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

5/9/2022

RE: GRAS Notification of *Lactococcus lactis* CBT SL6  
**II1104.1-CBI.1.3**

To Whom It Concerns,

In accordance with 21 CFR, Part 170, Subpart E, we as the agent [REJIMUS, INC., 600 W. Santa Ana Blvd. Ste 1100, Santa Ana, CA 92701], respectfully provides notice of a claim that the addition of the microorganism *Lactococcus lactis* CBT SL6 to the foods identified in this notice at the specified levels is exempt from the premarket approval requirement of the Federal Food, Drug and Cosmetic Act because the notifier [Cell Biotech Co. Ltd., 50, Agibong-ro, 409 Beon-gil, Wolgot-myeon, Gimpo, Republic of Korea] has determined that the intended uses are generally recognized as safe (GRAS). The attached documents contain the specific information and data that address the safety of the substance for use in human food applications.

Respectfully,

Jim Lassiter, COO  
REJIMUS, INC.  
[jim@rejimus.com](mailto: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. (herein referred to as CBI) has undertaken an independent safety evaluation of the substance in this notification:

*Lactococcus lactis* CBT SL6

### Intended Conditions of Use and Levels of Inclusion

The intended use of *Lactococcus lactis* CBT SL6 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  $1 \times 10^{11}$  CFU per serving.



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RE: GRAS Notification of *Lactococcus lactis* CBT SL6

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*Lactococcus lactis* CBT SL6 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. *Lactococcus lactis* CBT SL6 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 *Lactococcus lactis* CBT SL6 is GRAS for its intended conditions of use as stated in this notification and, such use of *Lactococcus lactis* CBT SL6 is not subject to the premarket approval requirements of the *Federal Food, Drug, and Cosmetic Act*.

### **Availability of Information**

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

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

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

### **Trade Secrets**

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

### **Authorization for FDA to share information with FSIS**

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

### **Certification**

Cell Biotech Co. Ltd. has concluded that *Lactococcus lactis* CBT SL6 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



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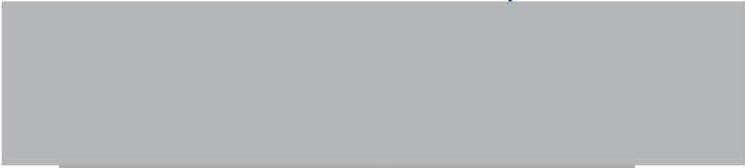
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submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of *Lactococcus lactis* CBT SL6.

Respectfully submitted,



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

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

Common Name: *Lactococcus lactis* subsp. *lactis* CBT SL6 (KCTC 11865BP)

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

Kingdom: Bacteria

Subkingdom: Posibacteria

Phylum: Firmicutes

Class: Bacilli

Order: Lactobacillales

Family: Streptococcaceae

Genus: *Lactococcus*

Species: *lactis*

Strain: CBT SL6

The *lactic acid producing bacteria* (LAB) are a diverse group of organisms, but commonly include *Lactobacillus*, *Enterococcus*, and *Lactococcus*, amongst many others (Lahtinen, 2012). Some *Lactobacillus* species are exclusively found naturally in specific habitats (e.g., *L. helveticus* and *L. delbrueckii* ssp. *bulgaricus* in dairy products, *L. johnsonii* and *L. gasseri* in vertebrate gastrointestinal tracts) whereas other species, such as *L. plantarum* and *L. casei*, may be found in a variety of different environments. In healthy humans, *Lactobacilli* are normally present at a population density of approximately  $10^3$ – $10^7$  CFU/g in the oral cavity,  $10^3$ – $10^7$  CFU/g in the ileum,  $10^4$ – $10^8$  CFU/g the colon, and are the dominant microorganism in the vagina (Bernardeau 2006).

Previously designated *Lactobacillus xylosus*, this organism has been reclassified as *Lactococcus lacti* subsp. *lactis*, although its historical designation as a *Lactobacillus* most likely had been made on the basis of its rod shape coupled with its ability to ferment xylose. It is the most prevalent organism used in the production of fermented milk products. It is a gram positive, rod shaped, non-spore forming, facultative anaerobe that generally grows poorly in air. *Lactococcus lactis* are auxotrophic for a number of different nutrients and hence grow best in richly supplemented complex media.

### Identification

The organism that is the subject of notified substance, originally isolated from fermented food (e.g., kimchi), is identified as *Lactococcus lactis* subsp. *lactis* and has been uniquely characterized by means of genomic typing as a distinct strain, known as CBT SL6. The strain was deposited in the Korean Collection for Type Cultures, accession number KCTC 11865BP.

### Carbohydrate Utilization

Fermentative characteristics of *Lactococcus lactis* CBT SL6 were analyzed using API 50 CHL kit. Results are shown in Table 1.

**TABLE 1.** Fermentative characteristics of *Lactococcus lactis* CBT SL6 obtained with an API 50 CHL Kit. (Cellbiotech R&D Center (2018))

No	Carbohydrates	Utilized	No	Carbohydrates	Utilized
0	Control	-	25	Esculine	+
1	Glycerol	-	26	Salicine	+
2	Erythritol	-	27	Cellobiose	+
3	D-Arabinose	-	28	Maltose	+
4	L-Arabinose	-	29	Lactose	+
5	Ribose	+	30	Melibiose	-
6	D-Xylose	+	31	Saccharose	-
7	L-Xylose	-	32	Trehalose	+
8	Adonitol	-	33	Inuline	-
9	$\beta$ -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	$\beta$ -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	$\alpha$ -Methyl-D-mannoside	-	45	D-Arabitol	-
21	$\alpha$ -Methyl-D-glucoside	-	46	L-Arabitol	-
22	N-Acetyl glucosamine	+	47	Gluconate	W
23	Amygdaline	+	48	2-Ceto-gluconate	-
24	Arbutine	+	49	5-Ceto-gluconate	-

### Genomic Classification, Sequence, and Profile

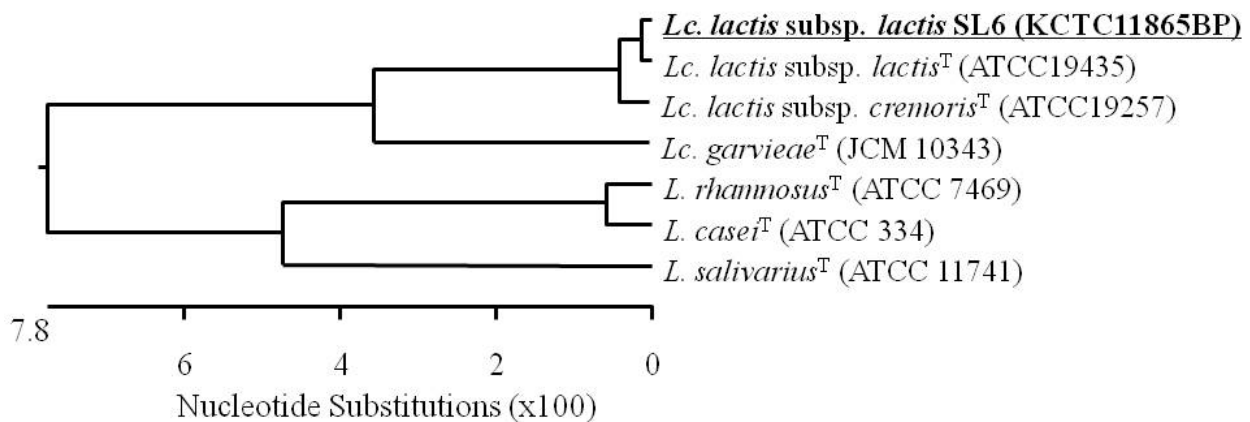
The 16S rRNA gene sequence were aligned and compared with different *Lactococcus* strains: *Lc. lactis* subsp. *lactis* SL6 (KCTC 11865BP), *Lc. lactis* subsp. *lactis* (ATCC 19435), *Lc. lactis* subsp. *cremoris* (ATCC 19257) *Lc. garvieae* (JBC 10343), *L. salivarius* (ATCC 11741), and *L. rhamnosus* (ATCC 7469). Percent identity and divergence were compared between *Lactococcus* and *Lactobacillus* species as presented in Table 2 below, distinctive sequences of 16S rRNA genes were used to generate the phylogenetic tree shown in Figure 1 (Cellbiotech R&D Center 2018).

