GRAS Associates, LLC
11810 Grand Park Ave
Suite 500
North Bethesda, MD 20852
T: 519.341.3667 | F: 888.531.3466
www.gras-associates.com

March 14, 2022

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

Attention: Dr. Susan Carlson
Re: GRAS Notification – *Weissella cibaria* Strain CMU

Dear Dr. Carlson:

GRAS Associates, LLC, acting as the Agent for OraPharm, Inc. (Republic of Korea), is submitting for FDA review Form 3667 and the enclosed CD, free of viruses, containing a GRAS Notification for *Weissella cibaria* Strain CMU. Along with OraPharm, Inc.'s determination of safety, an Expert Panel of qualified persons was assembled to assess the composite safety information of the subject substance with the intended use as a food ingredient in selected conventional foods including yogurt, frozen desserts (dairy, ices, sorbets and sherbets) and mixes, hard candy and chewing gum at use levels to provide 1×10^8 CFU per serving throughout the shelf life of the product (with initial addition levels of 2×10^8 CFU to 8×10^9 CFU per serving depending on the specific product). The attached documentation contains the specific information that addresses the safe human food uses for the subject notified substance as discussed in the GRAS guidance document.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via telephone or email.

We look forward to your feedback.

Sincerely,

[redacted]

William J. Rowe

President
Agent for OraPharm, Inc.
GRAS Associates, LLC
1810 Grand Park Ave, Suite 500
North Bethesda, MD 20852
wrowe@nutrasource.ca
Enclosure: GRAS Notification for OraPharm, Inc. – *Weissella cibaria* Strain CMU

Safety Evaluation Dossier Supporting the Generally Recognized as Safe (GRAS) Conclusion

of

Weissella cibaria
Strain CMU

Food Usage Conditions for General Recognition of Safety

on behalf of

OraPharm, Inc.

905 ho, Bluestone Tower, 9-16, Yeonmujang 5-gil,
Seongdong-gu, Seoul, Republic of Korea

3/11/22

TABLE OF CONTENTS

FIGURES

TABLES

FOREWORD

OraPharm, Inc. (“OraPharm”) based our Generally Recognized as Safe (GRAS) assessment of the *Weissella cibaria* (*W. cibaria*) strain CMU, primarily on the composite safety information, i.e., scientific procedures with corroboration from history of use. The safety/toxicity of *W. cibaria*, history of use of *W. cibaria*, and compositional details, specifications, and method of preparation of the subject ingredient were reviewed. In addition, a search of the scientific and regulatory literature was conducted through October 11, 2021, with particular attention paid to adverse reports, as well as those that supported conclusions of safety. Those references that were deemed pertinent to this review are listed in Part 7. The composite safety/toxicity studies, in concert with dietary exposure information, ultimately provide the specific scientific foundation for the GRAS conclusion.

At OraPharm’s request, GRAS Associates, LLC (“GA”) convened an Expert Panel to complete an independent safety evaluation of OraPharm’s *W. cibaria* CMU product. The purpose of the evaluation is to ascertain whether OraPharm’s *W. cibaria* strain CMU is generally recognized as safe, i.e., GRAS, under the intended conditions of use. In addition, OraPharm has asked GA to act as Agent for the submission of this GRAS notification to FDA.

PART 1. SIGNED STATEMENTS AND CERTIFICATION

A. Claim of Exemption from the Requirement for Premarket Approval Pursuant to 21 CFR 170.30

OraPharm has concluded that our *Weissella cibaria* strain CMU, referred to as “*W. cibaria* CMU”, “strain CMU” or “CMU”, and which meets the specifications described below, is GRAS in accordance with Section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). This conclusion was made in concert with an appropriately convened panel of experts who are qualified by scientific training and experience. The GRAS conclusion is based on scientific procedures as described in the following sections. The evaluation accurately reflects the intended conditions of food use for the designated *W. cibaria* CMU preparation.

This signed statement and certification has been prepared in accordance with the requirements of 21 CFR 170.225.

(a) This certification is signed by a responsible official of GRAS Associates, LLC acting as agent for OraPharm.

(b) This GRAS dossier did not rely on any confidential information.

(c) (1) This Independent GRAS Assessment was conducted in accordance with Subpart E of 21 CFR Part 170.

(c) (2) Names and addresses of organizations:

Sponsoring Party:
OraPharm, Inc.
905 ho, Bluestone Tower, 9-16, Yeonmujang 5-gil,
Seongdong-gu, Seoul, Republic of Korea

Agent:
GRAS Associates, LLC
11810 Grand Park Avenue
Suite 500
North Bethesda, MD 20852

(c) (3) The name of the ingredient is *Weissella cibaria* CMU.

(c) (4) *Weissella cibaria* CMU will be used as an ingredient in frozen dairy desserts and mixes, yogurt and hard candy, including mints and chewing gum.

(c) (5) The statutory basis for our conclusion of GRAS status is through scientific procedures in accordance with § 170.30(a) and (b).

(c) (6) It is our view that the ingredient is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on our conclusion that the notified substance is GRAS under the conditions of its intended use.

(c) (7) If FDA were to ask to see the data and information that are the basis for our conclusion of GRAS status, either during or after FDA evaluation of this notice, we agree to:

(i) make the data and information available to FDA; and

(ii) agree to both of the following procedures for making the data and information available to FDA:

(A) Upon FDA's request, we will allow FDA to review and copy the data and information during customary business hours at our address specified where these data and information will be available; and

(B) Upon request by FDA, we will provide FDA with a complete copy of the data and information either in an electronic format that is accessible for their evaluation or on paper.

(c) (8) None of the data and information in Parts 2 through 7 of this GRAS notice are exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552 (e.g., as trade secret or as commercial or financial information that is privileged or confidential).

(c) (9) We certify that, to the best of our knowledge, this GRAS Assessment is a complete, representative, and balanced review 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 the substance.

(c) (10) OraPharm does not intend to add *Weissella cibaria* CMU to any meat and/or poultry products that come under FSIS/USDA jurisdiction. Therefore, 21 CFR 170.270 does not apply.

(c) (11) Signature

Agent for OraPharm

William J. Rowe
President
GRAS Associates, LLC
11810 Grand Park Ave
Suite 500
North Bethesda, MD 20852

Date: March 11, 2022

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

A. Notified Substance *Weissella cibaria* CMU Identification

1. Common or Usual Name

Weissella cibaria strain CMU.

"*W. cibaria* CMU", "strain CMU" or "CMU" are terms used throughout this document when referring to the notified substance. The notified substance is also referred to as oraCMU in the literature and other publications as this strain has been commercially available in Korea as oraCMU® since 2017.

2. Historical Information on *Weissella cibaria*

The *Weissella* genus includes a number of heterofermentative Leuconostoc-like lactic acid bacteria (LAB) that are generally isolated from fermented foods (Ennahar and Cai, 2004; Abriouel et al., 2015). Introduced in 1993, the genus *Weissella* includes some species previously belonging to the *Leuconostoc mesenteroides* species group (Bourdichon et al., 2012; Collins et al., 1993). *W. cibaria* strains are commonly found in fermented foods like cassava, meat/fish, kimchi, tarhana, and sourdough (Bourdichon et al., 2012; Lim et al., 2018).

W. cibaria is described by Kang et al. (2017) as a "short, rod-shaped, Gram-positive, non-spore-forming, nonmotile, heterofermentative, and catalase-negative lactic acid bacterium". The phenotype is characteristic of the genus *Weissella* (Collins et al., 1993; Vos et al., 2009).

3. Characterization of *Weissella cibaria* CMU

The complete genome for *W. cibaria* CMU has been sequenced and deposited in GenBank under accession number CP013936 (NCBI GenBank, 2021; Kang et al., 2017). Strain CMU was deposited in the Korean Collection for Type Cultures on June 04, 2004, with the accession number KCTC 10650BP. *W. cibaria* strain CMU is not genetically modified.

As reported by Kang et al. (2019) strain CMU was isolated from "saliva samples from 460 kindergarten children aged 4 to 7 residing in Gwangju, South Korea". It should be noted that the strain isolation source was originally published as being from infant saliva (Kang et al., 2017) which is also the source information currently identified in the NCBI database for strain CMU; however, OraPharm has confirmed that the source reported in the Kang et al. (2019) publication is the correct information.

The taxonomy for *W. cibaria* CMU is presented in Table 1.

Table 1. Taxonomy of *W. cibaria* CMU

Super Kingdom	Bacteria
Clade	Terrabacteria group
Phylum	Firmicutes
Class	Bacilli
Order	Lactobacillales
Family	*Lactobacillaceae / Leuconostocaceae*
Genus	*Weissella*
Species	*cibaria*
Strain	CMU

NCBI Genome (2021); NCBI Taxonomy (2021); UniProt Taxonomy (2021)

Cell morphology of strain CMU is documented by Lim et al. (2018) and is shown in Figure 1. Consistent with morphology for the *Weissella* species, strain CMU is described as short rods that grow in pairs with the dimensions of 0.5–0.7 µm wide and 1.3–2.5 µm long.

Figure 1. Cell Morphology of *W. cibaria* CMU[a]

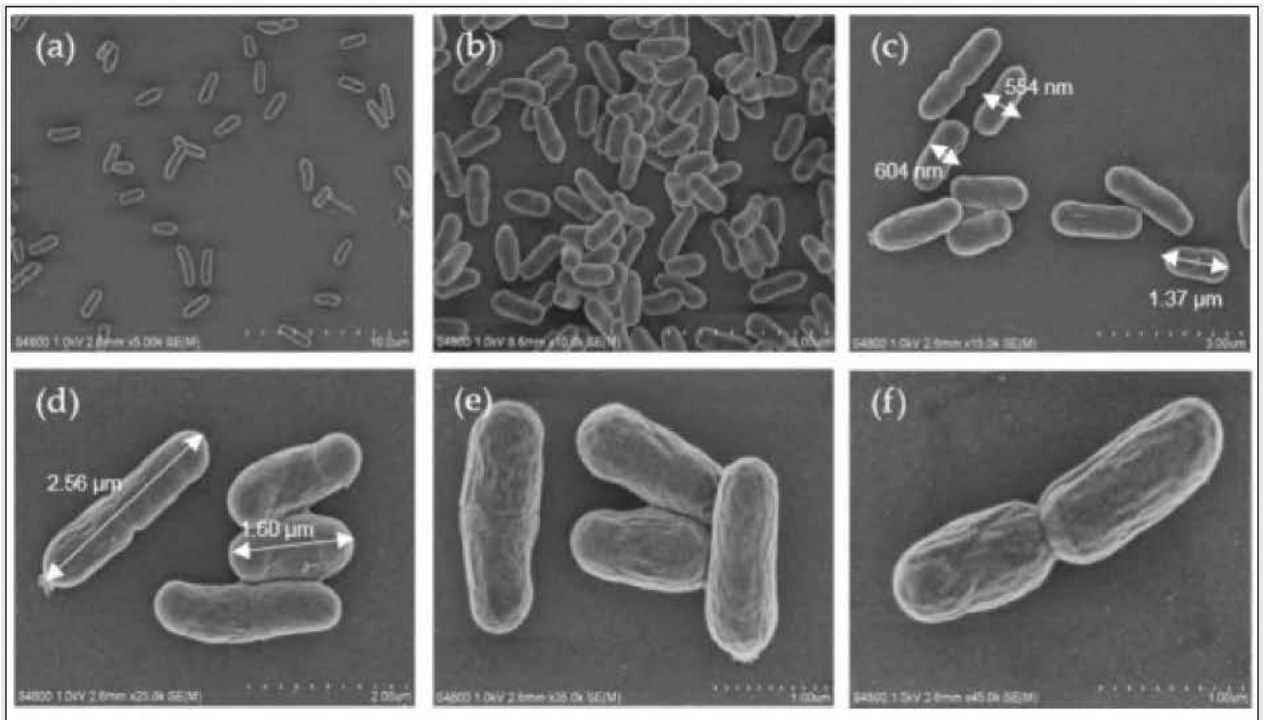


Figure 1. Scanning electron microscopic (SEM) images of oraCMU at various magnifications: 5000× (**a**), 10,000× (**b**), 15,000× (**c**), 25,000× (**d**), 35,000× (**e**), and 45,000× (**f**).

[a] Lim et al. (2018)

W. cibaria strain CMU is a strain that has been commercially available in Korea since 2017. Strain CMU is also known under the trade name oraCMU® and OraPharm owns the exclusive license for the U.S. patent[1] for "lactic acid bacteria inhibiting halitosis".

Strain CMU has been identified as *W. cibaria* based on whole genome sequence (WGS) analysis, 16S ribosomal ribonucleic acid (rRNA) alignment and phylogenetic homology, average nucleotide identity (ANI), and phenotypic evaluations. The National Center for Biotechnology Information (NCBI) database also includes identity information for strain CMU which is included in the review below. Taken together, the CMU isolate is well established as *W. cibaria*.

a. Genomic Characterization

Strain CMU has a whole genome sequence (WGS) and is available in the NCBI database (NCBI GenBank, 2021). The methods of DNA isolation and sequencing are provided in Kang et al. (2017). The CMU isolate was designated as *W. cibaria*. The genomic information and comparisons of the Genome Assembly and Annotation reports from the NCBI database are summarized in Table 2.

Analysis of the CMU genome identified one plasmid (Kang et al., 2017; NCBI Genome Assembly and Annotation, 2021). Strain CMU has not been genetically modified.

NCBI data notes that strain CMU has symmetrical identity of 89.7517% and gapped identity of 98.4144% with the closest species reference genome (BC14) (NCBI Genome Neighbor Report CMU, 2021). NCBI data also notes that strain CMU has symmetrical identity of >99% with three *W. cibaria* genomes (strains CMS1, CMS2, CMS3), with the closest genome being strain CMS3 with a symmetrical identity of 99.5524% and gapped identity of 99.99% (NCBI Genome Assembly and Annotation, 2021). The calculated alignments of strain CMU to strain BC14 and strain CMS3 are available from the NCBI database and are shown in Appendix 1 (NCBI Genome Neighbor Report CMU, 2021). The *W. cibaria* genome tree and cladogram are also available from the NCBI database and support the identification of strain CMU as shown in Appendix 1 (NCBI Genome Tree Report CMU, 2021).

