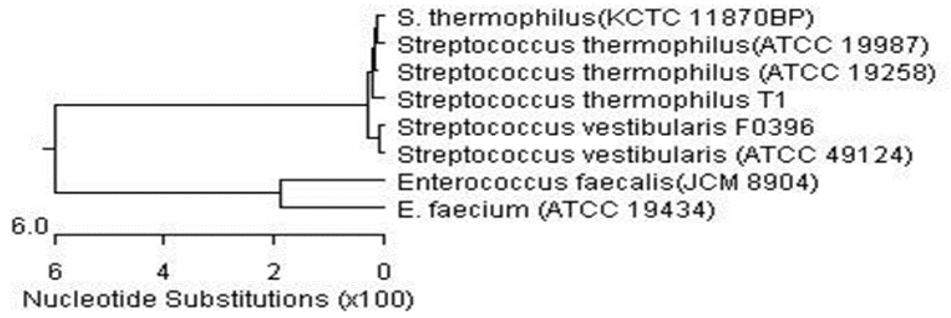
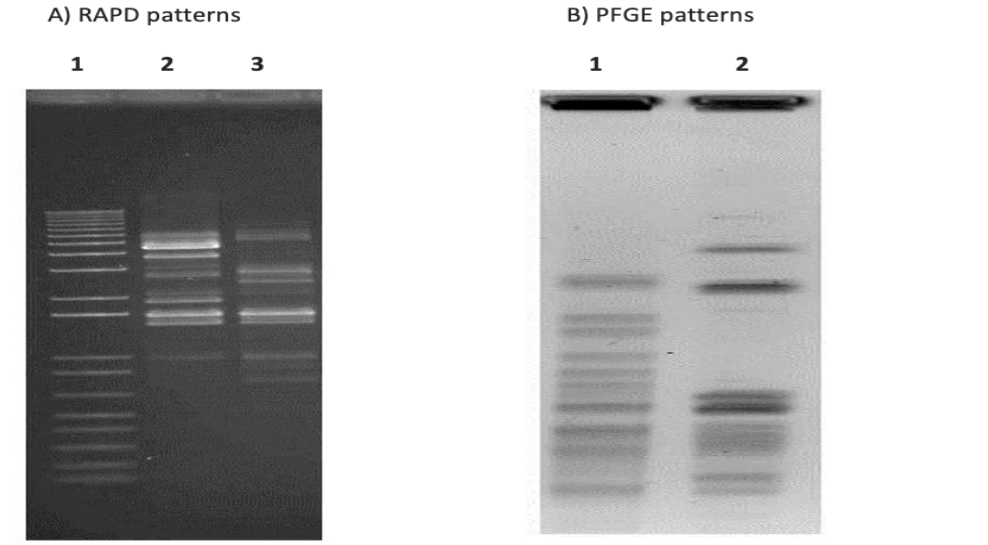


Figure 4. RAPD and PFGE patterns for *Streptococcus thermophilus* CBT ST3 and *S. thermophilus* (ATCC 19258)(Cell Biotech Co. Ltd., 2018).



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.