Random Amplified Polymorphic DNA (RAPD) is a method used to obtain a molecular “fingerprint” from random DNA segments of genomic DNA that have been amplified using a single primer of an arbitrary nucleotide sequence. *Lactococcus lactis* CBT SL6 DNA was compared using RAPD with *Lc. lactis* subsp. *lactis* ATCC 19435 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’ – GTGGTGGTGGTGGT – 3’) using genomic DNA as a template and analyzed in 0.8% agarose gel (Syngene, UK).

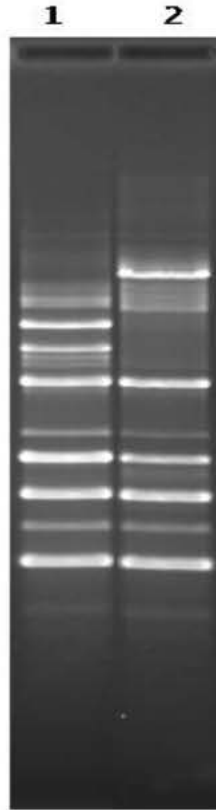
**Table 2.** Percent identity of *Lactococcus lactis* CBT SL6 with some closely related species based on 16S rRNA gene sequences. (Cellbiotech R&D Center 2018).

		Percent Identity						
		1	2	3	4	5	6	
Divergence	1		99.7	99.2	91.6	82.0	77.6	<b>1 <i>Lc. lactis</i> subsp. <i>lactis</i> SL6 (KCTC 11865BP)</b>
	2	0.3		99.0	91.5	81.8	77.5	<b>2 <i>Lc. lactis</i> subsp. <i>lactis</i><sup>T</sup> ATCC 19435</b>
	3	0.7	0.8		91.6	81.9	77.5	<b>3 <i>Lc. lactis</i> subsp. <i>cremoris</i><sup>T</sup> ATCC 19257</b>
	4	7.2	7.3	7.0		81.5	79.3	<b>4 <i>Lc. garvieae</i><sup>T</sup> JBC 10343</b>
	5	15.6	15.9	15.4	15.3		88.2	<b>5 <i>L. salivarius</i><sup>T</sup> ATCC 11741</b>
	6	15.4	15.6	15.5	15.5	9.5		<b>6 <i>L. rhamnosus</i><sup>T</sup> ATCC 7469</b>

**Figure 1.** Phylogenetic tree between *Lactococcus lactis* CBT SL6 (KCTC 11865BP) and other closely related *Lactococcus/lactobacillus* spp. based on 16S rRNA gene sequence. (Cellbiotech R&D Center 2018)



**Figure 2.** RAPD results between *Lactococcus lactis* subsp. *lactis* (ATCC 19435) – Lane 1 and *Lactococcus lactis* CBT SL6 (KCTC 11865BP). (Cellbiotech R&D Center 2018)



## Manufacturing

### Components

All components employed in the manufacture of *Lactococcus lactis* CBT SL6 are suitably used for one or more effects described within FDA’s Substances Added to Food Inventory as identified in Table 3.

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

Fermentation Medium Ingredient	CAS No.	Reference
Fructose	[9010-10-0]	21 CFR §184.1866
Soy Peptone	[73049-73-7]	21 CFR §184.1553
Yeast Extract Powder	[8013-01-1]	21 CFR §184.1983
Potassium Phosphate, Dibasic	[7758-11-4]	21 CFR §182.6285
Calcium Chloride	[10035-04-8]	21 CFR §184.1193



Magnesium Sulfate	[10034-99-8]	21 CFR §184.1443
Polysorbate 80	[9005-65-6]	21 CFR §178.3400
Coating Ingredient	CAS No.	Reference
Trehalose	[6138-23-4]	FEMA No. 4600 (FEMA GRAS Publication No. 24)
L-Arginine	[74-79-3]	21 CFR §172.320
Potassium Phosphate, Dibasic	[7758-11-4]	21 CFR §182.6285
Potassium Phosphate, Monobasic	[7778-7-0]	21 CFR §175.105
Xanthan Gum	[11138-66-2]	21 CFR §172.695
Cornstarch	[977050-21-3]	21 CFR §182.70 / 21 CFR §182.90
Sodium Carboxymethylcellulose	[9004-32-4]	21 CFR §182.1745
Sodium Chloride	[7647-14-5]	21 CFR §182.1
Excipient	CAS No.	Reference
Cornstarch	[977050-21-3]	21 CFR §182.70 / 21 CFR §182.90

### Process Description and Flow Chart

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

#### Preparation of culture medium

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

#### Cultivation

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

#### Preparation of coating materials

Coating ingredients are added to water, mixed, and sterilized with saturated steam.

#### Blending

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

#### Drying

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



Milling

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

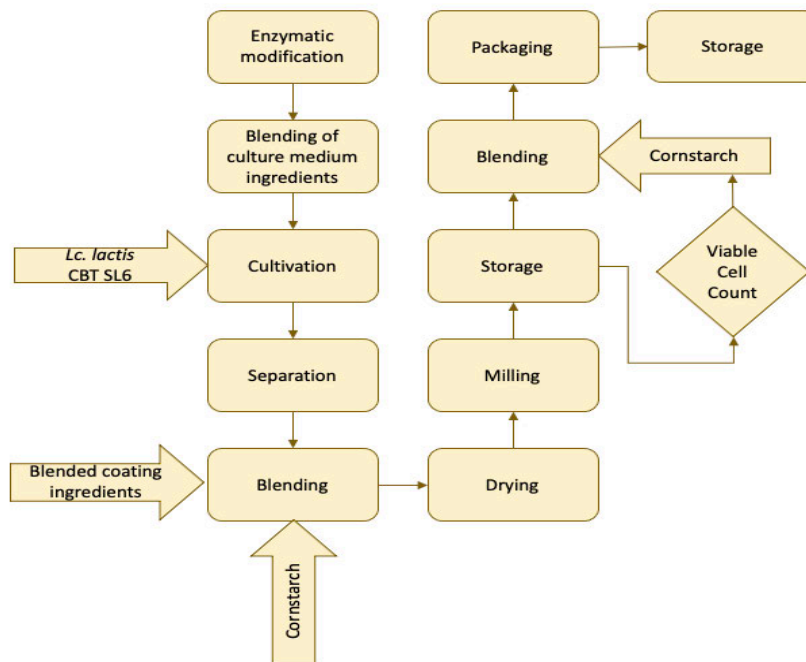
Standardization

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

Packaging

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

**Figure 3.** Manufacturing process flow chart.

**Specifications**

Food grade specifications for *Lactococcus lactis* CBT SL6 have been established as shown in Table 4. Test results of three production batches are additionally presented in demonstration of the ability to consistently produce the notified substance in conformance with these specifications. Consistency of conformance to specifications is further evidenced by stability study results.



Table 4. *Lactococcus lactis* CBT SL6 food grade specifications and conforming test results.

Parameter	Limits	Method	Batch 11R	Batch 21R	Batch 28R
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	USP <2022> or equivalent	Conforms	Conforms	Conforms
Coliforms	Absent in 10g	USP <2023> or equivalent	Conforms	Conforms	Conforms

## Stability Data

In order to determine the stability of *Lactococcus lactis* CBT SL6, the food ingredient was placed in a stability study by Cell Biotech Co. Ltd.

A 12-month stability study was conducted at  $5 \pm 3^\circ\text{C}$  using 3 different batches of *Lactococcus lactis* CBT SL6. 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 *Lactococcus lactis* CBT SL6 at  $5 \pm 3^\circ\text{C}$ .