Table 2. Genome Comparison of *W. cibaria* strains

	Assembly Level	Contigs	Total Length (Mb)	GC%	Protein Count	rRNA	tRNA	Other RNA	Gene	Pseudogene
***W. cibaria* median values (n=51 genome assemblies)** [a]	N/A	N/A	2.45564	44.9	2200	N/A	N/A	N/A	N/A	N/A
***W. cibaria* BC14** [b]	Contig	3	2.51323	44.9	2242	28	88	3	2386	25
***W. cibaria* 12495** [c]	Contig	25	2.32395	45.1	2088	11	77	3	2195	16
***W. cibaria* CH2** [d]	Complete	7	2.57773	44.746	2294	25	88	3	2515	105
***W. cibaria* CMS3** [e]	Complete	2	2.36349	45.239	2080	28	88	3	2221	22

[1] See https://patents.google.com/patent/US7250162B2/en. Accessed May 28, 2021.

	Assembly Level	Contigs	Total Length (Mb)	GC%	Protein Count	rRNA	tRNA	Other RNA	Gene	Pseudogene
CMS3 Chromosome	N/A	N/A	2.34	45.3	2058	28	88	3	2198	21
CMS3 Plasmid	N/A	N/A	0.02	38.3	22	--	--	--	23	1
***W. cibaria* CMU [f]**	Complete	2	2.38147	45.245	2084	33	90	3	2236	26
CMU Chromosome	N/A	N/A	2.36	45.3	2063	33	90	3	2214	25
CMU Plasmid	N/A	N/A	0.02	38.4	21	--	--	--	22	1

[a] Available at: https://www.ncbi.nlm.nih.gov/genome/3287. Accessed Aug 26, 2021.
[b] *W. cibaria* BC14. NCBI species reference. Available at: https://www.ncbi.nlm.nih.gov/genome/3287?genome_assembly_id=648503. Accessed Aug 26, 2021.
[c] *W. cibaria* 12495. Species reference. Available at: https://www.ncbi.nlm.nih.gov/genome/3287?genome_assembly_id=524481. Accessed Aug 26, 2021.
[d] *W. cibaria* CH2. Species reference. Values in this row include both the chromosome and plasmids (strain CH2 is listed as having 6 plasmids – these are not included individually in this table). Available at: https://www.ncbi.nlm.nih.gov/genome/3287?genome_assembly_id=278405. Accessed Aug 26, 2021.
[e] *W. cibaria* CMS3. NCBI closest genome to strain CMU. Values in this row include both the chromosome and plasmid. Available at: https://www.ncbi.nlm.nih.gov/genome/3287?genome_assembly_id=301995. Accessed Aug 26, 2021.
[f] *W. cibaria* CMU. Values in this row include both the chromosome and plasmid. Available at: https://www.ncbi.nlm.nih.gov/genome/3287?genome_assembly_id=418159. Accessed Aug 26, 2021.

GC – guanine-cytosine; Mb – megabases; N/A – not available; n – number; RNA – ribonucleic acid; rRNA – ribosomal ribonucleic acid; tRNA – transfer ribonucleic acid

b. 16S rRNA Alignment

Macrogen (Seoul, South Korea) performed 16S rRNA analyses on several lots of strain CMU. 16S sequence similarity of >98.7% to the type strain is generally considered the appropriate cutoff for the species boundary (Chun et al., 2018). The results from the 16S rRNA alignment and phylogenetic analysis are consistent with species similarity and support designation of strain CMU as *W. cibaria*. The 16S rRNA alignment data is summarized for six samples in Table 3. A representative image for one CMU sample is presented in Figure 2 which shows phylogenetic homology with *W. cibaria*. The 16S reports and the phylogenetic homology images for each lot in Table 3 are presented in Appendix 2. The 16S reports and the phylogenetic homology support the identity of strain CMU as *W. cibaria*. The 16S reports did also show that strain CMU shared a 99% identity with *W. confusa* strain JCM 1093. The strong similarity between *W. cibaria* and *W. confusa* is consistent with what is known in the literature (Fusco et al., 2015; Vos et al., 2009). Based on the ANI analyses (Part 2.A.3.c) and the phenotypic analyses (Part 2.A.3.d), however, OraPharm clearly distinguished strain CMU from *W. confusa* and confirmed the identity as *W. cibaria*.

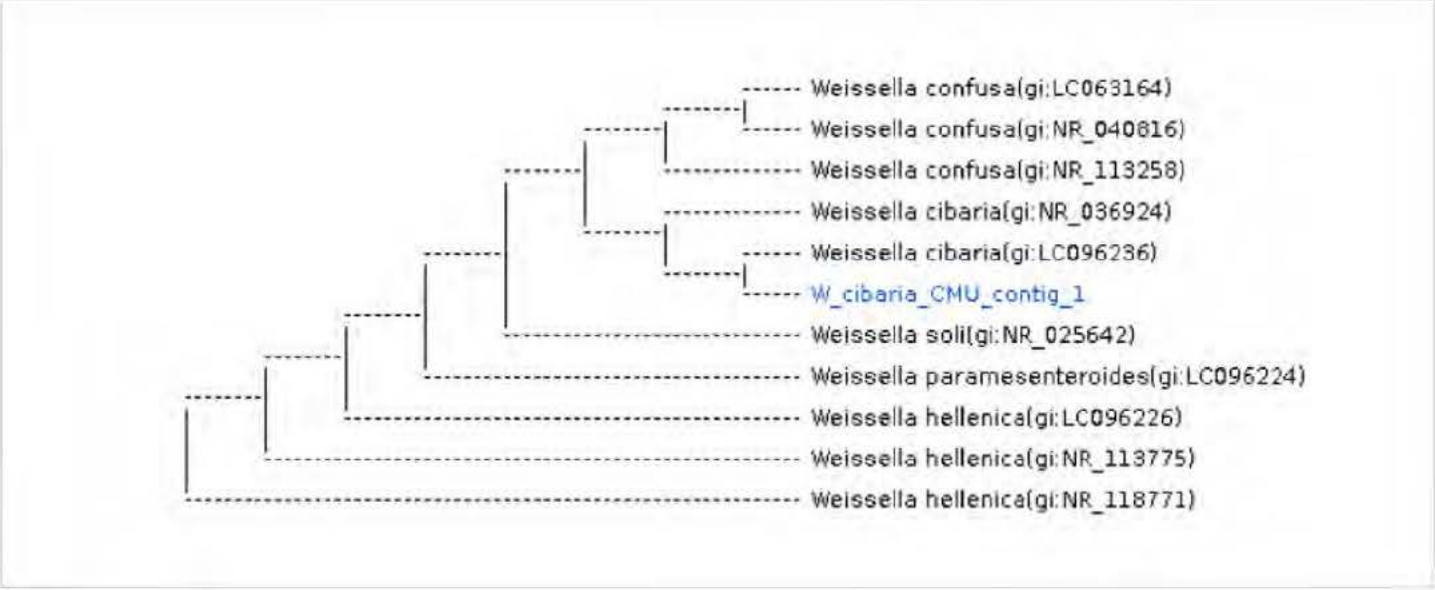
Table 3. 16S rRNA Alignment Data of Strain CMU to *W. cibaria* by Lot Number

	Subject						Score		Identities	
Sample [a]	**Accession**	**Description**	**Length**	**Start**	**End**	**Coverage**	**Bit**	**E-Value**	**Match / Total**	**Pct (%)**
W_cibaria_CMU_contig_1	LC096236.1	*Weissella cibaria*	1516	7	1509	99	2758	0.0	1501/1505	99
Lot_CI11-0115N_contig_1	LC096236.1	*Weissella cibaria*	1516	10	1516	99	2772	0.0	1505/1507	99
Lot_CI11-0116N_contig_1	LC096236.1	*Weissella cibaria*	1516	6	1516	99	2787	0.0	1510/1511	99

	Subject						Score		Identities	
Sample [a]	Accession	Description	Length	Start	End	Coverage	Bit	E-Value	Match / Total	Pct (%)
Lot_CI11-0117N_contig_1	LC096236.1	*Weissella cibaria*	1516	6	1516	99	2787	0.0	1510/1511	99
Lot CI11-0362N_contig_1	LC096236.1	*Weissella cibaria*	1516	4	1513	99	2780	0.0	1509/1511	99
Lot CI11-0366N_contig_1	LC096236.1	*Weissella cibaria*	1516	6	1514	99	2776	0.0	1507/1509	99

[a] Reference strain is *W. cibaria* strain JCM 12495

Figure 2. Representative Image Showing Phylogenetic Homology of Strain CMU to *W. cibaria* Reference Strains JCM 12495 (LC096236) and II-I-5 (NR_036924)



c. Average Nucleotide Identity (ANI)

ANI analysis is an appropriate method for species identification and an ANI value of ~95.0% can be considered a boundary for species delineation in bacteria (Goris et al., 2007; Richter and Rossello-Mora, 2009). Chun et al. (2018) recommend using a combination of 16S similarity (with the cutoff of 98.7% similar or higher) along with methods like ANI for taxonomy identification.

OraPharm analyzed strain CMU with several established algorithms:

- OrthoANI with USEARCH[2] (Yoon et al., 2017; Lee et al., 2016)
  - Online calculator that uses the OrthoANIu algorithm, with USEARCH instead of BLAST

[2] See: https://www.ezbiocloud.net/tools/ani (Accessed Nov. 24, 2021)

- JSpeciesWS[3] (Richter et al., 2016)
  - Online database for *in silico* calculation of the extent of identity between two genomes based on BLAST+ (ANIb) and MUMmer (ANIm) and through the Tetra correlation search (TCS) and Tetra-nucleotide signature correlation index
    - The Tetra Correlation Search function (TCS) allows to rapidly compare selected genomes against a continuously updated online reference database with currently about 32,000 published whole and draft genome sequences.
    - Tetra-nucleotide signature correlation index (Tetra) is an alignment-free parameter correlating with the ANI and provides a list of the most similar genomes based on their resulting Tetra-nucleotide signature correlation index.
- ANI Calculator[4] (Goris et al., 2007)
  - Estimates the ANI with best hits (one-way ANI) and reciprocal best hits (two-way ANI) between the two genomic datasets and calculated as described by Goris et al. (2007). Results above 95% are typical for genomes in the same species.

The ANI analyses assessed strain CMU similarity with six *W. cibaria* strains (strains BC14, CH2, JCM 12495, CMS1, CMS2, CMS3) along with six strains belonging to other *Weissella* species (*W. confusa* VTT E-133279, *W. hellenica* CCUG 33494, *W. kandleri* DSM 20593, *W. paramesenteroides* FDAARGOS 414, *W. soli* KACC 11848, and *W. thailandensis* JCM 10695).

As shown below and in Appendix 3, the pairwise genome comparisons consistently find strain CMU above the specified thresholds for species identification as *W. cibaria*. Results from these methods of analysis demonstrated that strain CMU consistently met the recognized thresholds to confirm identification as *W. cibaria*. Taken together, these results support the 16S ID reports, confirm strain CMU identity as *W. cibaria*, and distinguish strain CMU from other *Weissella* species.

OrthoANIu

As shown in Appendix 3 and Table 4, the OrthoANIu results show that strain CMU is consistently above the 95% threshold compared to the other *W. cibaria* strains but not the other *Weissella* species, supporting identification of strain CMU as *W. cibaria*.

Table 4. OrthoANIu Results by Genome

Genome Sequence A	Genome Sequence B	OrthoANIu Value (%)	Genome A Length (bp)	Genome B Length (bp)	Average Aligned Length (bp)	Genome A Coverage (%)	Genome B Coverage (%)
W. cibaria CMU.fasta	*W. cibaria* CMS1.fasta	99.90	2,362,320	2,341,920	1,266,485	53.61	54.08
W. cibaria CMU.fasta	*W. cibaria* CMS2.fasta	99.93	2,362,320	2,341,920	1,531,922	64.85	65.41

[3] See: http://jspecies.ribohost.com/jspeciesws/ (Accessed Nov. 24, 2021)
[4] See: http://enve-omics.ce.gatech.edu/ani/ (Accessed Nov. 24, 2021)

Genome Sequence A	Genome Sequence B	OrthoANIu Value (%)	Genome A Length (bp)	Genome B Length (bp)	Average Aligned Length (bp)	Genome A Coverage (%)	Genome B Coverage (%)
W. cibaria CMU.fasta	*W. cibaria* CMS3.fasta	99.92	2,362,320	2,341,920	1,679,193	71.08	71.70
W. cibaria CMU.fasta	*W. cibaria* JCM 12495.fasta	99.94	2,362,320	405,960	270,773	11.46	66.70
W. cibaria CMU.fasta	*W. cibaria* BC14.fasta	98.45	2,362,320	2,472,480	1,644,774	69.63	66.52
W. cibaria CMU.fasta	*W. cibaria* CH2.fasta	96.90	2,362,320	2,466, 360	1,526,677	64.63	61.90
W. cibaria CMU.fasta	*W. confusa* VTT E-133279.fasta	79.01	2,362,320	2,211,360	957,212	40.52	43.29
W. cibaria CMU.fasta	*W. hellenica* CCUG 33494.fasta	74.05	2,362,320	379,440	127,025	5.38	33.48
W. cibaria CMU.fasta	*W. kandleri* DSM 20593.fasta	68.16	2,362,320	326,400	66,726	2.82	20.44
W. cibaria CMU.fasta	*W. soli* KACC 11848.fasta	71.75	2,362,320	1,683,000	480,099	20.32	28.53
W. cibaria CMU.fasta	*W. thailandensis* JCM 10695.fasta	69.79	2,362,320	197.880	30,349	1.28	15.34

bp = base pairs
Green text indicates results are above the cutoff (>95%)
Red text indicates results are below the cutoff (<95%)

JSpeciesWS

Strain CMU ANIb results for aligned nucleotides indicated a similarity with the six *W. cibaria* strains above the 95% threshold, whereas the similarity with all other *Weissella* species, including *W. confusa*, was only 67.32–78.23% (see Appendix 3). The ANIb summary results by genome are shown in Table 5. Similarly, the ANIm results for strain CMU showed the ANIm values were above the cutoff of 95% for the six *W. cibaria* strains evaluated but were below the 95% cutoff for all other *Weissella* species, including *W. confusa* (see Appendix 3). The ANIm summary results by genome are shown in Table 6. The Tetra Correlation Search (TCS) function results were consistent with identification as W. cibaria (see Appendix 3). The Tetra-nucleotide signature correlation index (Tetra) results indicate that similarity of strain CMU with the five of the six *W. cibaria* strains evaluated was above (>0.999) or in range (>0.989) of the threshold cutoff, whereas all other *Weissella* species were below the threshold cutoff (see Appendix 3). The tetra-nucleotide signature correlation index summary results by genome are shown in Table 7.