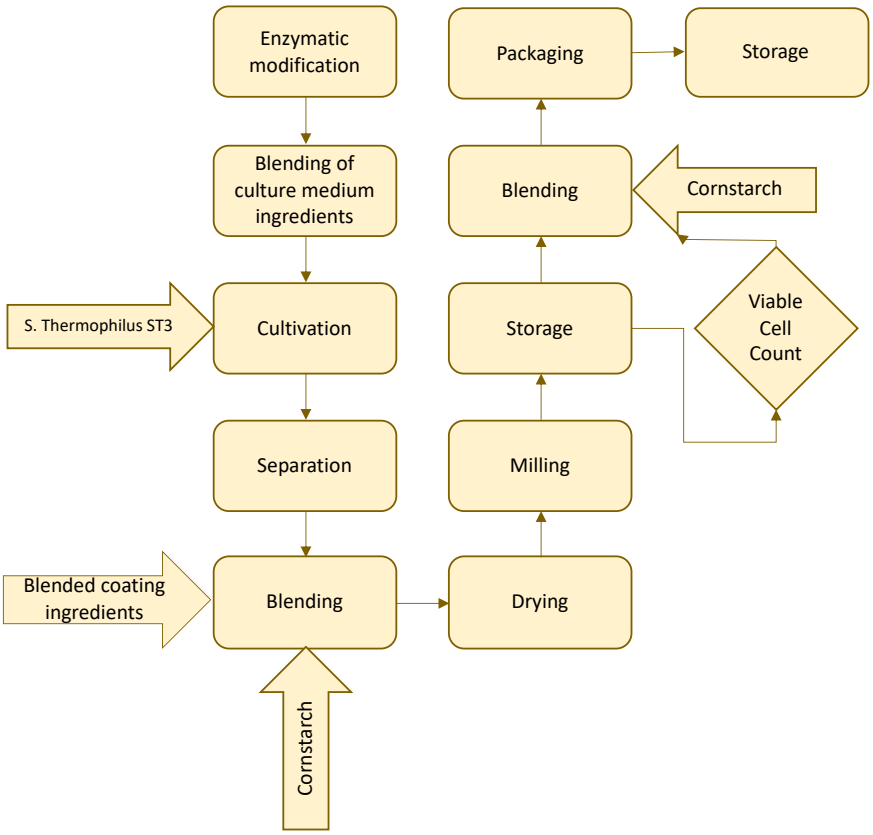
Standardization

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

Table 7. EDIs of *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).

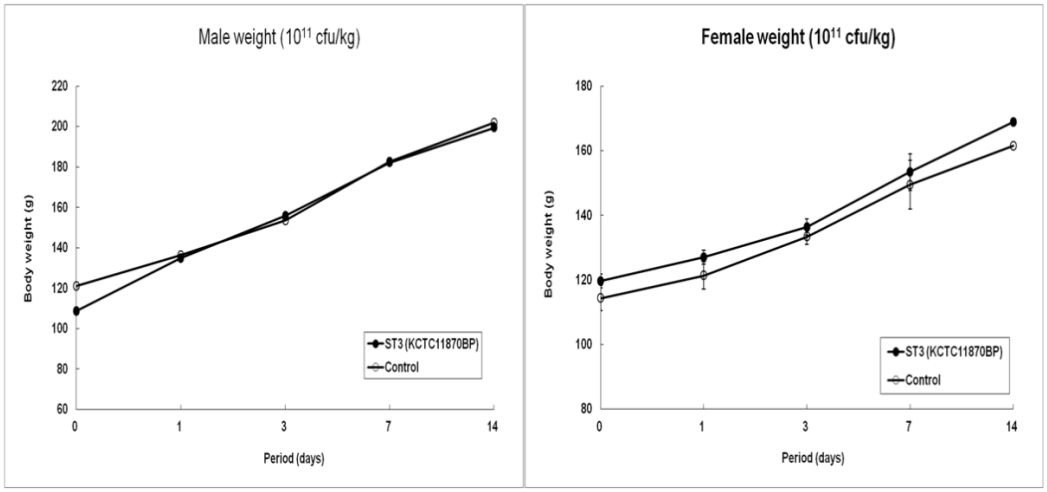


Table 11. Clinical findings of male and female rats orally administered with 10^{11} CFU/kg *Streptococcus thermophilus* CBT ST3 (Cellbiotech R&D Center 2018).

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).

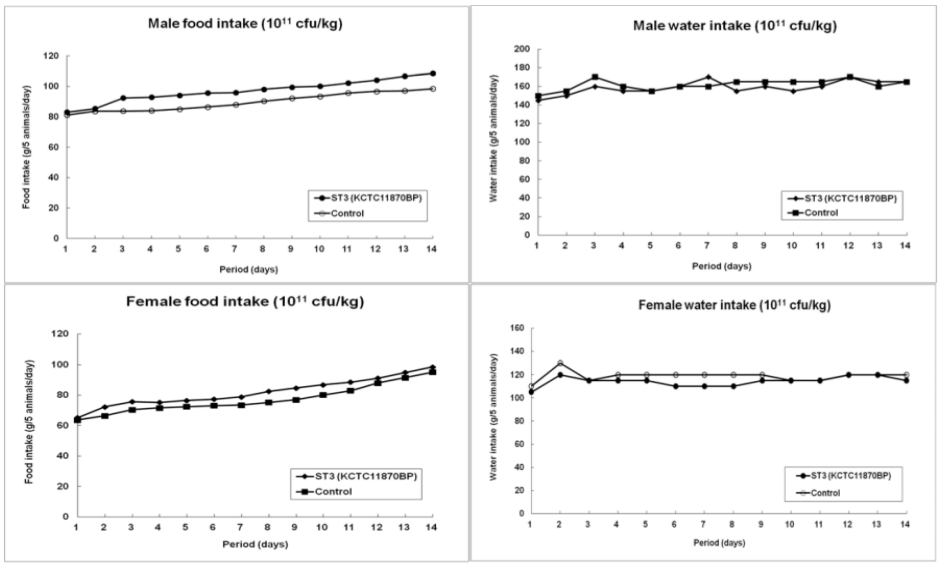


Table 12. Absolute organ weights (g) of male and female orally administered with 10^{11} CFU/kg *Streptococcus thermophilus* CBT ST3 (Cellbiotech R&D Center 2018).

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

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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