Strain	Batch No.	Test	Time Point				
			Initial	3 Months	6 Months	9 Months	12 Months
<i>Lactococcus lactis</i> CBT SL6	11R	VCC (CFU/g)	$1.44 \times 10^{12}$	$1.22 \times 10^{12}$	$1.11 \times 10^{12}$	$9.90 \times 10^{11}$	$8.87 \times 10^{11}$
		Survival Rate (%)	100.0	85.2	77.3	68.9	61.7
	21R	VCC (CFU/g)	$1.28 \times 10^{12}$	$1.12 \times 10^{12}$	$9.83 \times 10^{11}$	$8.63 \times 10^{11}$	$8.03 \times 10^{11}$
		Survival Rate (%)	100.0	87.8	76.8	67.5	62.8
	28R	VCC (CFU/g)	$2.09 \times 10^{12}$	$1.73 \times 10^{12}$	$1.44 \times 10^{12}$	$1.28 \times 10^{11}$	$1.18 \times 10^{11}$
		Survival Rate (%)	100.0	82.8	68.7	61.3	56.2
	Average Survival Rate (%)		100.0	85.3	74.3	65.9	60.2

## Technical Effects

This substance will be used to provide as a dietary source of *Lactococcus lactis* CBT SL6 as a food ingredient to dairy products.

## PART 3 – DIETARY EXPOSURE

### Intended Use and All Sources in the Diet

The intended use of *Lactococcus lactis* CBT SL6 is as a food ingredient for inclusion in dairy products to provide at least  $1 \times 10^{11}$  CFU per serving.

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

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

Description	Claim	Criteria*	Minimum level of evidence required to make claim	Comments
<b>Not probiotic</b>				
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 $1 \times 10^9$ CFU per serving <sup>73</sup>	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’ <sup>74,75</sup> )
<b>Probiotic</b>				
Probiotic in food or supplement without health claim	“Contains probiotics”	A member(s) of a safe <sup>76,77</sup> 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 <sup>73</sup>	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 <sup>73</sup>	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, <sup>78</sup> PASSCLAIM, <sup>79</sup> or GRADE; <sup>80</sup> well-conducted RCT(s) OR strong evidence from large observational studies <sup>81</sup>	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.



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United States Food and Drug Administration – **Office of Food Additive Safety (HFS-200)**

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

Table 7. EDIs of *Lactococcus lactis* CBT SL6 from proposed uses in dairy products across all users based on 2017-2018 NHANES.

Group	% (n)	Dairy intake g/day		Dairy, serving/day		<i>Lactococcus lactis</i> CBT SL6, cfu/day	
		Mean	90 <sup>th</sup> percentile	Mean	90 <sup>th</sup> percentile	Mean	90 <sup>th</sup> percentile
Children, 3-11	74.04 (739)	360.44	456.85	0.97	1.87	9.74×10 <sup>10</sup>	1.87×10 <sup>11</sup>
Females, 12-19	42.44 (191)	186.02	362.90	0.76	1.49	7.62×10 <sup>10</sup>	1.49×10 <sup>11</sup>
Males, 12-19	54.73 (243)	265.10	477.28	1.09	1.96	1.09×10 <sup>11</sup>	1.96×10 <sup>11</sup>
Females, 20 and up	38.21(826)	179.05	360.87	0.73	1.48	7.34×10 <sup>10</sup>	1.48×10 <sup>11</sup>
Males, 20 and up	44.06(871)	222.93	499.63	0.91	2.05	9.13×10 <sup>10</sup>	2.05×10 <sup>11</sup>
All users	47.61(3161)	218.16	452.44	0.89	1.85	8.94×10 <sup>10</sup>	1.85×10 <sup>11</sup>

Assuming all servings of the intended dairy products consumed contain *Lactococcus lactis* CBT SL6, the suggested three daily servings would result in a cumulative exposure of  $2.68 \times 10^{11}$  CFU per day ( $8.94 \times 10^{10} \times 3$ ). The estimated 90<sup>th</sup> 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  $5.55 \times 10^{11}$  CFU per day *Lactococcus lactis* CBT SL6. The LD<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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  $9.6 \times 10^{11}$  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  $2.68 \times 10^{11}$  CFU per day and the cumulative exposure at an estimated 90<sup>th</sup> percentile of  $5.55 \times 10^{11}$  CFU per day is less than the LD<sub>50</sub> levels of greater than  $10^{11}$  CFU/kg (or  $9.6 \times 10^{11}$ ) of *Lactococcus lactis* CBT SL6.



## 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 *Lactococcus lactis* CBT SL6 is included. The metabolic by-products from *Lactococcus lactis* CBT SL6 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. *Lactococcus lactis* CBT SL6 is not known to secrete any exotoxins or any other substances that are classified as harmful to humans. Additionally, the number of viable organisms will decline during a product's shelf life to further minimize the exposure to any of the metabolic by-products.

## Substances Naturally Present or Due to Manufacturing

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

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

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

## PART 4 – SELF-LIMITING LEVELS OF USE

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

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

As the conclusion of general recognition of safety is through scientific procedures, this Part is not applicable. Information about the current international marketplace availability of products containing *Lactococcus lactis* CBT SL6 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 *Lactococcus* and specifically *Lactococcus lactis* is discussed in Part 6.

## PART 6 – NARRATIVE

### Introduction

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

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

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

### History of GRAS Notices

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

*Lactococcus lactis* is related to other lactic acid bacteria such as *Lactobacillus acidophilus* in our intestinal tract and *Streptococcus salivarius* in the mouth (Textbook of Bacteriology). GRAS notices of food ingredient substances containing the same species as *Lactococcus lactis* CBT SL6 which FDA has no questions are presented below in Table 8. These GRAS notices reference and address a large body of

established scientific procedures evidencing the safe and common use of various strains of *Lactococcus lactis* and its subspecies.

**Table 8.** GRAS notices of LAB organisms closely related to *Lactococcus lactis* CBT SL6 receiving reply from FDA of no questions (GRAS Notices Inventory Database)

GRAS No.	Date of Closure	Substance
429	10-Apr-2012	<i>Lactobacillus casei</i> strain Shirota
231	29-May-2008	<i>Lactobacillus casei</i> subsp. <i>rhamnosus</i> strain GG
807	06-Jun-2019	<i>Streptococcus salivarius</i> M1
591	25-Jan-2016	<i>Streptococcus salivarius</i> K12

### Approved Use

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

### Antibiotic Resistance

Determination of the minimal inhibitory concentration (MIC) of select antibiotics [ampicillin (AMP), gentamycin (GEN), kanamycin (KAN), streptomycin (STM), erythromycin (ERM), clindamycin (CLM), synergid (QU+DA), tetracycline (TET), and chloramphenicol (CP)] was performed in accordance with ISO 10932:2010 using *Lactococcus lactis* CBT SL6 as the test strain. Observed MIC values for *Lactococcus lactis* CBT SL6 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 9 and this strain is therefore susceptible to AMP, VAN, GEN, KAN, STM, ERM, CLM, QU+DA, TET, and CP.

**Table 9.** Antibiotic sensitivity of *Lactococcus* CBT SL6 (Cellbiotech R&D Center (2018))

Strain	Minimum Inhibitory Concentrations (µg/mL) of Antibiotics									
	AMP	VAN	GEN	KAN	STM	ERM	CLM	QU+DA	TET	CP
<i>Lc. lactis</i> CBT SL6	2	1	4	2	16	1	1	0.25	1	4
EFSA Cut-off Value	2	4	32	64	64	2	4	4	4	8

## Current Marketplace Availability of *Lactococcus lactis* CBT SL6

While the conclusion of general recognition of safety (GRAS) is based upon scientific procedures, there is a history of use of *Lactococcus lactis* CBT SL6 in foreign countries and in multiple food products.

## *In vitro* Toxicity Studies

### Hemolysis Assay

The Cell Biotech R&D Center tested *Lactococcus lactis* CBT SL6 for its hemolytic activity by inoculating the 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 *Lactococcus lactis* CBT SL6 were investigated using male and female Sprague-Dawley rats (5 of each sex in each group). The animals were intragastrically administered either 0.85% saline solution or  $1 \times 10^{11}$  CFU/kg *Lactococcus lactis* CBT SL6 and observed for the ensuing 14 days. The net body weight gain, gross pathological findings, feed and water consumption, organ weight, and body temperature were monitored and recorded for two (2) weeks.