Table 5. ANIb Summary Results by Genome

Genome Sequence A	Genome Sequence B	ANIb (%)	Aligned (%)	Aligned (bp)	Total (bp)
W. cibaria CMU.fasta	*W. cibaria* CMS1.fasta	99.99	99.91	2,360,306	2,362,501
W. cibaria CMU.fasta	*W. cibaria* CMS2.fasta	99.99	99.94	2,360,990	2,362,501
W. cibaria CMU.fasta	*W. cibaria* CMS3.fasta	99.99	99.95	2,361,358	2,362,501
W. cibaria CMU.fasta	*W. cibaria* JCM 12495.fasta	98.01*	17.84	421,460	2,362,501
W. cibaria CMU.fasta	*W. cibaria* BC14.fasta	98.29	93.94	2,219,251	2,362,501
W. cibaria CMU.fasta	*W. cibaria* CH2.fasta	96.72	91.75	2,167,678	2,362,501
W. cibaria CMU.fasta	*W. confusa* VTT E-133279.fasta	78.23	63.61	1,502,901	2,362,501
W. cibaria CMU.fasta	*W. hellenica* CCUG 33494.fasta	71.75*	8.50	200,719	2,362,501
W. cibaria CMU.fasta	*W. kandleri* DSM 20593.fasta	67.32*	4.42	104,393	2,362,501
W. cibaria CMU.fasta	*W. soli* KACC 11848.fasta	71.28	35.65	842,158	2,362,501
W. cibaria CMU.fasta	*W. thailandensis* JCM 10695.fasta	68.45*	2.24	52,935	2,362,501
W. cibaria CMU.fasta	*W. paramesenteroides FDAARGOS* 414.fasta	72.22	43.07	1,017,454	2,362,501

Green text indicates results are above the cutoff (>95%)
Red text indicates results are below the cutoff (<95%)
*Denotes suspicious alignment

Table 6. ANIm Summary Results by Genome

Genome Sequence A	Genome Sequence B	ANIb (%)	Aligned (%)	Aligned (bp)	Total (bp)
W. cibaria CMU.fasta	*W. cibaria* CMS1.fasta	99.98	100.00	2,362,501	2,362,501
W. cibaria CMU.fasta	*W. cibaria* CMS2.fasta	99.99	100.00	2,362,501	2,362,501
W. cibaria CMU.fasta	*W. cibaria* CMS3.fasta	99.99	100.00	2,362,500	2,362,501
W. cibaria CMU.fasta	*W. cibaria* JCM 12495.fasta	99.99*	17.54	414,378	2,362,501
W. cibaria CMU.fasta	*W. cibaria* BC14.fasta	98.48	94.79	2,239,482	2,362,501
W. cibaria CMU.fasta	*W. cibaria* CH2.fasta	96.93	93.14	2,200,403	2,362,501
W. cibaria CMU.fasta	*W. confusa* VTT E-133279.fasta	87.36	28.14	664,875	2,362,501
W. cibaria CMU.fasta	*W. hellenica* CCUG 33494.fasta	87.39*	1.39	32,954	2,362,501
W. cibaria CMU.fasta	*W. kandleri* DSM 20593.fasta	84.86*	0.12	2,797	2,362,501
W. cibaria CMU.fasta	*W. soli* KACC 11848.fasta	86.41*	5.56	131,443	2,362,501

Genome Sequence A	Genome Sequence B	ANIb (%)	Aligned (%)	Aligned (bp)	Total (bp)
W. cibaria CMU.fasta	*W. thailandensis* JCM 10695.fasta	85.65*	0.02	476	2,362,501
W. cibaria CMU.fasta	*W. paramesenteroides FDAARGOS* 414.fasta	88.26*	6.11	144,336	2,362,501

Green text indicates results are above the cutoff (>95%)
Red text indicates results are below the cutoff (<95%)
*Denotes suspicious alignment

Table 7. Tetra-Nucleotide Signature Correlation Index Summary Results by Genome

Genome Sequence A	Genome Sequence B	PCC
W. cibaria CMU.fasta	*W. cibaria* CMS1.fasta	0.99998
W. cibaria CMU.fasta	*W. cibaria* CMS2.fasta	0.99998
W. cibaria CMU.fasta	*W. cibaria* CMS3.fasta	0.99998
W. cibaria CMU.fasta	*W. cibaria* JCM 12495.fasta	0.97501
W. cibaria CMU.fasta	*W. cibaria* BC14.fasta	0.9991
W. cibaria CMU.fasta	*W. cibaria* CH2.fasta	0.99891
W. cibaria CMU.fasta	*W. confusa* VTT E-133279.fasta	0.97489
W. cibaria CMU.fasta	*W. hellenica* CCUG 33494.fasta	0.81143
W. cibaria CMU.fasta	*W. kandleri* DSM 20593.fasta	0.67592
W. cibaria CMU.fasta	*W. soli* KACC 11848.fasta	0.9047
W. cibaria CMU.fasta	*W. thailandensis* JCM 10695.fasta	0.76344
W. cibaria CMU.fasta	*W. paramesenteroides* FDAARGOS 414.fasta	0.83494

Green text indicates results are above the cutoff (>0.999)
Blue text indicates results are in range of the cutoff (>0.989)
Red text indicates results are below the cutoff (<0.989)
PCC = Pearson Correlation Coefficient

ANI Calculator

As shown in Appendix 3 and Table 8, the ANI calculator results shows that strain CMU is consistently above the 95% threshold compared to the other *W. cibaria* strains but not the other *Weissella* species, supporting identification of strain CMU as *W. cibaria*.

Table 8. ANI Calculator Summary Results by Genome

Genome Sequence A	Genome Sequence B	§ ANI (%)	One-Way ANI 1 (%)	One-Way ANI 2 (%)	Two-Way ANI (%)
W. cibaria CMU.fasta	*W. cibaria* CMS1.fasta	100.00	99.99	100.00	100.00

Genome Sequence A	Genome Sequence B	§ ANI (%)	One-Way ANI 1 (%)	One-Way ANI 2 (%)	Two-Way ANI (%)
			(SD:0.13%)	(SD: 0.06%)	(SD: 0.06%)
W. cibaria CMU.fasta	*W. cibaria* CMS2.fasta	100.00	99.99 (SD:0.11%)	100.00 (SD: 0.02%)	100.00 (SD: 0.02%)
W. cibaria CMU.fasta	*W. cibaria* CMS3.fasta	100.00	99.99 (SD: 0.14%)	99.99 (SD: 0.11%)	100.00 (SD: 0.08%)
W. cibaria CMU.fasta	*W. cibaria* JCM 12495.fasta	100.00	99.93 (SD: 1.34%)	100.00 (SD: 0.01%)	100.00 (SD: 0.01%)
W. cibaria CMU.fasta	*W. cibaria* BC14.fasta	98.39	98.29 (SD: 2.12%)	98.30 (SD: 2.08%)	98.39 (SD: 1.80%)
W. cibaria CMU.fasta	*W. cibaria* CH2.fasta	96.65	96.57 (SD: 2.57%)	96.56 (SD: 2.52%)	96.65 (SD: 2.35%)
W. cibaria CMU.fasta	*W. confusa* VTT E-133279.fasta	83.87	83.91 (SD: 7.85%)	83.75 (SD: 7.77%)	83.87 (SD: 7.52%)
W. cibaria CMU.fasta	*W. hellenica* CCUG 33494.fasta	81.95	82.07 (SD: 6.81%)	82.27 (SD: 6.68%)	81.95 (SD: 6.95%)
W. cibaria CMU.fasta	*W. kandleri* DSM 20593.fasta	Insufficient hits to estimate			
W. cibaria CMU.fasta	*W. soli* KACC 11848.fasta	81.01	83.81 (SD: 8.66%)	82.19 (SD: 8.25%)	81.01 (SD: 7.53%)
W. cibaria CMU.fasta	*W. thailandensis* JCM 10695.fasta	Insufficient hits to estimate			
W. cibaria CMU.fasta	*W. paramesenteroides FDAARGOS* 414.fasta	81.95	83.63 (SD: 8.99%)	82.86 (SD: 8.83%)	81.95 (SD: 8.13%)

Green text indicates results are above the cutoff (>95%)
Red text indicates results are below the cutoff (<95%)
SD = standard deviation

d. Phenotypic Characterization

Phenotypic characterization data was also assessed. The cell morphology, enzymatic profile (API ZYM) and carbohydrate fermentation profile (API 50) all support the identity strain CMU as *W. cibaria* and clearly distinguish this organism from other similar *Weissella* species (Fusco et al., 2015).

Cell morphology of strain CMU is documented by Lim et al. (2018) as shown in Part 2.A.3 and is consistent with the *W. cibaria* species.

As shown in Table 9, the enzymatic profile as assessed with the API ZYM test for strain CMU showed that the *W. cibaria* strains evaluated exhibited negative results for all reactions, except for acid phosphatase and naphthol-AS-BI-phosphohydrolase. This was the same profile exhibited by two other *W. cibaria* strains evaluated but was not consistent with the profile exhibited by strains in other *Weissella* species. The results that were different between the *W. cibaria* and *W. confusa* strains are highlighted in orange text in Table 9. In addition, this profile is generally consistent with results for *W.*

cibaria G44, isolated from fermented curly kale (Michalak et al., 2018; Kang et al., 2019). Therefore, by phenotypic analysis based on the API ZYM, strain CMU is consistent with *W. cibaria* strains and does not appear to be a strain of *W. confusa*.

Table 9. API ZYM Enzymatic Activity Profile of *Weissella cibaria* CMU[1]

Enzyme Substrate	*W. cibaria* CMU	*W. cibaria* KCTC 3807	*W. cibaria* KCTC 3746	*W. cibaria* G44	*W. confusa* KCTC 3499	*W. thailandensis* KCTC 3551	*W. viridescens* KCTC 3504	*W. soli* KCTC 3789	*W. paramesenteroides* KCTC3531	*W. minor* KCTC 3604	*W. kandleri* KCTC 3610	*W. halotolerans* KCTC 3595
Alkaline phosphatase	-	-	-	-	-	-	-	-	-	-	-	-
Esterase (C4)	-	-	-	-	-	-	-	-	+(3)	-	-	+(3)
Esterase lipase (C8)	-	-	-	-	-	-	-	-	-	-	-	-
Lipase (C14)	-	-	-	-	-	-	-	-	-	-	-	-
Leucine arylamidase	-	-	-	-	-	-	+(3)	-	+(4)	-	-	-
Valine arylamidase	-	-	-	-	-	-	-	-	-	-	-	-
Cystine arylamidase	-	-	-	-	-	-	-	-	-	-	-	-
Trypsin	-	-	-	-	-	-	-	-	-	-	-	-
α-chymotrypsin	-	-	-	-	-	-	-	-	-	-	-	-
Acid phosphatase	+(3)	+(3)	+(3)	4	+(5)	-	-	+(3)	-	-	-	-
Naphthol-AS-BI-phosphohydrolase	+(3)	+(3)	+(3)	3	+(3)	+(3)	+(4)	+(3)	-	+(3)	+(3)	+(4)
α-galactosidase	-	-	-	-	-	-	-	-	+(3)	-	-	-
β-galactosidase	-	-	-	-	-	-	-	+(3)	+(5)	-	-	-
β-glucuronidase	-	-	-	-	-	-	-	-	-	-	-	-
α-glucosidase	-	-	-	-	-	+(3)	-	-	+(5)	-	-	+(5)
β-glucosidase	-	-	-	-	-	-	-	+(5)	-	-	-	-
N-acetyl-β-glucosaminidase	-	-	-	-	-	-	-	-	-	-	-	-
α-mannosidase	-	-	-	-	-	-	-	-	-	-	-	-
α-fucosidase	-	-	-	-	-	-	-	-	-	-	-	-

[1] All results are from internal analysis completed by OraPharm, except for *W. cibaria* strain G44 which is from Michalak et al. (2018)
Orange text indicates that the results were different between the *W. cibaria* and *W. confusa* strains

Fermentable sugar profiles were compared with *W. cibaria* CCUG 41967 and *W. cibaria* CMU, CMS2, CMS3 and *W. confusa* ATCC 10881 (Table 10). All the isolates and W. cibaria CCUG 41967 fermented L-arabinose, D-xylose, D-glucose, D-fructose, D-mannose, N-acetylglucosamine, amygdaline, aesculin (esculin), salicin, D-cellobiose, D-maltose, sucrose (D-saccharose) and gentiobiose. They were defective in fermenting glycerol, erythritol, D-arabinose, D-ribose, L-xylose, D-adonitol, β-methyl-D-xyloside (Methyl-βD-Xylopyranoside), D-galactose, L-sorbose, L-rhamnose, dulcitol, inositol, D-mannitol, D-sorbitol, α-methyl-D-mannose mannoside (Methyl-αD-

Mannopyranoside), α-methyl-D-glucoside (Methyl-αD-Glucopyranoside), arbutin, D-lactose, D-melibiose, D-trehalose, inulin, D-melezitose, D-raffinose, amidon, glycogen, xylitol, D-turanose, D-lyxose, D-tagatose, D-fucose, L-fucose, D-arabitol, L-arabitol, potassium gluconate, potassium 2-ketogluconate and potassium 5-ketogluconate. *W. confusa* similarly fermented carbohydrates. However, *W. confusa* fermented ribose and galactose and did not ferment L-arabinose. Dextran was formed from sucrose by all the tested strains. The results that were different between the *W. cibaria* and *W. confusa* strains are highlighted in orange text in Table 10 (L-arabinose, D-ribose, and D-galactose). These results are also consistent with the profile reported by Fusco et al. (2015) and Vos et al. (2009). Therefore, by phenotypic analysis based on the API 50, strain CMU is consistent with *W. cibaria* strains and does not appear to be a strain of *W. confusa*.