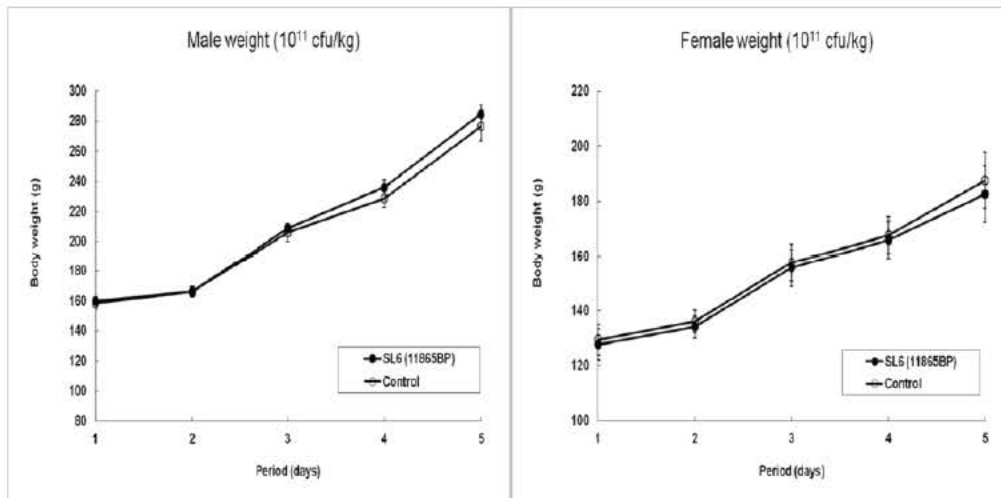
This investigation revealed no mortalities or obvious adverse clinical signs in rats administered with the live bacterial cells at the investigated dose level as shown on Table 10. In addition, results indicate no significant differences in net body weight gain (Figure 4), gross pathological findings (Table 11), feed and water consumption (Figure 5), organ weight (Table 12), and body temperature (Table 13) among the different treatment groups and between the treated and control rats (Cell Biotech R&D Center 2018).

**Table 10.** Mortality of male and female rats orally administered with  $1 \times 10^{11}$  CFU/kg *Lactococcus lactis* CBT SL6 (Cellbiotech R&D Center (2018))

Sex	Group	Days After Administration														Final Mortality (%)	LD <sub>50</sub>	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14			
Male	CBT SL6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	> $1 \times 10^{11}$ CFU/kg
	Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Female	CBT SL6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	> $1 \times 10^{11}$ CFU/kg
	Control	0	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 *Lactococcus lactis* CBT SL6 and control for 14 days. Values are mean  $\pm$  SE. (Cellbiotech R&D Center (2018))

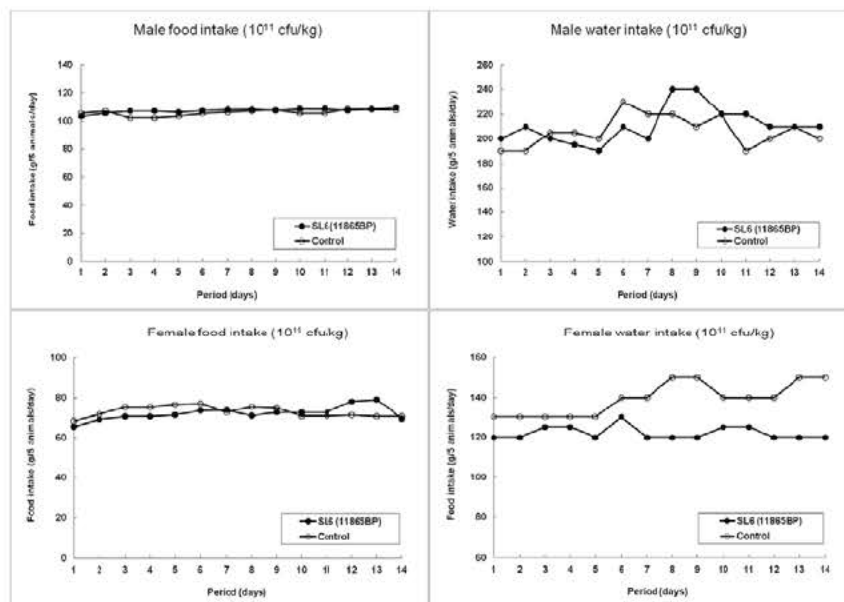


**Table 11.** Clinical findings of male and female rats orally administered with  $10^{11}$  CFU/kg *Lactococcus lactis* CBT SL6 (Cellbiotech R&D Center (2018))

Sex	LAB Strain	Clinical Signs	Hours after treatment				Days after treatment				
			1	2	5	6	1	3	5	7	14
Male	CBT SL6	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 SL6	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 *Lactococcus lactis* CBT SL6 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 *Lactococcus lactis* CBT SL6 (Cellbiotech R&D Center (2018))

Sex	Parameters	Lab	CBT SL6	Control
		No. of Animals	5	5
Male	Body weight (g)		284.80 ± 5.60	276.66 ± 10.10
	Liver (g)		10.68 ± 0.28	10.15 ± 0.99
	Spleen (g)		1.03 ± 0.05	1.00 ± 0.04
	Kidney (g)	Right	1.02 ± 0.08	1.02 ± 0.07
		Left	0.57 ± 0.08	0.61 ± 0.05
Female	Body weight (g)		182.62 ± 5.19	187.64 ± 10.16
	Liver (g)		6.05 ± 0.50	5.51 ± 0.49
	Spleen (g)		0.66 ± 0.04	0.07 ± 0.06
	Kidney (g)	Right	0.66 ± 0.04	0.71 ± 0.06
		Left	0.54 ± 0.12	0.45 ± 0.08

**Table 13.** Body temperature changes in male and female orally treated with  $10^{11}$  CFU/kg *Lactococcus lactis* SL6 (Cellbiotech R&D Center (2018))

Day	No.	Male body temperature		Female body temperature	
		CBT SL6 (°C)	Control (°C)	CBT SL6 (°C)	Control (°C)
Pre-treatment	Ave	35.30	34.96	35.40	35.60
	SEM	0.49	0.30	0.48	0.46
Day 1	Ave	35.56	35.60	35.94	35.82
	SEM	0.40	0.45	0.55	0.61
Day 2	Ave	35.88	36.00	35.92	35.86
	SEM	0.32	0.25	0.60	0.24
Day 3	Ave	36.06	35.88	35.92	35.94
	SEM	0.49	0.22	0.52	0.38
Day 4	Ave	36.06	35.84	35.62	35.68
	SEM	0.39	0.40	0.40	0.46

## Other Animal Studies

### Study 1

Shin et al. (2016) investigated the effects of a microorganism mixture in male mice induced with atopic dermatitis-like skin lesions by using a 1-chloro-2,4-dinitrobenzene (DNCB). The microorganism mixture contained seven microorganisms which included *Lactococcus lactis* CBT SL6 with an unknown concentration. The seven microorganisms were mixed equally to produce  $10^7$  CFU/mL. The 48 male mice were divided into 4 groups: control, DNCB with the excipient of GI7, DNCB with GI7-L ( $10^7$  CFU/day), and DNCB with GI7-H ( $10^9$  CFU/day). The mice were fed excipient or GI7 for 8 weeks. The investigation revealed that the administration of GI7 suppressed AD-like symptoms in DNCB-treated mice. No adverse effects were reported due to the use of the *Lactococcus lactis* CBT SL6.

## Human Studies

### Study 1

Hod et al. (2017 and 2018) investigated the effects of a microorganism mixture in 107 adult women diagnosed with diarrhea-dominant-IBS (IBS-D). The study was designed as a randomized double-blind, placebo-controlled, parallel-group trial with a 2-week run-in period prior to treatment and a treatment period for 8 weeks. Those subjects in the BIO-25 group were given a BIO-25 capsule containing  $2.5 \times 10^{10}$

CFU microorganism mixture of 11 bacteria twice daily that contained  $2 \times 10^9$  CFU *Lactococcus lactis* CBT SL6. A total of 54 subjects were used in the BIO-25 group and 53 subjects were used in the placebo group. Nine subjects in the placebo group and five subjects in the BIO-25 group did not complete the study. No serious adverse events were reported in either group.

## CONCLUSION

The scientific data, information, methods, and principles described in this notification provide the basis for conclusion that *Lactococcus lactis* CBT SL6 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 *Lactococcus lactis* in the food supply serves as the foundation on which the safety of this uniquely identified strain is established.

Inclusion of *Lactococcus lactis* 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 *Lactococcus lactis*, other species of *Lactococcus*, as well as members of other genera of lactic acid-producing bacteria, intended for inclusion as food ingredients. The applicable GRAS notices, referenced in Table 8 within Part 6 of this notice, incorporate myriad studies demonstrating the safety of ingestion of substances closely related to *Lactococcus lactis* CBT SL6.

*Lactococcus lactis* CBT SL6 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. *Lactococcus lactis* CBT SL6's potential for antibiotic resistance was tested in accordance with EFSA guidelines.

Additional efficacy studies in humans and animals have been performed without the occurrence of observation of adverse events. An LD<sub>50</sub> of greater than  $10^{11}$  CFU/kg was established in rats which corresponds to a human equivalent amount of  $9.6 \times 10^{11}$  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 *Lactococcus* CBT SL6 at the 90<sup>th</sup> percentile of high-level consumers of products of the intended inclusion food is  $5.55 \times 10^{11}$  CFU per day of *Lactococcus lactis* CBT SL6. The 90<sup>th</sup> percentile for actual consumption of  $5.55 \times 10^{11}$  CFU/day is below the maximum safe starting dose of  $9.6 \times 10^{11}$  CFU/serving.

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

## PART 7 – SUPPORTING DATA AND INFORMATION

### Generally Unavailable

Cellbiotech R&D Center (2018) Identification. Molecular Typing and Safety Assessment of *Lactococcus lactis* CBT SL6 (KCTC12202BP).

### Generally Available

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Shin JH, Chung MJ, and Seo JG (2016). A multi-strain probiotic formulation attenuates skin symptoms of atopic dermatitis in a mouse model through the generation of CD4<sup>+</sup>Foxp3<sup>+</sup> T cells. *Food & Nutrition Research* 60:1, 32550, DOI: 10.3402/fnr.v60.32550.

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.

United States Department of Agriculture: Economic Research Service. Fluid beverage milk sales quantities by product (millions of pounds). Ers.usda.gov. <https://www.ers.usda.gov/data-products/dairy-data/>.

United States Department of Health and Human Services and United States Department of Agriculture. Dietary Guidelines for Americans 2015-2020 Eighth Edition. <https://health.gov/dietaryguidelines/2015/guidelines/>.

United States Food and Drug Administration. GRAS Notices Inventory. <https://www.accessdata.fda.gov/scripts/fdcc/?set=grasnotices>.

United States Food and Drug Administration. Substances Added to Food Inventory. [https://www.accessdata.fda.gov/scripts/fdcc/?set=FoodSubstances&sort=Sortterm&order=ASC&startrow=1&type=basic&search=.](https://www.accessdata.fda.gov/scripts/fdcc/?set=FoodSubstances&sort=Sortterm&order=ASC&startrow=1&type=basic&search=)

**Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Determination of Cell Biotech Co. Ltd. *Lactococcus lactis* subsp. *lactis* CBT SL6**

**February 26, 2021**

Cell Biotech Co. Ltd. intends to market *Lactococcus lactis* subsp. *lactis* CBT SL6 as an ingredient in dairy products. *Lactococcus lactis* subsp. *lactis* CBT SL6 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 *Lactococcus lactis* subsp. *lactis* CBT SL6 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 *Lactococcus lactis* subsp. *lactis* CBT SL6 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. *Lactococcus lactis* subsp. *lactis* CBT SL6, 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. *Lactococcus lactis* subsp. *lactis* CBT SL6 in accordance with the described applications and levels specified in the dossier, manufactured according to current

**Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS)  
Determination of Cell Biotech Co. Ltd. *Lactococcus lactis* subsp. *lactis* CBT SL6**

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 *Lactococcus lactis* subsp. *lactis* CBT SL6 is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature:



Date: \_\_\_\_\_

Steven Dentali, Ph.D.  
Dentali Botanical Sciences





**Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS)  
Determination of Cell Biotech Co. Ltd. *Lactococcus lactis* CBT SL6**

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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. *Lactococcus lactis* CBT SL6, 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. *Lactococcus lactis* CBT SL6 in accordance with the described applications and levels specified in the dossier, manufactured according to current Good Manufacturing Practice

**Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS)  
Determination of Cell Biotech Co. Ltd. *Lactococcus lactis* CBT SL6**

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

The individual endorsement pages follow hereunder.

**ENDORSEMENT BY JEANNE MOLDENHAUER, M. SC.**

I, Jeanne Moldenhauer, hereby affirm that *Lactococcus lactis* CBT SL6 is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature



Date:

6 APR 21

Jeanne Moldenhauer, Ph.D.  
Excellent Pharma Consulting

MSc  
JM 6 APR 21



**Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS)  
Determination of Cell Biotech Co. Ltd. *Lactococcus lactis* CBT SL6**

**February 26, 2021**

Cell Biotech Co. Ltd. intends to market *Lactococcus lactis* CBT SL6 as an ingredient in dairy products. *Lactococcus lactis* CBT SL6 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 *Lactococcus lactis* CBT SL6 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 *Lactococcus lactis* CBT SL6 as an ingredient in dairy products is safe, suitable, and would be Generally Recognized as Safe (GRAS) based on a combination of historic use and scientific procedures. The Expert Panel consisted of following experts: Steven Dentali, Ph.D. (Dentali Botanical Sciences), Mary C. Mulry, Ph.D. CFS (FoodWise One LLC), and Ms. Jeanne Moldenhauer, M.Sc. (Excellent Pharma Consulting).

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

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

In addition, the Expert Panel evaluated all other information deemed necessary and/or sufficient in order to arrive at its independent, critical evaluation of these data and information. The Expert Panel has attained a unanimous conclusion that the intended uses described herein for Cell Biotech Co. Ltd. *Lactococcus lactis* CBT SL6, 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. *Lactococcus lactis* CBT SL6 in accordance with the described applications and levels specified in the dossier, manufactured according to current Good Manufacturing Practice

**Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS)  
Determination of Cell Biotech Co. Ltd. *Lactococcus lactis* CBT SL6**

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

The individual endorsement pages follow hereunder.

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

I, Mary Mulry, hereby affirm that *Lactococcus lactis* CBT SL6 is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature: \_\_\_\_\_



Date: 3/18/21

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



**FDA USE ONLY**

GRN NUMBER 001088	DATE OF RECEIPT May 12, 2022
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Food and Drug Administration

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

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      If yes, enter the date of communication (*yyyy/mm/dd*): \_\_\_\_\_  
 No

**SECTION B – INFORMATION ABOUT THE NOTIFIER**

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

## SECTION C – GENERAL ADMINISTRATIVE INFORMATION

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

Lactococcus lactis CBT SL6

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 32

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 Lactococcus lactis CBT SL6 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  $1 \times 10^{11}$  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 Lactococcus lactis CBT SL6

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

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 of 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

Jim Lassiter

Digitally signed by Jim Lassiter  
Date: 2022.05.09 12:21:29 -07'00'

Printed Name and Title

Jim Lassiter, President/COO

Date (mm/dd/yyyy)