Table 10. API 50 Carbohydrate Fermentation Profile of *Weissella cibaria* CMU

Substrate	*W. cibaria* CMU	*W. cibaria* CMS2	*W. cibaria* CMS3	*W. cibaria* CCUG 41967	*W. confusa* ATCC 10881	*W. cibaria**	*W. confusa**	*W. cibaria***	*W. confusa***
Glycerol	-	-	-	-	-	NR	NR	NR	NR
Erythritol	-	-	-	-	-	NR	NR	NR	NR
D-arabinose	-	-	-	-	-	+ (D,L not specified)	- (D,L not specified)	NR	NR
L-arabinose	+	+	+	+	-	+ (D,L not specified)	- (D,L not specified)	+	-
D-ribose	-	-	-	-	+	- (D,L not specified)	+ (D,L not specified)	- (D,L not specified)	+ (D,L not specified)
D-xylose	+	+	+	+	+	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)
L-xylose	-	-	-	-	-	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)
D-adonitol	-	-	-	-	-	NR	NR	NR	NR
Methyl-βD-Xylopyranoside	-	-	-	-	-	NR	NR	NR	NR
D-galactose	-	-	-	-	+	- (D,L not specified)	+ (D,L not specified)	- (D,L not specified)	+ (D,L not specified)
D-glucose	+	+	+	+	+	NR	NR	NR	NR
D-fructose	+	+	+	+	+	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)	ND
D-mannose	+	+	+	+	+	NR	NR	+ (D,L not specified)	ND
L-sorbose	-	-	-	-	-	NR	NR	NR	NR

Substrate	*W. cibaria* CMU	*W. cibaria* CMS2	*W. cibaria* CMS3	*W. cibaria* CCUG 41967	*W. confusa* ATCC 10881	*W. cibaria**	*W. confusa**	*W. cibaria***	*W. confusa***
L-rhamnose	-	-	-	-	-	NR	NR	NR	NR
Dulcitol	-	-	-	-	-	NR	NR	NR	NR
Inositol	-	-	-	-	-	NR	NR	NR	NR
D-mannitol	-	-	-	-	-	NR	NR	- (D,L not specified)	ND
D-sorbitol	-	-	-	-	-	NR	NR	NR	NR
Methyl-αD-Mannopyranoside	-	-	-	-	-	NR	NR	NR	NR
Methyl-αD-Glucopyranoside	-	-	-	-	-	NR	NR	NR	NR
N-Acetylglucosamine	+	+	+	+	+	NR	NR	NR	NR
Amygdalin	+	+	+	+	+	NR	NR	+	ND
Arbutin	-	-	-	-	-	NR	NR	+	ND
Esculin ferric citrate	+	+	+	+	+	+ (Esculin hydrolysis)	+ (Esculin hydrolysis)	+ (Esculin hydrolysis)	+ (Esculin hydrolysis)
Salicin	+	+	+	+	+	NR	NR	+	ND
D-Cellobiose	+	+	+	+	+	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)
D-Maltose	+	+	+	+	+	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)
D-Lactose (bovine origin)	-	-	-	-	-	NR	NR	-	ND
D-melibiose	-	-	-	-	-	- (D,L not specified)	- (D,L not specified)	- (D,L not specified)	- (D,L not specified)
D-saccharose (sucrose)	+	+	+	+	+	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)
D-trehalose	-	-	-	-	-	- (D,L not specified)	- (D,L not specified)	- (D,L not specified)	- (D,L not specified)
Inulin	-	-	-	-	-	NR	NR	NR	NR
D-Melezitose	-	-	-	-	-	NR	NR	NR	NR
D-Raffinose	-	-	-	-	-	- (D,L not specified)	- (D,L not specified)	- (D,L not specified)	- (D,L not specified)
Amidon(starch)	-	-	-	-	-	NR	NR	NR	NR
Glycogen	-	-	-	-	-	NR	NR	NR	NR
Xylitol	-	-	-	-	-	NR	NR	NR	NR

Substrate	*W. cibaria* CMU	*W. cibaria* CMS2	*W. cibaria* CMS3	*W. cibaria* CCUG 41967	*W. confusa* ATCC 10881	*W. cibaria**	*W. confusa**	*W. cibaria***	*W. confusa***
Gentiobiose	+	+	+	+	+	NR	NR	NR	NR
D-Turanose	-	-	-	-	-	NR	NR	NR	NR
D-Lyxose	-	-	-	-	-	NR	NR	NR	NR
D-Tagatose	-	-	-	-	-	NR	NR	NR	NR
D-Fucose	-	-	-	-	-	NR	NR	NR	NR
L-Fucose	-	-	-	-	-	NR	NR	NR	NR
D-Arabitol	-	-	-	-	-	NR	NR	NR	NR
L-Arabitol	-	-	-	-	-	NR	NR	NR	NR
Potassium Gluconate	-	-	-	-	-	NR	NR	NR	NR
Potassium 2-KetoGluconate	-	-	-	-	-	NR	NR	NR	NR
Potassium 5-KetoGluconate	-	-	-	-	-	NR	NR	NR	NR

* As reported by (Fusco et al., 2015)
** As reported by (Vos et al., 2009)
ND = not determined; NR = not reported
Orange text indicates that the results were different between the *W. cibaria* and *W. confusa* strains

e. Strain Specific Identification

Methods that can consistently identify the organism to the strain level differentiate it from other *W. cibaria* strains and provide evidence that the finished product is definitively the CMU strain. OraPharm developed a strain specific analysis performed by BioFACT Co. (Daejun, South Korea) using a random amplification of polymorphic DNA-polymerase chain reaction (RAPD-PCR) method.

The RAPD-PCR pattern for the CMU strain from the master stock was compared to other *Weissella* and *W. cibaria* strains and was then compared to five different production lots of CMU on a 3% agarose gel (10 uL loading). The RAPD-PCR showed that CMU can be differentiated from other *Weissella* and *W. cibaria* strains and that the production results had a consistent pattern compared to the master stock of strain CMU (Appendix 3).

B. Manufacturing Processes

The manufacturer operates under good manufacturing practice applicable with Korean regulations, and documentation for this cGMP certification is found in Appendix 4. OraPharm's *W. cibaria* CMU is produced in accordance with FDA Current Good Manufacturing Practices (cGMP) per 21 CFR Part 117.

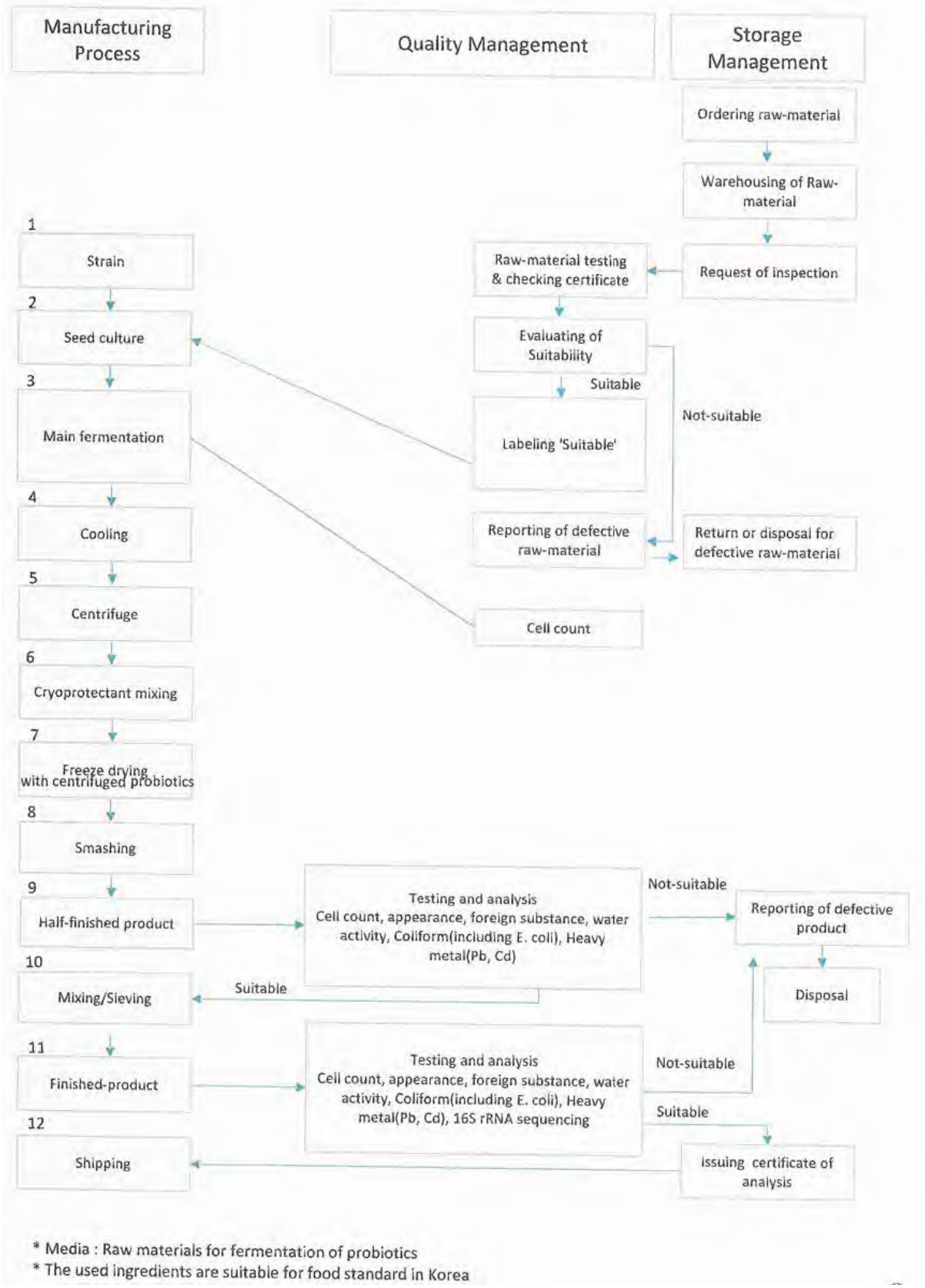
The manufacturing process includes rigorous testing of the final production batches to verify adherence to quality control specifications and are manufactured consistent with cGMPs for food (21 CFR Part 117). There are hygiene management standards for tools, fermenters, and workplaces, and the manufacturing process is managed by clean-in-place (CIP) procedures. The raw materials and processing aids used in the manufacturing process are food grade and discussed in more detail in Part 2.B.1.

The manufacturing process includes specific quality control steps to confirm genetic identity and limit genetic drift by confirming the starter strain as *W. cibaria* CMU through 16S ribosomal DNA analysis and maintaining the master stock. For long-term storage, stock cultures are maintained at -80℃ in MRS broth containing 20% glycerol. The quality of the *W. cibaria* CMU ingredient is routinely checked during the production process to ensure that the genetic identity is consistent with that of the original stock and the finished products are free of contaminants. Specifically, identification (microscopic inspection, 16S rRNA), cell counts, and microbial purity (Coliforms, yeasts and molds, E. coli) are performed, at the steps as indicated in Figure 3.

The manufacturing process is summarized in the flow charts provided in Figure 3. In brief, the seed vial of *Weissella cibaria* CMU (Country of Origin: Republic of Korea) is first inoculated into a sterilized liquid medium. The seed vial is obtained from the master stock and undergoes quality and identity checks with 16S rRNA analysis. The precultured medium undergoes fermentation steps and is then inoculated into the sterilized fermenter. Termination of the culture is induced by cooling. After the termination of incubation, contamination and culture-condition is assessed (cell counts and microbial purity for Coliforms, yeasts and molds, *E. coli*). The culture broth is then transferred to the centrifugal facility through a drain-line. The transferred culture-broth is centrifuged and then the live microbial pellet is mixed with the prepared cryoprotectant within the Vertical mixer. The live microbial mixture is then freeze-dried within the freeze dryer and pulverized using a dry grinding process. Packing of the products and samples are done separately using sanitized polyethylene bags, and the samples are sent to the Quality Control (QC) department for quality analysis, which includes analysis for: identification (microscopic inspection, 16S rRNA), cell counts, appearance, foreign substances, water activity, microbial purity (Coliforms, yeasts and molds, *E. coli*), and heavy metals (lead, cadmium). The QC approved product is then mixed/sieved with food grade excipients and stored in a low temperature (0-4°C) warehouse ready for shipping.

[Remainder of page left intentionally blank]

Figure 3. Manufacturing Process Flow Chart



1. Raw Materials

All raw materials, processing aids, and additives used to manufacture *W. cibaria* CMU are listed in Table 11. All substances used in the manufacture meet Korean food standards and are comparable to FDA standards and of a purity suitable for the intended use.

Table 11. Ingredients Used in the Manufacturing Process

Component	Purpose
Dextrose monohydrate	Fermentation Media Ingredient
K_2HPO_4	Fermentation Media Ingredient
$MnSO_4$	Fermentation Media Ingredient
Potassium citrate	Fermentation Media Ingredient
Sodium acetate	Fermentation Media Ingredient
Soy peptone	Fermentation Media Ingredient
Tween-80	Fermentation Media Ingredient
Yeast extract	Fermentation Media Ingredient
Chicory root extract	Cryoprotectant Ingredient
KH_2PO_4	Cryoprotectant Ingredient
Skim milk	Cryoprotectant Ingredient
Processed Starch (88% potato starch + 12% maltodextrin)	Excipient

C. Product Specifications

The food grade specifications for *W. cibaria* CMU are summarized in Table 12, and conformance to specifications and consistency of *W. cibaria* CMU manufacturing is demonstrated by the analyses of five non-consecutive lots of commercially representative *W. cibaria* CMU. The analytical results for the production lots are summarized in Table 13 and certificates of analysis are provided in Appendix 2.

Three representative production lots were analyzed for the presence of milk, soy, and gluten. The allergen reports are provided in Appendix 5. Based on these results, gluten and soy were not detected[5]; however, milk was detected in all three samples (Method Detection Limit = 1 ng/µL). Therefore, the ingredient will be labeled with an allergen declaration for milk according to the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA).

Three representative production lots were analyzed for the presence of 245 pesticides, including β-hexachlorocyclohexane (BHC), Dichlorodiphenyltrichloroethane (DDT), aldrin, dieldrin, and endrin. As shown in Appendix 6, no pesticides were detected in the production samples. There is no reason

[5] The limit of quantification for gluten was 5 mg/kg and the limit of detection for soy was 1 ng/µL.

to expect future production lots would be any different, therefore, pesticides are not tested on every lot.

The collection of these reports demonstrates that the substance is well characterized and meets the established purity criteria.