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_II1104.1-CBI.1.3_Lactococcus_lactis_CBT_SL6_2022-05-09.pdf	Administrative
	Cell_Biotech_Co_Ltd_Lactococcus_lactis_CBT_SL6_2018.pdf	GRAS Notice
	Bernardeau_2006.pdf	GRAS Notice
	CDER_Starting_dose_in_Initial_Clinical_Trials_and_Therapeutics_in_Adult_Healthy_Volunteers_2005.pdf	GRAS Notice
	Dirar_1992.pdf	GRAS Notice
	EFSA_2012.pdf	GRAS Notice
	EFSA_Scientific_Opinion_on_the_Update_of_the_list_of_QPS-recommended_biological_agents.pdf	GRAS Notice
	Hesseltine_1981.pdf	GRAS Notice

**OMB Statement:** Public reporting burden for this collection of information is estimated to average 170 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services, Food and Drug Administration, Office of Chief Information Officer, [PRASStaff@fda.hhs.gov](mailto:PRASStaff@fda.hhs.gov). (Please do NOT return the form to this address.). An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

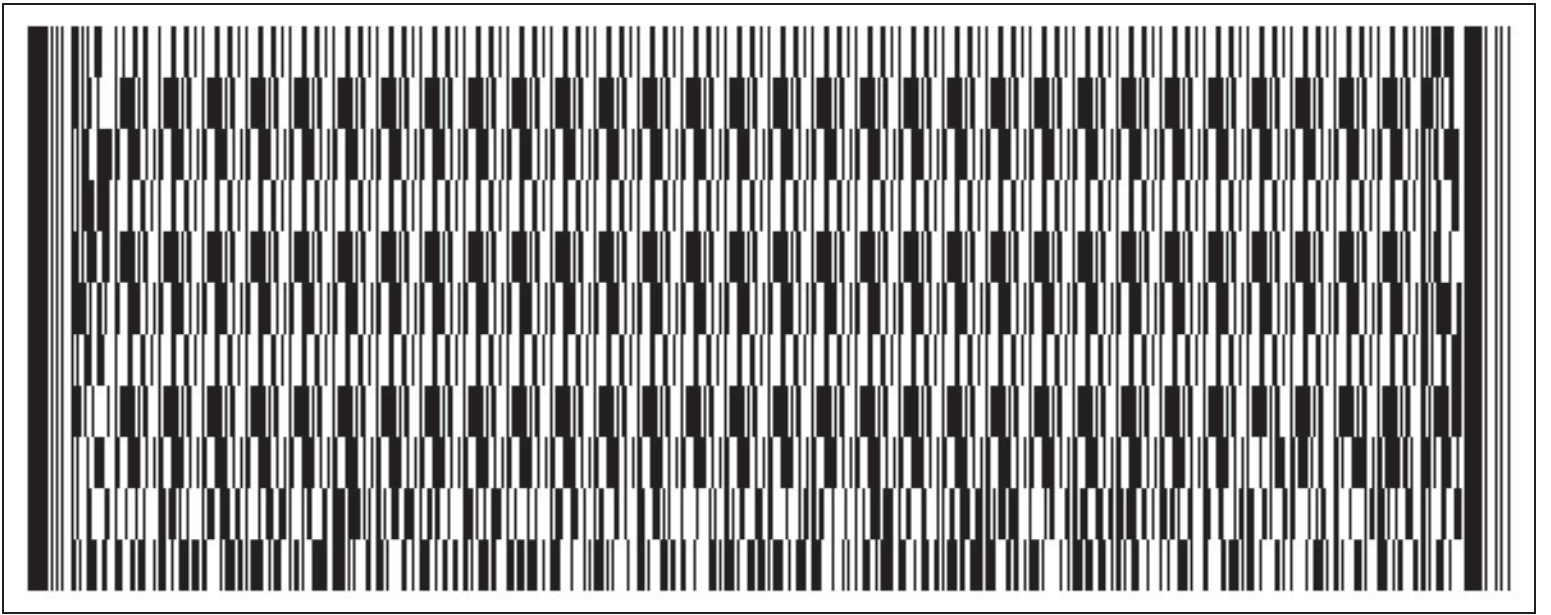


## SECTION G – LIST OF ATTACHMENTS

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)
	Hill_2014.pdf	GRAS Notice
	Hod_2017.pdf	GRAS Notice
	Hod_2018.pdf	GRAS Notice
	Lahtinen2012.pdf	GRAS Notice
	Nout_1992.pdf	GRAS Notice
	Nout_1992_15159.pdf	GRAS Notice
	Shin_2016.pdf	GRAS Notice
	Steinkraus_1992.pdf	GRAS Notice
	USDA_Economic_Research_Service.pdf	GRAS Notice

**OMB Statement:** Public reporting burden for this collection of information is estimated to average 170 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services, Food and Drug Administration, Office of Chief Information Officer, [PRAStaff@fda.hhs.gov](mailto:PRAStaff@fda.hhs.gov). (Please do NOT return the form to this address.). An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



## Viebrock, Lauren

---

**From:** Joel Villareal <joel@rejimus.com>  
**Sent:** Friday, May 26, 2023 8:37 PM  
**To:** Viebrock, Lauren  
**Cc:** Jim Lassiter; Kenneth Cairns; Brandon M. Griffin; Kent Phan; Livia Consedine  
**Subject:** [EXTERNAL] FW: GRN 001088 Questions  
**Attachments:** II1104.1-CBI.4.pdf

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

**CAUTION:** This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Dr. VieBrock,

In response to the document "2023\_05\_12 Questions GRN 1088" for the request for more information for GRN 001088 (*Lactococcus lactis* CBT SL6) and in accordance with the below correspondence, attached you will find responses to the questions/comments (II1104.1-CBI.4) 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 1088. 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](mailto:joel@rejimus.com)



REJIMUS INC.  
600 W. Santa Ana Blvd. Suite 1100 & 1110  
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**From:** Joel Villareal <joel@rejimus.com>  
**Date:** Thursday, May 18, 2023 at 10:17 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 001088 Questions

Dear Dr. VieBrock,

Thank you for your email with the questions regarding GRN 001088, on behalf of our client Cell Biotech Co. Ltd., for *Lactococcus lactis* CBT SL6. 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](mailto:joel@rejimus.com)



REJIMUS INC.  
600 W. Santa Ana Blvd. Suite 1100 & 1110  
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[www.rejimus.com](http://www.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 001088 Questions

Dear Mr. Lassiter,

During our review of GRAS Notice No. 001088, 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](mailto:lauren.viebrock@fda.hhs.gov)



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600 W. SANTA ANA BLVD. SUITE 1100

P: 949-485-2112

F: 949-200-8546

WWW.REJIMUS.COM

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 001088**  
II1104.1-CBI.4

Dear Dr. VieBrock,

REJIMUS, INC. received your email dated 5/12/23 regarding additional FDA questions/comments to GRN 001088. 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



REJIMUS, INC.™ 2023

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## FDA QUESTIONS/COMMENTS REGARDING GRN 001088

### Question 1

Please confirm that *Lactococcus lactis* strain KCTC 11865BP 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  $1 \times 10^{11}$  CFU/kg. In addition, according to the Pathogenicity Island Database ([http://www.paidb.re.kr/about\\_paidb.php?m=h](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 *Lactococcus lactis* strain KCTC 11865BP is non-pathogenic and non-toxigenic.*

### Question 2

Please identify the source that the organism was isolated from.

#### Response

*Lactococcus lactis CBT SL6 (KCTC 11865BP) was isolated from human feces.*

### 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 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. This major allergen is 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 (pages 10 and 11). The CAS numbers provided for yeast extract powder, 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 name for the ingredient

designated by CAS numbers 10034-99-8 is magnesium sulfate heptahydrate. Please confirm the name of this ingredient.

## 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]
Monobasic potassium phosphate	[7778-77-0]
Sodium carboxymethyl cellulose	[9004-32-4]

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	
<b>CAS Reg. No. (or other ID)*:</b>	10034-99-8
<b>Substance*:</b>	MAGNESIUM SULFATE
<b>Other Names:</b>	<ul style="list-style-type: none"> <li>◆ MAGNESIUM SULFATE</li> <li>◆ EPSOM SALT</li> <li>◆ MAGNESIUM SULFATE HEPTAHYDRATE</li> <li>◆ SULFURIC ACID MAGNESIUM SALT (1:1), HEPTAHYDRATE</li> <li>◆ MAGNESIUM SULFATE (1:1), HEPTAHYDRATE</li> </ul>
<b>Used for†† (Technical Effect):</b>	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
<b>Food additive and GRAS regulations (21 CFR Parts 170-186)*:</b>	184.1443

## Question 8

In Table 3, the notifier cites 21 CFR 172.320 to support the regulatory status of the use of L-arginine as a “coating ingredient” (page 11). We note that 21 CFR 172.320 authorizes the use of L-arginine as a nutrient added to food and is not applicable to its use as a coating ingredient. FDA has not evaluated its use as a coating ingredient. Therefore, we respectfully request that you provide a statement stating that you will remove the use of arginine as a coating ingredient.





## Response

*The formulation of the microorganism delivered in dry form will not use L-arginine as a coating ingredient. The coating system for the microorganism consists of the remaining ingredients shown in the original Table 3.*

Coating Ingredient	CAS No.	Reference
Trehalose	[6138-23-4]	GRN 000045
Potassium Phosphate, Dibasic	[7758-11-4]	SCOGS Report No. 32
Potassium Phosphate, Monobasic	[7778-7-0]	SCOGS Report No. 32
Xanthan Gum	[11138-66-2]	21 CFR §172.695
Corn starch	[977050-21-3]	SCOGS Report No. 115
Sodium Carboxymethylcellulose	[9004-32-4]	21 CFR §182.1745
Sodium Chloride	[7647-14-5]	21 CFR §182.1

## Question 9

In Table 4, the notifier lists specification for microorganisms, but does not provide 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 *L. lactis* strain KCTC 11865BP 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: II1104.1-CBI.4-A1*

## Question 10

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 11

On page 14, the notifier states *L. lactis* strain KCTC 11865BP is intended to be added to dairy products at concentrations needed to provide at least  $1 \times 10^{11}$  CFU per serving. According to the stability study (Table 5, page 13), the survival rate decreases ~40% during 12-months of storage. Considering the loss during storage, please provide narrative how the notifier ensures that  $1 \times 10^{11}$  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 12

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 13

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 14

On page 16, the notifier states, “three daily servings would result in a cumulative exposure of  $2.68 \times 10^{11}$  CFU per day ( $8.94 \times 10^{10} \times 3$ )”. Further, the notifier states, “the recommended levels of the cumulative exposure of  $2.68 \times 10^{11}$  CFU per day and the cumulative exposure at an estimated 90th percentile of  $5.55 \times 10^{11}$  CFU per day”. Please note that the cumulative dietary exposure should consider background sources, and all current and proposed uses of *L. lactis* strain KCTC 11865BP. 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, Lactococcus lactis strain KCTC 11865BP 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.

5/26/23

Lauren VieBrock, PhD. – United States Food and Drug Administration  
**RE: First Response to FDA Questions/Comments Regarding GRN 001088**  
II1104.1-CBI.4

**Attachments**

II1104.1-CBI.4-A1	Certificate of Analysis
-------------------	-------------------------



Attachment  
II1104.1-CBI.4-A1



## Certificate of Analysis

Product Name : *Lactococcus lactis*

Place of Production: KOREA

Batch(Lot) No. : SL6 11R

Issued Date: 08 Apr. 2020

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 17 Mar. 2017

Exp. Date: 16 Mar. 2018

Manufacturing origin country: KOREA

Shipping Origin country: KOREA

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

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

  
 Director, Head of Quality Management Division

## Certificate of Analysis

Product Name : *Lactococcus lactis*

Place of Production: KOREA

Batch(Lot) No. : SL6 21R

Issued Date: 08 Apr. 2020

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 10 May. 2017

Exp. Date: 09 May. 2018

Manufacturing origin country: KOREA

Shipping Origin country: KOREA

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

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

  
 Director, Head of Quality Management Division

## Certificate of Analysis

Product Name : *Lactococcus lactis*

Place of Production: KOREA

Batch(Lot) No. : SL6 28R

Issued Date: 08 Apr. 2020

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 15 Aug. 2017

Exp. Date: 14 Aug. 2018

Manufacturing origin country: KOREA

Shipping Origin country: KOREA

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

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

  
 Director, Head of Quality Management Division

## Viebrock, Lauren

---

**From:** Joel Villareal <joel@rejimus.com>  
**Sent:** Friday, June 23, 2023 6:51 PM  
**To:** Viebrock, Lauren  
**Cc:** Jim Lassiter; Kenneth Cairns; Brandon M. Griffin; Kent Phan; Livia Consedine  
**Subject:** [EXTERNAL] Re: GRN 001088 Questions  
**Attachments:** II1104.1-CBI.5.pdf

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Dear Dr. VieBrock,

In response to the document "2023\_05\_12 Questions GRN 1088" for the request for more information for GRN 001088 (*Lactococcus lactis* CBT SL6) and in accordance with the below correspondence, attached you will find responses to the remaining questions (II1104.1-CBI.5).

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](mailto:joel@rejimus.com)



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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 001088 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 1088 mentioned from the previous correspondence. Therefore, we anticipate to provide a response to these remaining three 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](mailto:joel@rejimus.com)



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---

**From:** Joel Villareal <joel@rejimus.com>

**Date:** Friday, May 26, 2023 at 5:37 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 001088 Questions

Dear Dr. VieBrock,

In response to the document "2023\_05\_12 Questions GRN 1088" for the request for more information for GRN 001088 (*Lactococcus lactis* CBT SL6) and in accordance with the below correspondence, attached you will find responses to the questions/comments (II1104.1-CBI.4) 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 1088. 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](mailto:joel@rejimus.com)



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---

**From:** Joel Villareal <[joel@rejimus.com](mailto:joel@rejimus.com)>  
**Date:** Thursday, May 18, 2023 at 10:17 AM  
**To:** Lauren.Viebrock@fda.hhs.gov <[Lauren.Viebrock@fda.hhs.gov](mailto:Lauren.Viebrock@fda.hhs.gov)>  
**Cc:** Jim Lassiter <[jim@rejimus.com](mailto:jim@rejimus.com)>, Brandon M. Griffin <[brandon@rejimus.com](mailto:brandon@rejimus.com)>, Kenneth Cairns <[kenneth@rejimus.com](mailto:kenneth@rejimus.com)>, Kent Phan <[kent@rejimus.com](mailto:kent@rejimus.com)>, Livia Consedine <[livia@rejimus.com](mailto:livia@rejimus.com)>  
**Subject:** FW: GRN 001088 Questions

Dear Dr. VieBrock,

Thank you for your email with the questions regarding GRN 001088, on behalf of our client Cell Biotech Co. Ltd., for *Lactococcus lactis* CBT SL6. 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](mailto: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 001088 Questions

Dear Mr. Lassiter,

During our review of GRAS Notice No. 001088, 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](mailto:lauren.viebrock@fda.hhs.gov)



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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 001088**  
II1104.1-CBI.5

Dear Dr. VieBrock,

REJIMUS, INC. received your email dated 5/12/23 regarding additional FDA questions/comments to GRN 001088. 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



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## FDA QUESTIONS/COMMENTS REGARDING GRN 001088

### Question 11

On page 14, the notifier states *L. lactis* strain KCTC 11865BP is intended to be added to dairy products at concentrations needed to provide at least  $1 \times 10^{11}$  CFU per serving. According to the stability study (Table 5, page 13), the survival rate decreases ~40% during 12-months of storage. Considering the loss during storage, please provide narrative how the notifier ensures that  $1 \times 10^{11}$  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 *L. lactis* KCTC 11865BP, the intended maximum use levels have been updated to up to  $1 \times 10^9$  CFU/serving of the ingredient.*

*With respect to the updated intended maximum use level of up to  $1 \times 10^9$  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  $1 \times 10^9$  CFU/serving.*

### Question 12

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  $1 \times 10^9$  CFU/serving. The food serving size for the food subcategories of milk is based on the reference amounts customarily consumed (RACC).*

<b>Food Code</b>	<b>Food Subcategories</b>	<b>Serving Size</b>	<b>Food Serving</b>
11100000	Milk, NFS	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11111000	Milk, whole	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11111100	Milk, low sodium, whole	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11111150	Milk, calcium fortified, whole	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11111160	Milk, calcium fortified, low fat (1%)	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11111170	Milk, calcium fortified, fat free (skim)	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11112110	Milk, reduced fat (2%)	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11112210	Milk, low fat (1%)	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11113000	Milk, fat free (skim)	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11114300	Milk, lactose free, low fat (1%)	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11114320	Milk, lactose free, fat free (skim)	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11114330	Milk, lactose free, reduced fat (2%)	Up to $1 \times 10^9$ CFU/serving	8 fl oz or 240mL
11114350	Milk, lactose free, whole	Up to $1 \times 10^9$ 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  $1 \times 10^9$  CFU/serving is reasonable to be safe for consumption.