Table 12. Food Grade Specifications for *W. cibaria* CMU

Physical and Chemical Parameters	Specification (Acceptable Target/Range)	Analytical Method
Identity	Confirm as strain CMU	16S rRNA sequencing
Appearance	Yellowish white powder with no off-taste and off-flavor	Organoleptic
Viable cell count (CFU/g)	NLT 1.0 x 10^9	KHFSC 4/3/3-57 (ISO 27205:2010)
Moisture (%)	NMT 5.0	KFSC 8/2/2.1/2.1.1 (AOAC 941.14)
Ash (%)	NMT 2.0	KFSC 8/2/2.1/2.1.2 (AOAC 900.02)
Heavy Metals		
Lead (mg/kg)	NMT 1.0	KHFSC 8/9/9.1 (AOAC 2013.06)
Cadmium (mg/kg)	NMT 0.3	KHFSC 8/9/9.1 (AOAC 2013.06)
Arsenic (mg/kg)	NMT 1.0	KHFSC 8/9/9.1 (AOAC 2013.06)
Mercury (mg/kg)	NMT 0.5	KHFSC 8/9/9.1 (AOAC 2013.06)
Microbiological Limits		
Coliforms (CFU/g)	Negative	KHFSC 8/4/4.7 (AOAC 991.14)
Yeast and Mold (CFU/g)	NMT 100	KFSC 7/4/4.10 (AOAC 2002.11)
***E. coli* (Per 25 g)**	Negative	KFSC 7/4/4.8 (AOAC 991.14)
***Salmonella* (Per 25 g)**	Negative	KFSC 7/4/4.15 (AOAC 989.14)
***Listeria* (Per 25 g)**	Negative	KFSC 7/4/4.15 (AOAC 998.08)
***S. aureus* (CFU/g)**	Negative	KFSC 7/4/4.21 (AOAC 975.55)

AOAC – Association of Official Agricultural Chemists; CFU – Colony Forming Unit; g – gram; ISO – International Organization for Standardization; KFSC – Korean Food Standards Codex; KHFSC – Korean Health Functional Food Standards Codex; kg – kilogram; mg – milligram; NA – Not applicable; NLT – Not less than; NMT – Not more than

Table 13. Analytical Results for *W. cibaria* CMU

Physical and Chemical Parameters	Specification (Acceptable Target/Range)	Analytical Method	Lot CI11-0115N	Lot CI11-0116N	Lot CI11-0117N	Lot CI11-0362N	Lot CI11-0366N
Identity	Confirm as strain CMU	16S rRNA sequencing	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed
Appearance	Yellowish white powder with no off-taste and off-flavor	Organoleptic	Yellowish white powder	Yellowish white powder	Yellowish white powder	Yellowish white powder	Yellowish white powder
Viable cell count (CFU/g)	NLT 1.0 x 10^9	KHFSC 4/3/3-57 (ISO 27205:2010)	1.2 x 10^{11} CFU/g	1.5 x 10^{11} CFU/g	1.5 x 10^{11} CFU/g	1.5 x 10^{11} CFU/g	1.1 x 10^{11} CFU/g
Moisture (%)	NMT 5.0	KFSC 8/2/2.1/2.1.1	3.8	2.85	3.05	3.03	3.34

Physical and Chemical Parameters	Specification (Acceptable Target/Range)	Analytical Method	Lot CI11-0115N	Lot CI11-0116N	Lot CI11-0117N	Lot CI11-0362N	Lot CI11-0366N
		(AOAC 941.14)					
Ash (%)	NMT 2.0	KFSC 8/2/2.1/2.1.2 (AOAC 900.02)	0.6	1.30	1.16	1.29	1.29
Heavy Metals							
Lead (mg/kg)	NMT 1.0	KHFSC 8/9/9.1 (AOAC 2013.06)	0.01	0.01	0.02	0.0107	0.0096
Cadmium (mg/kg)	NMT 0.3	KHFSC 8/9/9.1 (AOAC 2013.06)	0.04	0.05	0.04	0.0398	0..0383
Arsenic (mg/kg)	NMT 1.0	KHFSC 8/9/9.1 (AOAC 2013.06)	0.00	0.00	0.01	0.0067	0.0048
Mercury (mg/kg)	NMT 0.5	KHFSC 8/9/9.1 (AOAC 2013.06)	ND	ND	ND	0.0016	0.0022
Microbiological Limits							
Coliforms (CFU/g)	Negative	KHFSC 8/4/4.7 (AOAC 991.14)	Negative	Negative	Negative	Negative	Negative
Yeast and Mold (CFU/g)	NMT 100	KFSC 7/4/4.10 (AOAC 2002.11)	Negative	Negative	Negative	Negative	Negative
***E. coli* (per g)**	Negative	KFSC 7/4/4.8 (AOAC 991.14)	Negative	Negative	Negative	Negative	Negative
***Salmonella* (CFU/g)**	Negative	KFSC 7/4/4.15 (AOAC 989.14)	Negative	Negative	Negative	Negative	Negative
***Listeria monocytogenes* (CFU/g)**	Negative	KFSC 7/4/4.15 (AOAC 998.08)	Negative	Negative	Negative	Negative	Negative
***S. aureus* (per g)**	Negative	KFSC 7/4/4.21 (AOAC 975.55)	Negative	Negative	Negative	Negative	Negative

AOAC – Association of Official Agricultural Chemists; CFU – Colony Forming Unit; g – gram; ISO – International Organization for Standardization; KFSC – Korean Food Standards Codex; KHFSC – Korean Health Functional Food Standards Codex; kg – kilogram; mg – milligram; NA – Not applicable; NLT – Not less than; NMT – Not more than

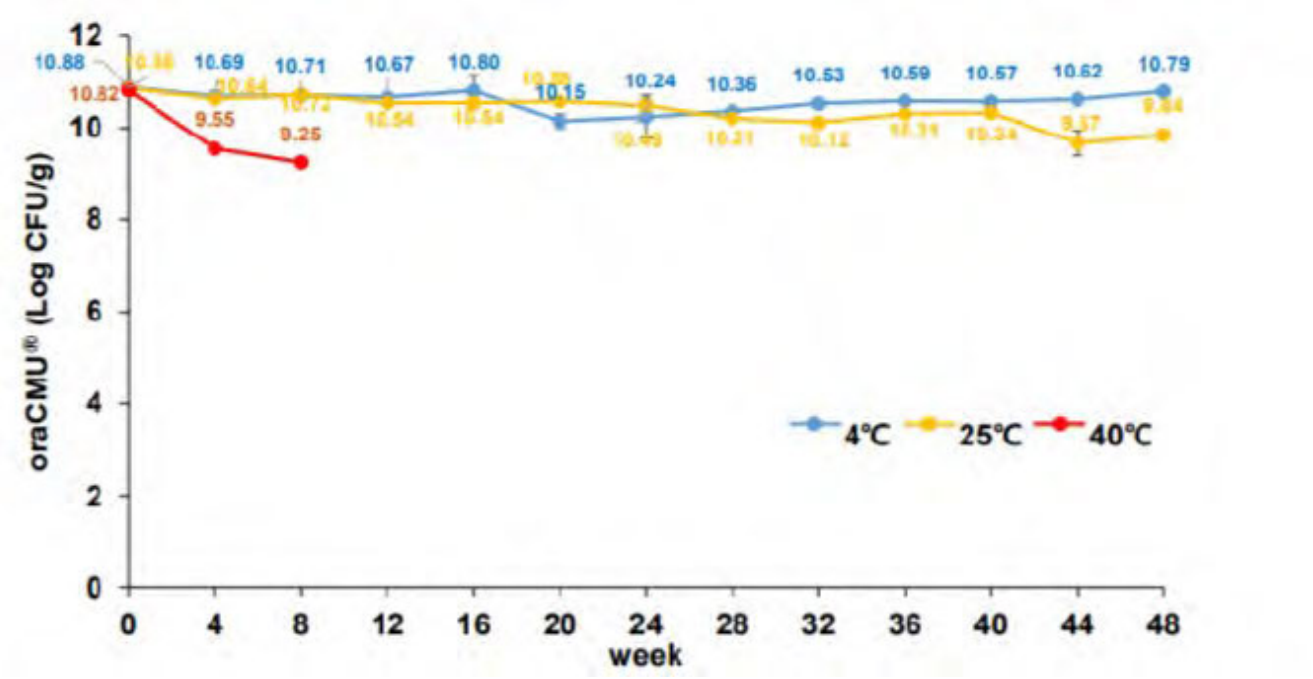
D. Physical or Technical Effect

The substance will be used to provide a dietary source of *W. cibaria* CMU as a food ingredient to selected conventional foods.

E. Stability Data

OraPharm completed stability studies of *W. cibaria* CMU (oraCMU) for 48 weeks at 4°C, 25°C, and for 8 weeks at 40°C. The stability results shown in Figure 4 were conducted with the finished product in an aluminum pouch under the conditions of 36.5±5% relative humidity. Results indicate *W. cibaria* CMU is stable for up to 48 weeks at refrigerated and ambient temperature.

Figure 4. Stability Data of *W. cibaria* CMU Lyophilized Commercial Product Stored in Various Conditions for 48 weeks.



PART 3. DIETARY EXPOSURE

A. Proposed Uses

OraPharm's *W. cibaria* CMU is intended for use as an ingredient in yogurt, frozen desserts (dairy, ices, sorbets and sherbets) and mixes, hard candy and chewing gum with an intended use level of 1 x 10^8 CFU per serving throughout the shelf life of the products. One gram of OraPharm's *W. cibaria* CMU provides at least 1.0 x 10^8 CFU. OraPharm considers that the initial addition level of *W. cibaria* CMU in the products may be as high as 8.0 x 10^9 CFU per serving to allow for loss of viability over time and the intended use levels may vary by food category. Use in hard candy and chewing gum would require the highest overage while use in frozen desserts and yogurt would likely be 5.0 x 10^8 CFU and 2.0 x 10^8 CFU per serving, respectively.

B. Estimated Dietary Intake (EDI)

The EDI of *W. cibaria* CMU is estimated using the proposed intended use levels and food intake of those foods as reported by National Health and Nutrition Examination Survey (NHANES) 2017-2018 survey (CDC, 2020). The Per Capita data reported includes all survey participants, while Consumer-only data represents high users as the intake of the food was reported at least one of the two days of the survey. The Consumer-only data is considered to a high use scenario and is utilized for calculation of the EDI.

The EDI of yogurt, frozen desserts (dairy, ices, sorbets and sherbets) and mixes, hard candy (including mints) and chewing gum are shown in Table 14, Table 15, and Table 16, respectively. The food codes utilized to estimate these intakes are provided in Appendix 7.

Table 14. Daily Intake of Yogurt (2017-2018 NHANES)

Age Group	Gender	Grams per Day Intake		N	Grams/kg bw/Day	
		Mean	90th Percentile		Mean	90th Percentile
Infants	Male	53.90*	137.49*	20	5.96*	13.95*
Infants	Female	44.32*	61.23*	19	5.06*	6.99*
Children (1-5 years)	Male	77.01	122.31	93	4.90	8.89
Children (1-5 years)	Female	91.87	169.39	89	5.44	11.50
Children (6-11 years)	Male	73.59	138.07*	53	2.36	4.32*
Children (6-11 years)	Female	82.20	145.70	82	2.38	4.14
Teenage (12-18 years)	Male	103.41*	133.16*	13	1.44*	1.85*
Teenage (12-18 years)	Female	121.29*	192.26*	28	2.03*	3.14*
Adults (19+ years)	Male	111.33	192.65	156	1.25	2.34
Adults (19+ years)	Female	102.32	179.26	296	1.33	2.34
All ages	Total Population	98.38	179.55	849	1.53	2.89

*Indicates an intake estimate that may not be statistically reliable as the sample size does not meet minimum reporting requirements (mean n<30; percentile 90 n<80); bw = body weight; kg = kilogram; N = the number of individuals reporting eating the food during the two-day survey.

Yogurt intake at the 90th percentile may not be statistically reliable for infants, male children aged 6-11 years and male and female teenagers due to low reporting numbers.

Table 15. Daily Intake of Frozen Desserts (2017-2018 NHANES)

Age Group	Gender	Grams per Day Intake		N	Grams/kg bw/Day	
		Mean	90th Percentile		Mean	90th Percentile
Infants	Male	24.31*	43.03*	5	2.59*	4.19*
Infants	Female	27.65*	56.30*	8	3.30*	6.66*
Children (1-5 years)	Male	46.84	72.93*	77	2.68	4.45*
Children (1-5 years)	Female	55.17	124.71	103	3.34	6.84
Children (6-11 years)	Male	70.46	121.22	107	2.14	3.56
Children (6-11 years)	Female	81.2	163.29	142	2.21	4.52
Teenage (12-18 years)	Male	84.09	151.39	88	1.13	2.06
Teenage (12-18 years)	Female	100.91	190.87	120	1.54	3.08

Age Group	Gender	Grams per Day Intake		N	Grams/kg bw/Day	
		Mean	90th Percentile		Mean	90th Percentile
Adults (19+ years)	Male	98.31	179.43	427	1.05	2.16
Adults (19+ years)	Female	77.53	157.57	469	1.01	2.06
All ages	Total Population	83.68	159.96	1546	1.17	2.53

*Indicates an intake estimate that may not be statistically reliable as the sample size does not meet minimum reporting requirements (mean n<30; percentile 90 n<80); bw = body weight; kg = kilogram; N = the number of individuals reporting eating the food during the two-day survey.

The survey data shows that reporting of consumption of frozen desserts provides statistically reliable estimates for all populations other than infants and male children ages 1-5 years at the 90th percentile.

Table 16. Daily Intake of Hard Candy and Chewing Gum

Age Group	Gender	Grams per Day Intake		N	Grams/kg bw/Day	
		Mean	90th Percentile		Mean	90th Percentile
Infants	Male	0	0	0	0	0
Infants	Female	10.50*	10.50*	1	1.15*	1.15*
Children (1-5 years)	Male	7.06	13.42*	42	0.39	0.88*
Children (1-5 years)	Female	5.36	9.43*	39	0.28	0.54*
Children (6-11 years)	Male	11.85	35.72*	52	0.39	0.99*
Children (6-11 years)	Female	12.26	37.64*	69	0.36	0.95*
Teenage (12-18 years)	Male	5.81	7.13*	35	0.1	0.17*
Teenage (12-18 years)	Female	9.11	17.12*	58	0.15	0.31*
Adults (19+ years)	Male	7.78	23.73	128	0.09	0.25
Adults (19+ years)	Female	4.86	10.73	187	0.06	0.15
All ages	Total Population	7.19	14.63	611	0.11	0.23

*Indicates an intake estimate that may not be statistically reliable as the sample size does not meet minimum reporting requirements (mean n<30; percentile 90 n<80); bw = body weight; kg = kilogram; N = the number of individuals reporting eating the food during the two-day survey.

The survey data shows that only adult and total populations at the 90th percentile reported consumption of hard candy and chewing gum at a sample size large enough to be considered statistically reliable.

The usage of *W. cibaria* CMU in the foods utilized for intake calculations are as follows:

- 2 mg per 170 gram serving of yogurt

- 5 mg per 150 gram serving of frozen dessert
- 80 mg per 3 gram serving of hard candy/mints/chewing gum. The reference amount customarily consumed (RACC) per 21 CFR § 101.12 for breath mints varies from 2-5 grams depending on the type, while the RACC for chewing gum is 3 grams. For calculation purposes a 3-gram serving size was utilized.