### Question 13

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  $1 \times 10^9$  CFU/serving, the estimated dietary exposure, based suggested three daily servings, is shown below:



6/23/23

Lauren VieBrock, PhD. – United States Food and Drug Administration  
**RE: Second Response to FDA Questions/Comments Regarding GRN 001088**  
II1104.1-CBI.5

<i>Population Group</i>	<i>Age Group</i>	<i>Eaters only (CFU/day)</i>	
		<i>Mean</i>	<i>90th Percentile</i>
<i>Total Population (eaters-only)</i>	<i>2 years old and older</i>	<i>2.68 x 10<sup>9</sup></i>	<i>5.55 x 10<sup>9</sup></i>

## 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 complete.

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

**CAUTION:** This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

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](mailto:joel@rejimus.com)



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---

**From:** Highbarger, Lane A <[Lane.Highbarger@fda.hhs.gov](mailto:Lane.Highbarger@fda.hhs.gov)>  
**Date:** Wednesday, October 4, 2023 at 6:25 AM  
**To:** Jim Lassiter <[jim@rejimus.com](mailto: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

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## Viebrock, Lauren

---

**From:** Joel Villareal <joel@rejimus.com>  
**Sent:** Tuesday, October 17, 2023 7:18 PM  
**To:** Viebrock, Lauren  
**Cc:** Jim Lassiter; Brandon M. Griffin; Kenneth Cairns; Jonathan Fink; Kent Phan; Livia Consedine  
**Subject:** [EXTERNAL] FW: GRN 001088 Questions  
**Attachments:** II1104.1-CBI.6.pdf

**CAUTION:** This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Dr. VieBrock,

In response to the document "2023\_10\_13 Questions GRN 1088" for the request for more information for GRN 001088 (*Lactococcus lactis* CBT SL6), attached you will find responses to the questions (II1104.1-CBI.6) 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](mailto: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 001088 Questions

Dear Mr. Lassiter,

During our review of GRAS Notice No. 001088, 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

U.S. Food and Drug Administration

Tel: 301-796-7454

[lauren.viebrock@fda.hhs.gov](mailto:lauren.viebrock@fda.hhs.gov)



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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

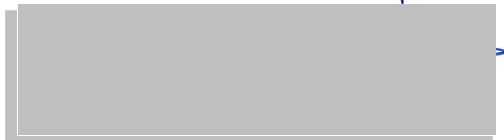
**RE: Response to FDA Questions/Comments Regarding GRN 001088 Received on 10/13/23**  
II1104.1-CBI.6

Dear Dr. VieBrock,

REJIMUS, INC. received your email dated 10/13/23 regarding additional FDA questions/comments to GRN 001088. 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



REJIMUS, INC. ™ 2023

10/17/23

Lauren VieBrock, PhD. – United States Food and Drug Administration

**RE: Response to FDA Questions/Comments Regarding GRN 001088 Received on 10/13/23**

II1104.1-CBI.6

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REJIMUS, INC. ™ 2023



## FDA QUESTIONS/COMMENTS REGARDING GRN 001088

### Question 1

1. In the May 26, 2023 amendment (response to question 9), 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  $\leq 1$  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  $\leq 1$  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  $\leq 0.1$  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  $\leq 1$ mg/kg, the specification in the attached COAs was based on production from 2017. 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  $\leq 10$  ppb ( $\leq 0.01$  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  $\leq 0.1$  mg/kg.

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

<b>Parameter</b>	<b>Limits</b>	<b>Method</b>
Appearance	Light brown powder	Visual
Viable Cell Count	$\geq 1.0 \times 10^{11}$ 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	$\leq 10$ 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	$\leq 0.01$ mg/kg	Korean FDA Food Code, VIII. Food Analytical Method, 9.1 Heavy Metal
Cadmium	$\leq 0.1$ mg/kg	Korean FDA Food Code, VIII. Food Analytical Method, 9.1 Heavy Metal
Mercury	$\leq 0.1$ mg/kg	Korean FDA Food Code, VIII. Food Analytical Method, 9.1 Heavy Metal
Arsenic	$\leq 0.1$ mg/kg	Korean FDA Food Code, VIII. Food Analytical Method, 9.1 Heavy Metal

Attachment(s) II1104.1-CBI.6-A1

## Question 2

2. In the amendment dated June 23, 2023 (response to Question 13)), the notifier multiplied the values of  $8.94 \times 10^8$  CFU/person (p)/d and  $1.85 \times 10^9$  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  $8.94 \times 10^8$  CFU/p/d and  $1.85 \times 10^9$  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  $8.94 \times 10^8$  CFU /p/d at the mean and  $1.85 \times 10^9$  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 001088 that the estimated eaters-only dietary exposure of the ingredient for the U.S. population aged 2 years and older is  $8.94 \times 10^8$  CFU/p/d at the mean and  $1.85 \times 10^9$  CFU/p/d at the 90th percentile. As such, the updated dietary exposure estimates would not affect the GRAS conclusion for GRN 001088.*

## 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

II1104.1-CBI.6-A1	Certificate of Analysis
-------------------	-------------------------

Attachment  
II1104.1-CBI.6-A1



## Certificate of Analysis

Product Name : *Lactococcus lactis*

Place of Production: KOREA

Batch(Lot) No. : SL6 11R

Issued Date: 08 Apr. 2020

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 17 Mar. 2017

Exp. Date: 16 Mar. 2018

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	0.0026 mg/kg
Cadmium (Cd)**	$\leq 0.3$ mg/kg	0.0022 mg/kg
Mercury (Hg)***	$\leq 0.1$ mg/kg	0.0024 mg/kg
Arsenic (As)****	$\leq 0.1$ mg/kg	0.0053 mg/kg

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

\* 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

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## Certificate of Analysis

Product Name : *Lactococcus lactis*

Place of Production: KOREA

Batch(Lot) No. : SL6 21R

Issued Date: 08 Apr. 2020

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 10 May. 2017

Exp. Date: 09 May. 2018

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	0.0033 mg/kg
Cadmium (Cd)**	$\leq 0.3$ mg/kg	0.0035 mg/kg
Mercury (Hg)***	$\leq 0.1$ mg/kg	0.0028 mg/kg
Arsenic (As)****	$\leq 0.1$ mg/kg	0.0046 mg/kg

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

\* 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

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## Certificate of Analysis

Product Name : *Lactococcus lactis*

Place of Production: KOREA

Batch(Lot) No. : SL6 28R

Issued Date: 08 Apr. 2020

Net Weight : 10kg(10kg × 1ea)

Mfg. Date: 15 Aug. 2017

Exp. Date: 14 Aug. 2018

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	0.0074 mg/kg
Cadmium (Cd)**	$\leq 0.3$ mg/kg	0.0005 mg/kg
Mercury (Hg)***	$\leq 0.1$ mg/kg	0.0002 mg/kg
Arsenic (As)****	$\leq 0.1$ mg/kg	0.0014 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.**

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Manufacturer : 397, Aegibong-ro, Wolgot-myeon, Gimpo-si, Gyeonggi-do, Korea

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