Utilizing the estimated intake of food by the Consumer-only data, the intended use of *W. cibaria* CMU in these foods based on the estimated overages used and assuming all of these foods consumed contain *W. cibaria* CMU a high intake scenario is provided in Table 17. The estimates for infants are excluded as these are not statistically reliable due to expected low numbers reporting consuming the food and the intended use is in foods that are not targeted to infants.

Table 17. Estimated Daily Intake of *W. cibaria* CMU

Population	Intake (mg/day)		Intake (mg/kg bw/day)	
	Mean	90th Percentile	Mean	90th Percentile
Children, male (1-5 years)	190.27	360.85	10.52	23.66
Children, female (1-5 years)	145.50	256.99	7.62	14.73
Children, male (6-11 years)	318.42	955.81	10.47	26.50
Children, female (6-11 years)	329.78	1008.36	9.68	25.47
Teens, male (12-18 years)	158.56	196.25	2.71	4.61
Teens, female (12-18 years)	247.11	464.00	4.07	8.39
Adults, male (19+ years)	211.53	639.45	2.44	6.75
Adults, female (19+ years)	133.06	292.77	1.65	4.09
All ages, total population	195.20	396.59	2.98	6.24

bw = body weight; mg = milligram; kg = kilogram

The highest usage rate is in the hard candy/mints/chewing gum and accounts for high amounts of intake in the calculation, especially for male and female children ages 6-11 years; however, only the adult and total populations at the 90th percentile reported consumption at a sample size large enough to be considered statistically reliable. Therefore, while the female children ages 6-11 years population has the highest intake on a mg/day basis, and the male children ages 6-11 years population has the highest intake on a mg/kg bw/day basis; these estimates are not considered statistically reliable. Therefore, all ages, total population is reasonable to utilize for the EDI.

Using all ages, total population, the 90th percentile intake is 397 mg/day. Using the specification of not less than $1x10^9$ CFU per gram, the EDI in terms of CFU per day is 3.97×10^8. On a body weight basis, intake is 6.24 mg/kg bw/day, or 6.24×10^6 CFU/kg bw/day. Similarly, for male children (6-11 yr), who are estimated to consume the highest amount per kg bw, the EDI is 2.65×10^7 CFU/kg bw/day. These high intake scenarios are unlikely in that they assume that all of the foods consumed contain *W. cibaria* CMU at the highest amount.

C. Estimated Dietary Exposure to Any Other Substance That is Expected to be Formed In or On Food

Not applicable.

D. Dietary Exposure to Contaminants or Byproducts

Potential contaminants of OraPharm's *W. cibaria* CMU include microbes and heavy metals. The specifications set for OraPharm's *W. cibaria* CMU place limits on the maximum permissible levels of these impurities to assure an acceptable final product. The analytical batch data for five different manufacturing lots document quality control of the final product and demonstrate that the ingredient consistently meets these specifications (Table 13).

As discussed in Part 2.C, allergen testing identified the presence of milk. In accordance with labeling requirements under The Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA), milk will be declared on product labeling. Allergen testing reports are provided in Appendix 5.

PART 4. SELF-LIMITING LEVELS OF USE

There are no inherent self-limiting levels of use for *W. cibaria* CMU.

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

The statutory basis for the conclusion of the GRAS status of *W. cibaria* CMU in this document is based on scientific procedures in accordance with 21 CFR 170.30(a)(b). Therefore, experience based on common use in food before 1958 does not apply. A discussion of the history of safe consumption of *W. cibaria* CMU is discussed in Part 6.

PART 6. NARRATIVE

A. History of Safe Consumption and Other Information On Dietary Exposure

Bacteria from the *Weissella* genus are commonly found in fermented foods that are traditionally consumed. Bourdichon et al. (2012) include *Weissella* species in a 2011 list of microorganisms with beneficial use and note the species are used for fermentation of meat, fish, cabbage (Kimchi), cassava, and cocoa. The following publications cite numerous strains of *Weissella* species, including *W. cibaria* that were identified from food sources (Chao et al., 2008; Chao et al., 2009; Chen et al., 2012; González-Quijano et al., 2014; Kopermsub and Yunchalard, 2010; Lan et al., 2009; Liu et al., 2012; Moroni et al., 2011; Ono et al., 2014; Scheirlinck et al., 2007; Sengun et al., 2009; Hansen, 2011; Kang et al., 2016; Fessard and Remize, 2017; Vos et al., 2009):

- Fermented brines used to make stinky tofu
- Suan-tsai and fu-tsai (traditional fermented mustard food products in Taiwan)

- Jiang-gua (traditional fermented cucumber food product in Taiwan)
- Fermented jalapeño pepper (*Capsicum annuum* L.)
- Plaa-som (traditional fermented fish product in Thailand)
- Yan-dong-gua (traditional fermented wax gourd food product in Taiwan)
- Douchi (traditional Chinese salt-fermented soybean food)
- Spontaneously-fermented buckwheat and teff sourdoughs
- Nukadoko (fermented rice bran mash traditionally used for pickling vegetables in Japan)
- Traditional Belgian sourdoughs
- Tarhana (traditional Turkish fermented food made from spontaneously fermented yogurt and wheat flour)
- Kimchi
- Dahi (Indian yogurt like product)
- Italian cheese
- Gari, Attieke, Lafun (cassava)
- Ham and processed meat

W. cibaria was identified in the International Dairy Federation (IDF) bulletins for microbial food cultures used in fermented food products. The IDF notes that the genus *Weissella* was introduced in 1993 for some species previously belonging to the *Leuconostoc mesenteroides* species group and *Weissella* species are used for fermentation of meat, cabbage (Kimchi), cassava, and cacao (International Dairy Federation, 2012). *W. cibaria* is specifically noted with food usage in vegetables dating to 2002 and taxonomy dating to 2002 (International Dairy Federation, 2012; International Dairy Federation, 2018).

W. cibaria strains are reported to be in foods commonly consumed (Chao et al., 2008; Scheirlinck et al., 2007; Chao et al., 2009). For example, Scheirlinck et al. (2007) reported the taxonomic distribution of LAB found in different traditional sourdough breads. The range of LAB reported was 10^7 to 10^9 CFU per gram sourdough (from LAB counts on MRS-5 agar), and the prevalence of *W. cibaria* was found to be 6%. Based on the assumption of the reference amount customarily consumed (RACC) for different bread products ranges from 50-110 grams per serving, the estimated amount of *W. cibaria* intake is roughly up to 6.6 x 10^9 CFU per serving of sourdough consumption[6]. Based on this, the intended use levels of *W. cibaria* CMU at inputs of up to 8.0 x 10^9 CFU per serving is not unreasonable compared to the amount one might consume in a serving of sourdough.

[6] Calculated as follows (authors also reported as log CFU/g which is not included in this table):

LAB Counts CFU/g	W. cibaria prevalence	W. cibaria /1 g	W. cibaria /50 g	W. cibaria /55 g	W. cibaria /110 g
1.00E+07	6%	6.00E+05	3.00E+07	3.30E+07	6.60E+07
1.00E+09	6%	6.00E+07	3.00E+09	3.30E+09	6.60E+09

1. U.S. Regulatory History

a. GRAS Status

No *Weissella cibaria* strains have been submitted to FDA through the GRAS notification procedure in the U.S. A search of the FDA GRAS database[7] revealed no notifications for the genus or species. One notification was identified for the search term "*Leuconostoc*" which was also searched as it is noted as a previous designation for *Weissella* in the IDF; the information for this ingredient is shown in Table 18. FDA received this Notice on April 28, 2020, and on April 19, 2021, issued a letter indicating that FDA had no questions regarding the GRAS determination (FDA GRN 936, 2021).

Table 18. Summary of FDA GRAS Inventory[1]

Substance	GRN #/ Closure Date	Intended Use	Use Rate	Company/ Reference
Leuconostoc carnosum DSM 32756	GRN 936 Apr. 19, 2021	Intended for use to inhibit the spoilage of raw cured meat products including but not limited to cured ham and bacon throughout its shelf-life	Use at levels up to 10^9 CFU/g of bacon	Chr. Hansen, Inc. FDA GRN 936 (2021)

[1] GRAS notifications presented here received a letter of "no questions" from FDA
CFU – colony forming unit; g – gram; GRN – GRAS notification

2. European Regulatory

The EFSA Panel on Biological Hazards (BIOHAZ) evaluates microbial species to determine whether they would recommend the species for Qualified Presumption of Safety (QPS) status. EFSA has not reviewed *Weissella* species to date[8] (BIOHAZ, 2021).

While EFSA has not reviewed *W. cibaria*, in general, the EFSA process to obtain QPS status considers the following:

> *Establishing a QPS status is based on four pillars: [1] the taxonomic grouping for which QPS is sought ('taxonomic identification'); [2] whether sufficient information is available about the proposed group of organisms to conclude on human/animal exposure by food/feed ('body of knowledge'); [3] whether the grouping proposed contains known pathogens ('safety') and, finally, [4] the intended end use ('intended use'). If a hazard related to a TU is identified, which can be tested at the strain or product level, a 'qualification' to exclude that hazard may be established. The subject of these qualifications for the microbial strain under investigation is evaluated by the EFSA Unit to which the application dossier has been allocated.* ***Absence of acquired genes***

[7] GRAS inventory available online at: https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices. GRN database search performed Jan. 04, 2022.
[8] See: https://zenodo.org/record/4498901#.YLEm0KhKj3Q. Accessed May 28, 2021.

> ***coding for resistance to antimicrobials relevant for humans and animals is a generic qualification for all bacterial taxonomic units*** *(BIOHAZ, 2021)*

EFSA guidance required for QPS status was considered in the evaluation of strain CMU for GRAS status.

3. Korean Regulatory History

Strain CMU is registered as a safe raw material by the Korea Food and Drug Administration (KFDA) under code number A 다 006800[9] and is found in several commercialized oral care live microbial products in Korea (Kang et al., 2019). In Korea, food item manufacturing reports (other processed products) are reported as containing oraCMU and *W. cibaria* CMU, and the raw material is listed as an edible strain on the Food Ingredients DB of the Korea Food and Drug Administration[10].

According to OraPharm, the available commercialized products provide a daily intake of *W. cibaria* CMU of 1 x 10^9 CFU to 2.4 x 10^{10} CFU per day, and to date, there are no reports of adverse reactions from distribution and sales. OraPharm reports that over 189,585 units of products containing strain CMU were sold from February 17, 2017, to Nov 04, 2021, and no adverse events have been reported. OraPharm provided the products and intake amounts presented in Table 19 and Table 20.

The intake amounts and rate of adverse events reported for the products commercially available in South Korea are supportive of safe use.

Table 19. Comparison of the Intended Daily Intake of *W. cibaria* CMU and the Daily Intake of the *W. cibaria* CMU in Korean Products

Intake/Product	Material	Commercial products (Conventional foods)		
		Probio Denti (other processed products)	OraDenti (sugar processed products)	GreenBreath (sugar processed products)
Strain	*Weissella cibaria* CMU	*Weissella cibaria* CMU	*Weissella cibaria* CMU	*Weissella cibaria* CMU
Daily intake (CFU/d)	3.97 x 10^8	1.0 x 10^9	1.2 x 10^{10}/ 3 tablets	2.4 x 10^{10}/ 3 tablets

[Remainder of page left intentionally blank]

[9] See http://www.foodsafetykorea.go.kr/foodcode/01_03.jsp?idx=12135. Accessed February 22,2022.
[10] See https://www.foodsafetykorea.go.kr/portal/safefoodlife/foodMeterial/foodMeterialDB.do. Accessed June 01, 2021.

Table 20. Distribution and Sales Status of Products Containing *W. cibaria* CMU as Available in South Korea

Food Category	Intended Use	Product Photos	Product Name	*W. cibaria* CMU Use-Level (mg/serving)	Serving size	*W. cibaria* CMU Use-Level (CFU/d)
Conventional Foods	Sugar processed products		Green Breath	240 mg	1~3 tablets per day (1000 mg~3000 mg per day)	2.4×10^{10} CFU/ 3 tablets/day
Conventional Foods	Sugar processed products		Ora Denti	120 mg	1~3 tablets per day (1000 mg~3000 mg per day)	1.2×10^{10} CFU/ 3 tablets/day
Baby and Toddler Foods	Other processed products		Probio Denti	60 mg	1 sachet per day (2000 mg per day)	1.0×10^{9} CFU/ 1 sachet/day
Conventional Foods	Other processed products		Dental Care Biotics	80 mg	1 sachet per day (2000 mg per day)	1.0×10^{9} CFU/ 1 sachet/day
Conventional Foods	Sugar processed products		Gigeunuk Bifidus Denti Fresh	64 mg	1 tablet per day (800 mg per day)	6.4×10^{8} CFU/ 1 tablet/day
Conventional Foods	Sugar processed products		Healthy Lactic acid bacterial Solution for Teeth	64 mg	1 tablet per day (800 mg per day)	6.4×10^{8} CFU/ 1 tablet/day
Conventional Foods	Other processed products		Eden Total Denti Care	64 mg	1 tablet per day (800 mg per day)	6.4×10^{8} CFU/ 1 tablet/day
Conventional Foods	Other processed products		Lactic acid bacteria in the Mouth 365	64 mg	1 tablet per day (800 mg per day)	6.4×10^{8} CFU/ 1 tablet/day

[Remainder of page left intentionally blank]

B. *W. cibaria* Strain CMU Safety Evaluation

1. Complete Genome Sequencing

As described in Part 2.A.3, the complete genome for *W. cibaria* CMU has been sequenced and deposited in GenBank (accession number CP013936) and in the Korean Collection for Type Cultures (accession number KCTC 10650BP) (NCBI GenBank, 2021; Kang et al., 2017). The complete genome of strain CMU was evaluated for potential risk ranging from antibiotic resistance to toxin production.

2. Assessment of Antibiotic Resistance

OraPharm evaluated *W. cibaria* CMU for antibiotic resistance through the following methods:

- A minimal inhibitory concentration (MIC) assay for 14 antibiotics, according to EFSA guidelines
- PCR Detection for known Antibiotic Resistance Genes (ARG)
- A genomic screening for ARGs Antibiotic Resistance Genes Database (ARDB) tool and the Resistance Gene Identifier (RGI).

Taken together, there is no evidence that *W. cibaria* CMU harbors acquired antibiotic resistance.

a. Antibiotic Susceptibility Testing (AST)

The European Food Safety Authority (EFSA) has established microbiological cut-off values for bacterial organisms based on the MICs determined using serial twofold dilution procedures in agar or broth (EFSA FEEDAP Panel, 2018b). When MIC values for the novel strain are below or equal to the Microbial Break Points (MBP) established by EFSA, this demonstrates that the novel strain follows the typical resistance patterns intrinsic to the genus / species and does not have acquired antimicrobial resistance. Intrinsic resistance refers to a type of resistance that is typical of the strains within a species that is not horizontally transferable, whereas acquired resistance is believed to have a greater risk because of the potential for horizontal gene transfer (HGT) within and between different species (Mathur and Singh, 2005). In cases where MIC values exceed the breakpoints established by EFSA, the organism should be evaluated further to determine potential risk of HGT.

Table 21 presents the MIC values for *W. cibaria* CMU compared to the EFSA values as reported by Kang et al. (2019). There are no specific MIC breakpoints established by EFSA for *Weissella* species (Quattrini et al., 2020; Kang et al., 2019). Therefore, Kang et al. (2019) compared the MIC values for strain CMU to the *Lactobacillus* obligate heterofermentative species and reported that the MIC values were equal to or lower than the EFSA cut-off values except for kanamycin. This is consistent with another evaluation of multiple *W. cibaria* strains by Quattrini et al. (2020) that compared *W. cibaria* for the EFSA values established for *Lactobacillus* / *Leuconostoc* from the 2012 publication (EFSA FEEDAP Panel, 2012).

Kang et al. (2019) reported that other commercially available *Lactobacillus* included in this analysis demonstrated the same values for kanamycin compared to strain CMU, nonetheless, they further evaluated the ability of strain CMU to transfer kanamycin and vancomycin resistance to donor strains and found no evidence of resistance transferability.

W. cibaria strains are typically resistant to aminoglycosides (gentamycin, kanamycin and streptomycin), but are susceptible to ampicillin, tetracycline and chloramphenicol (Quattrini et al., 2020). Aminoglycoside resistance is common to 70-80% of lactic acid bacteria (Quattrini et al., 2020). Intrinsic vancomycin resistance is also noted for *Weissella* species (Kamboj et al., 2015; Fusco et al., 2015; Quattrini et al., 2020). Quattrini et al. (2020) provided some evidence that aminoglycoside resistance is intrinsic with a low risk of horizontal transfer. Investigators reported that no genes for the most common mechanism for aminoglycoside resistance, aminoglycoside-modifying enzymes (AMEs), were found in the genomes for the *W. cibaria* strains evaluated, and that mutations of the ribosome or enzymatic modifications of the ribosome may be responsible for the resistance. Many lactic acid bacteria show a natural reduced sensibility towards these antimicrobials since most of them lack the complete pathway of ex-novo folic acid biosynthesis (the target of the sulphonamides) (Quattrini et al., 2020). Quattrini et al. (2020) reported that the same MIC values were obtained for the three commercial probiotic *Lactobacillus* strains that were used for comparison and that all *Weissella* and *Lactobacillus* strains tested showed resistance to methicillin. A multidrug efflux pump related to fosfomycin resistance was found in all *W. cibaria* genomes analyzed, as well as in strains of *Leuconostoc* and *Lactobacilli*. Therefore, Quattrini et al. (2020) consider resistance to fosfomycin as intrinsic. Abriouel et al. (2015) also found sulfonamide, methicillin resistance and fosfomycin resistance in *Weissella* strains.

Table 21. Minimum Inhibitory Concentrations of Antibiotics for *W. cibaria* CMU

	Ampicillin (Amp)	Vancomycin (Va)	Gentamycin (Gm)	Kanamycin (Km)	Streptomycin (Sm)	Erythromycin (Em)	Clindamycin (Cl)	Tetracycline (Tc)	Chloramphenicol (Ch)	Fusidic acid	Oxytetracycline	Rifampicin	Ciprofloxacin	Linezolid
	MIC µg/mL													
	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.
W. cibaria CMU[1]	0.5	>256	16	128	64	0.03	0.03	8	4	32	8	16	2	2
W. cibaria CMS1[1]	0.5	>256	4	32	16	0.03	0.03	4	4	16	4	8	2	1
W. cibaria CMS2[2]	0.5	>256	4	32	16	0.03	0.03	4	4	8	4	8	2	1
W. cibaria CMS3[2]	0.5	>256	4	64	16	0.06	0.03	4	4	16	4	16	2	1
L. reuteri Lr[3]	0.5	256	8	128	32	0.25	0.03	4	4	8	4	8	4	2
L. salivarius Ls[4]	0.5	>256	8	128	32	0.03	0.03	1	2	2	0.5	0.5	1	0.5
L. rhamnosus GG[5]	1	>256	8	32	8	0.03	0.03	0.25	1	256	0.1	0.1	0.25	0.5
E. faecalis ATCC 29212[6]	1	2	256	256	>256	2	16	32	4	4	8	2	1	2

	Ampicillin (Amp)	Vancomycin (Va)	Gentamycin (Gm)	Kanamycin (Km)	Streptomycin (Sm)	Erythromycin (Em)	Clindamycin (Cl)	Tetracycline (Tc)	Chloramphenicol (Ch)	Fusidic acid	Oxytetracycline	Rifampicin	Ciprofloxacin	Linezolid
	MIC µg/mL													
	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.
W. cibaria CM1[7]	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM6[7]	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM10[7]	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM18[7]	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM34[7]	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM23[7]	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM32[7]	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM9[7]	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM19[7]	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM27[7]	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
***Lactobacillus* Obligate Heterofermentative[8]**	**2**	**NR**	**16**	**32 (64)**	**64**	**1**	**1 (4)**	**8**	**4**	**ND**	**ND**	**ND**	**(NR)**	**ND**
Leuconostoc[8]	2	NR	16	16	64	1	1	8	4	ND	ND	ND	(NR)	ND
L. reuteri[8]	2	NR	8	64	64	1	1 (4)	16 (32)	4	ND	ND	ND	(NR)	ND
Lactobacillus facultative heterofermentative (*L. salivarius*)[8]	4	NR	16	64	64	1	1 (4)	8	4	ND	ND	ND	(NR)	ND
L. rhamnosus[8]	4	NR	16	64	32	1	1 (4)	8	4	ND	ND	ND	(NR)	ND
Enterococcus[8]	2	4	32	1024	128	4	4	4	16	ND	ND	ND	(NR)	ND

[1] As reported by Kang et al. (2019)
[2] As reported by OraPharm
[3] As reported by Kang et al. (2019): *L. reuteri* isolated from a commercial product (Sweden)
[4] As reported by Kang et al. (2019): *L. salivarius* isolated from a commercial product (Japan)
[5] As reported by Kang et al. (2019): *L. rhamnosus* GG (KCTC 5033)
[6] As reported by Kang et al. (2019): *E. faecalis* ATCC 29212
[7] As reported by Quattrini et al. (2020): S = susceptible (defined as MIC ≤ breakpoint (MBP in parentheses); R = resistance (defined as MIC > breakpoint (MBP in parentheses)
[8] EFSA taxonomy reflects genus name prior to publication of the taxonomy reclassification by Zheng et al. (2020). Any values that changed as reported by EFSA FEEDAP Panel (2018a) are noted in the footnotes as appropriate.
MBP as reported in EFSA (2012). Any values that changed as reported in EFSA (2018) are presented in parentheses (). Green text indicates values are at or below the MBP; red text indicates values are above the MBP
µg = microgram; mL = milliliter; MBP = Microbial Break Point; MIC = minimal inhibitory concentrations; ND = not determined; NR = not required

b. Genomic Assessment of Antibiotic Resistance Genes

Genomic screening for 28 known antibiotic resistance genes (ARG) (including KAN) was completed using a PCR analysis as reported by Kang et al. (2019). No ARGs in the chromosome and plasmid DNA of *W. cibaria* strain CMU were identified in OraPharm's analysis of CMU as confirmed in Kang et al. (2019).

Kang et al. (2019) concluded that “in this study, *W. cibaria* CMU and CMS1 strains were found to be safe strains because they did not have ARGs, antibiotic resistance transferability, or virulence factors, indicating that the safety of this species was strain-specific.” In the ARDB “resisGenes List” provided by OraPharm, kanamycin, fosfomycin, methicillin, and VanZ were included in this assessment. Further, it is important to note that although the organism is resistant to kanamycin in the MIC test, kanamycin and vancomycin resistance of the CMU strain is not transferable, as demonstrated by lack of transconjugants in a transfer test performed with *Lactobacillus rhamnosus* (a recipient strain that is susceptible to kanamycin) and *E. faecalis* (an organism with high vancomycin sensitivity) (Kang et al., 2019). As described in Kang et al. (2019), the amplicon for a conjugative transposon integron-specific genes on chromosome and plasmid were not found in the analysis for strain CMU.

The ARDB and Resistance Gene Identifier (RGI) were also used to analyze strain CMU for antibiotic resistance genes (Alcock et al., 2020; McArthur et al., 2013). RGI utilizes BLAST (Basic Local Alignment Search Tool) to predict complete resistomes from genomic and metagenomic data. The RGI database is regularly updated to ensure it contains the most current mechanisms of antibiotic resistance as identified in primary peer-reviewed literature. This database is a high-quality resource to evaluate the molecular basis of antimicrobial resistance and provides curated reference sequences and resources to analyze genome sequences (Jia et al., 2017; McArthur et al., 2013).

As reported by Kang et al. (2019) the analysis protocol used was described as follows:

> *similar to the analysis protocol provided by ARDB (http://ardb.cbcb.umd.edu/index.html), and the analysis proceeded without arbitrary adjustment values. CARD BLAST and RGI (https://card.mcmaster.ca/analyze/rgi) were also used for genome-based analysis of ARGs*

The ARDB evaluation analyzed 7828 ARGs and used an E value of 1×10^{-10} as the cutoff reference value, and included kanamycin, fosfomycin, methicillin, and vancomycin. The RGI analysis included 26 genomes registered in NCBI GenBank, including strain CMU chromosome (Filename = GenBank: CP013936.1) and strain CMU plasmid (Filename = GenBank: CP013937.1). The ARDB analysis showed that “no genes in *W. cibaria* strains [CMU] were homologous (% identical) at the chromosome and plasmid levels”. The RGI analysis also did not identify any ARGs for *W. cibaria* CMU.

3. Assessment of Antimicrobial and Secondary Metabolites

It is important to demonstrate that a live microbial strain does not produce antimicrobial substances that are used in medical or veterinary medicine. It is also important to demonstrate that CMU would not alter the normal microflora in a way that might provide an environment of selective pressure for antibiotic resistance gene acquisition (Pariza et al., 2015).

W. cibaria is reported to have antimicrobial activity and can produce a variety of antagonistic substances, including organic acids, bacteriocins, exopolysaccharides (EPS), and hydrolytic enzymes (Abriouel et al., 2015; Fessard and Remize, 2017).

Lim et al. (2018) investigated the antimicrobial activity and metabolite production for the cell-free supernatant (CFS) of strain CMU, reporting the production of organic acids and secreted proteins. CMU was found to produce hydrogen peroxide (H_2O_2) and had an H_2O_2-dependent inhibitory effect on oral bacteria *P. gingivalis* and *P. intermedia*. Jang et al. (2016) also confirmed the ability of strain CMU to produce H_2O_2 and inhibit growth of *S. mutans*, *Streptococcus sobrinus*, *Fusobacterium. nucleatum*, and *Porphyromonas gingivalis*. HPLC analysis confirmed the presence of lactic, acetic, and citric acids in the CFS and found inhibition of *P. gingivalis*, *P. intermedia*, and *F. nucleatum* in the presence of these acids (Lim et al., 2018). Oleic acid was also identified in this study and noted as having potential for antibacterial activity. Other substances were identified, including N-acetylmuramidase (lysozyme), and bacteriocins were also noted as potentially present (Lim et al., 2018). As shown in Part 6.B.4.b, CMU is not toxic to KB human mouth epithelial cells *in vitro,* indicating that concentrations of secondary metabolites that may be secreted by the organism are not high enough to cause toxicity to cells lining the human mouth.

While production of certain compounds might inhibit potentially pathogenic bacteria and therefore are a desirable trait for a live microbial, there could also be detrimental impacts on the normal, healthy flora. Therefore, OraPharm has conducted a study *in vitro* to determine the ability of *W. cibaria* CMU to inhibit growth of *L. acidophilus*, *L. fermentum*, and *L. reuteri.* The different species were mixed in the same amounts and cultured for 24 h. As a result of measuring the number of bacteria after 8 h and 24 h, respectively, CMU did not affect the growth of other common *Lactobacillus* strains (Appendix 8).

Based on this, there is no evidence that strain CMU has a negative impact on normal, healthy flora and combined with the toxicity data and clinical data discussed in Part 6.B.9 and Part 6.B.10, there is no reason to believe that strain CMU produces any compounds that pose a safety concern.

4. Assessment of Virulence

a. *In silico* Assessment

If a novel bacterial strain belongs to a taxonomic group with pathogenic or virulent potential, it is important to demonstrate a lack of virulence factors (Sanders et al., 2010). The literature for *Weissella* species does indicate some potential for virulence factors, including hemolysin genes, collagen adhesion genes, platelet associated adhesion genes, and mucus-binding protein genes (Abriouel et al., 2015; Quattrini et al., 2020). Therefore, strain CMU was thoroughly evaluated for any virulence factors or toxin production.

The assessment reported by Kang et al. (2019) using a publicly available web-based tool for WGS analysis hosted by the Center for Genomic Epidemiology (CGE) concluded that no virulence factors were present for the categories: “Shiga-toxin genes for *E. coli*, Virulence genes for *E. coli*, Virulence genes for *Listeria*, Exoenzyme genes for *S. aureus*, Toxin genes for *S. aureus*, Hostimm genes for *S. aureus*, Virulence genes for *Enterococcus*”. The search for virulence factors in *W. cibaria* CMU was

completed using the VirulenceFinder 2.0 Server, a component of the CGE[11] (Appendix 9). The database detects homologous sequences for the virulence genes related to *E. coli, Enterococcus, Listeria,* and *Staphylococcus aureus* in WGS data (Joensen et al., 2014). The output consists of best-matching genes from BLAST analysis of the selected database against the submitted genomes of *W. cibaria* CMU. The selected %ID threshold was set at 90% and the selected minimum length at 60%. In the event of a matching result, the output would show information on the predicted virulence gene, the %ID, the length of query and database gene, the position of the hit in the contig, and the accession number of the hit. The genome sequence of *W. cibaria* CMU was compared with the genome sequences of four well-known pathogens (*E. coli, Enterococcus, Listeria*, and *Staphylococcus aureus*). The virulence factors included *E. coli* Shiga toxin gene and *S. aureus* exoenzyme genes, host immune alteration or evasion genes, and toxin genes.

No virulence factors were found in the genomic sequence of *W. cibaria* CMU (Table 22). This result shows that the genomic sequence of *W. cibaria* CMU does not include toxic or pathogenic genes related to *E. coli, Enterococcus, Listeria*, or *S. aureus*.

Table 22. Virulence gene analysis of *W. cibaria* CMU

Virulence Genes	*W. cibaria* CMU
Shiga-toxin genes for *E. coli*	None found
Virulence genes for *E. coli*	None found
Virulence genes for *Listeria*	None found
Exoenzyme genes for *S. aureus*	None found
Toxin genes for *S. aureus*	None found
Hostimm genes for *S. aureus*	None found
Virulence genes for *Enterococcus*	None found

OraPharm also used the Gapped BLAST and PSI-BLAST to determine whether *W. cibaria* CMU has hemolysin genes or other virulence genes (Altschul et al., 1997; Schäffer et al., 2001).. BLASTP 2.3.0+ analysis was used for hemolysins. The database queried was contig1.faa, which consisted of 2126 sequences. Queries were specifically performed for *B. cereus* (tripartite hemolysin BL component L2, tripartite hemolysin BL component L1, tripartite hemolysin BL component B, CytK (partial) and cereulide peptide synthetase (partial)) and *B. cytotoxicus* (NheA, NheB, NheC). The results of this analysis showed no matches for any of the hemolysins with the exception of three sequences producing significant alignments with cereulide peptide synthetase (partial). The databases contig2.faa, which included 23 sequences and 3,858 total letters and contig3.faa which included 3 sequences and 434 total letters also were queried for all of the hemolysins mentioned above (including cereulide peptide synthetase (partial)) and no matches were found (Table 23).

[11] See http://www.genomicepidemiology.org/. Accessed May 05, 2021.

The Gapped BLAST and PSI-BLAST indicated that there were no hemolytic genes in *W. cibaria* CMU. In addition, the CMU genome was evaluated for a diarrhea-type toxin using enterotoxin and an emetic-type cereulide toxin. There was no homology with the diarrhea-type toxin, and the emetic toxin had a low homology of about 23-27% (identity%). Therefore, it was confirmed that *W. cibaria* CMU does not have toxin genes. Because results of the hemolysin analysis suggest the potential for cereulide peptide synthetase production, additional hemolysin analysis was performed.

Strain CMU was evaluated for β-hemolytic activity and was found to display no hemolysis in a 5% sheep blood agar assay, indicating that this strain lacks β-hemolysis activity (Kang et al., 2019).

While the *in silico* analysis disclosed the potential for production of cereulide peptide synthetase, the *in vitro* analysis for hemolysis was negative and the sheep blood agar assay were negative, indicating that strain CMU does not possess hemolytic activity.

Table 23. Toxin Evaluation of Diarrheal and Emetic Type Food Poisoning

Toxin gene	Gene/protein	Accession number	*W. cibaria* CMU
Hemolysin BL (HBL)	*hbl*C/L2	Accession: AY822584.1	None found
	*hbl*D/L1		None found
	*hbl*A/B		None found
Nonhemolytic enterotoxin (NHE)	*nhe*A/A	Accession: DQ885236.1	None found
	*nhe*B/B		None found
	*nhe*C/C		None found
Cytotoxin (CytK)	*Cyt*K/*Cyt*K	Accession: KP409163.1	None found
Emetic toxin (Cereulide)	*ces*/*ces*	Accession: AY691650.1	None found

b. Cytotoxicity Assay

As discussed in Part 6.B.3, *Weissella* species can produce a variety of secondary substances that are toxic to cells (Abriouel et al., 2015; Fessard and Remize, 2017). For novel microorganisms, it is important to establish that the strain is not toxic or hazardous.

Therefore, OraPharm performed a study to determine if CMU is toxic to KB human mouth epithelial cells *in vitro* (Kang et al., 2011). The cells were incubated with live *W. cibaria* at various concentrations (margin of exposure of 10, 100, 1,000) for 24 h. The specific numbers of cells added to the cultures were not stated. Cytotoxicity was assessed by an MTT ((3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay. This assay is based on the conversion of MTT into formazan crystals by living cells, which determines mitochondrial activity. Cell viability was ≥ 95% of the untreated control in all test conditions, indicating lack of toxicity of *W. cibaria* to the cells. The results indicate that the strain would not cause toxicity to cells lining the human mouth, even if in contact for 24 h.

5. Biogenic Amine Production

Biogenic amines are noted as potential concern for LAB in general and are identified for some *W. cibaria* species (Fessard and Remize, 2017). However, the *W. cibaria* strains evaluated by Fessard and Remize (2017) did not produce biogenic amines from histidine, lysine, ornithine or tyrosine and no genes encoding decarboxylases related to biogenic amine production were identified by Quattrini et al. (2020). OraPharm performed analyses of three representative samples of strain CMU for the ability to produce biogenic amines, using three methods and no biogenic amines were identified. Biogenic amines evaluated included: Histamine, Tryptamine, β-phenylethylamine, Putrescine, Cadaverine, Tyramine, Spermidine, and Spermine. Results from the representative samples are provided in Appendix 10.

- Strain CMU was first screened using methods described by Bover-Cid and Holzapfel (1999).
    - Cadaverine and putrescine were evaluated with commercially available lysine (MB-88014, MB cell) and ornithine (MB-88015, MB cell) decarboxylase test kits.
    - Histamine and tyramine were evaluated in a decarboxylase medium (pH 5.4) containing 1% histidine or tyrosine, 0.006% bromocresol purple, and 0.005% pyridoxal-5-phosphate and positive reactions were recorded when a purple color occurred (response to a pH shift of the bromocresol purple indicator).
- HPLC analysis of histamine was performed by SGS (Republic of Korea) which found no detectable levels of histamine (Limit of Quantitation: 5 mg/kg).
- Biogenic amines were further analyzed by the laboratory of the College of Science and Technology, Department of Food and Biotechnology, Korea University using chromatographic methods described by Eerola et al. (1993). No biogenic amines were identified in these analyses for Histamine, Tryptamine, β-phenylethylamine, Putrescine, Cadaverine, Tyramine, Spermidine, and Spermine.

6. Additional Safety Aspects Assessed

Other potential safety concerns were assessed by Kang et al. (2019), reporting several important negative results supportive of strain CMU safety:

- Strain CMU did not show an ability to degrade gelatin, indicating a lack of concern for protein degradation and cell invasion
- Strain CMU was found to not produce secondary bile salts (deoxycholic acid and lithocholic acid), D-lactic acid, urease, β-glucuronidase, indole, nitrate reductase
- Strain CMU did not show platelet aggregation capability
- Strain CMU did not produce the specific compound phenylpyruvic acid

7. Absorption, Distribution, Metabolism & Excretion (ADME) Studies

W. cibaria colonizes in the mouth, and significantly higher levels of *W. cibaria* are found in the mouths of subjects receiving 28 daily oral doses of 0.8×10^8 CFU *W. cibaria* strain CMU (Lee et al., 2020).

Continued administration for an additional 28 days did not cause a further increase in *W. cibaria* colonization in the subjects. The ultimate fate of *W. cibaria* has not been studied *in vivo*; however, it is likely that CFU that do not colonize in the mouth are likely to be swallowed.

8. Genetic Toxicity Studies

A reverse mutation test, an *in vitro* mammalian chromosome aberration test, and an *in vivo* micronucleus test have been conducted with *W. cibaria* CMU (Dolan et al., 2022). All studies were performed according to Good Laboratory Practice (GLP).

Results of the studies, which are all negative for genotoxicity, are tabulated below (Table 24).

Table 24. Genetic Toxicity of *W. cibaria* CMU

Endpoint	System	Concentrations Tested	Result	Reference
Reverse mutation (OECD 471)	*S. typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2*uvrA*	0, 62, 185, 556, 1667 and 5000 µg/plate ± S9 metabolic activation	Negative	Dolan et al. (2022)
In vitro chromosome aberration test (OECD 473)	Chinese Hamster Ovary (CHO-k1) cells	20.58, 61.73, 185.19 µg/ml, 24 hr incubation, -S9	Negative for chromosome aberrations, endoreduplication and polyploidy	
In vitro chromosome aberration test (OECD 473)	Chinese Hamster Ovary (CHO-k1) cells	61.73, 185.19, 555.56 µg/ml, 6 hr incubation, 18 hr recovery, -S9	Negative for chromosome aberrations, endoreduplication and polyploidy	
In vitro chromosome aberration test (OECD 473)	Chinese Hamster Ovary (CHO-k1) cells	185.19, 555.56, 1,666.67µg/ml, 6 hr incubation,18 hr recovery, +S9	Negative for chromosome aberrations, endoreduplication and polyploidy	
In vivo micronucleus, bone marrow (OECD 474)	SPF CrlOri:CD1(ICR) mice	1250, 2500 and 5000 mg/kg bw/day	Negative No cytotoxicity observed	

S9 – Supernatant fraction from liver homogenate of a male Sprague-Dawley rat induced with Aroclor-1254, centrifuged at 9000g, which contains microsomal enzymes

9. Toxicology Data

a. *In vivo* Toxicity Studies

A single dose oral toxicity study, a two week range finding study and a 13 week repeated oral dose study in male and female Sprague-Dawley rats have been conducted with *W. cibaria* CMU (Dolan et al., 2022). The single dose and 13 week studies were performed according to Good Laboratory Practice (GLP).

In the acute study, doses of 0, 1250, 2500 and 5000 mg/kg bw were administered once by gavage to groups of 5 rats/sex that had been fasted overnight (Dolan et al., 2022). Corresponding viable cell counts were 4.5×10^8, 9.0×10^8, and 1.8×10^9 CFU/kg bw, respectively. Animals were observed for clinical signs over 14 days and were weighed just prior to test material administration and on days 1,4,7 and 14 (before necropsy). None of the animals died and no abnormal clinical signs were observed during the study. The animals gained weight normally and there were no abnormal macroscopic findings at necropsy. The results indicate that the lethal dose of *W. cibaria* CMU in Sprague-Dawley rats is > 5000 mg/kg bw (1.8×10^9 CFU/kg bw).

For the range finding study, doses of 0, 1250, 2500 and 5000 mg/kg bw were administered once daily by gavage to groups of 5 rats/sex for a total of 14 days (Dolan et al., 2022). Corresponding viable cell counts were 4.5×10^8, 9.0×10^8, and 1.8×10^9 CFU/kg bw, respectively. Animals were observed daily for mortality and clinical signs and weekly for body weight, and food and water consumption. Animals were fasted overnight prior to blood collection on Day 14 for standard hematology and clinical chemistry. Testes, prostate, ovaries, uterus, spleen, liver, thymus, adrenals, kidneys, heart, lungs, brain, pituitary gland were collected from animals at necropsy on Day 14. All organs were weighed and placed in appropriate fixative. None of the animals died during the study and no abnormal clinical signs or necropsy findings were observed. There was no effect of the test material on body or organ weights or food or water consumption. The mean platelet volumes levels of mid and high dose males and the percentages of neutrophils in the low and mid dose female groups were increased compared to the vehicle control group ($p<0.05$). Increases in blood urea nitrogen and triglycerides were observed in the low dose female group compared to controls ($p<0.05$). The authors of the study did not consider any of these changes to be toxicologically significant because they were minor in nature and/or not dose dependent.

Based on results of the 14 day study, the authors chose doses of 0, 1250, 2500 and 5000 mg/kg bw for the 13 week gavage study in groups of 10 rats/sex (Dolan et al., 2022). The study was performed in compliance with GLP and OECD Test Guideline 408. The study included examinations for clinical signs, body weight, food consumption, ophthalmology, urinalysis, blood coagulation, serum thyroid hormones, clinical chemistry, hematology, estrus cycle, and weights and histopathology of all organs recommended by the guideline. None of the animals died during the study and no abnormal ophthalmological findings were observed. There was no effect of the test material on clinical signs, estrus cycle or thyroid hormones.

Body weights of all groups of males were generally significantly lower than controls during weeks 5-8 but normalized by week 9. Decreases in food consumption were observed in all groups of treated males from weeks four onward. The authors considered these effects to be related to administration of the test material but did not consider them to be adverse because the magnitude of the changes was <10%.

The specific gravity and the pH of urine from males and females showed dose-dependent increases. The urine volume of high dose males also was decreased compared to the vehicle control group.

However, the authors did not consider these changes to be toxicologically relevant because no abnormal changes in clinical pathology or histopathology related to kidney were observed.

Regarding hematology, white blood cell counts were decreased in low and high dose males and the percentages of eosinophils were decreased in low and mid dose females compared to controls. The prothrombin times of low and high dose males were also lower than controls. The only changes that occurred in clinical chemistry were increased bile acids and bilirubin in mid-dose females. These changes were not dose dependent and were within range of normal and therefore were not considered biologically significant.

Focal necrosis in the liver was observed in one control and one high dose female. Focal cell infiltration (mononuclear) and focal cortical scar in the kidney, focal cystic degeneration in the adrenal gland and focal atrophy of the acinar cells in the pancreas was observed in one female control animal. Harderian gland focal cell infiltration (mononuclear) also was observed in a female control animal. Ectopic thymus was observed in one female control animal and focal inflammatory cell infiltration in the lungs was observed in one male control animal. Ultimobranchial cysts in the thyroid were observed in 3 female controls, 3 male controls, 2 high dose females, and 5 high dose males. One male in the high dose group exhibited cardiomyopathy. The histopathological findings in test animals were considered to be incidental due to similar incidences in control animals.

There was a decrease in the left adrenal gland weight of low dose males and in the right thyroid weight of mid dose males and an increase in the right thyroid weight of high dose males compared to controls. In the case of relative organ weights, there was an increase in the right thyroid weight of high dose males compared to the control group. The authors of the study did not consider these changes to be related to administration of the test substance because of lack of a dose-response relationship and lack of corresponding histopathological findings. Further, there were no effects of the test material on thyroid hormones.

The results of the study indicate that the no observed adverse effect level (NOAEL) of *W. cibaria* CMU in Sprague-Dawley rats is 5,000 mg/kg/day (1.8×10^9 CFU/kg bw/day), the highest dose tested.

One study in mice with ligature-induced periodontitis and two in beagle dogs investigated the effect of the strain on oral health (Do et al., 2018; Do et al., 2019; Kim et al., 2020b). Up to 1×10^9 CFU/day was tested in mice for 14 days and 2×10^9 CFU/day for 6 weeks in dogs. The strain was applied to the teeth or gums. The authors of the study in mice stated: “all animals remained healthy during the experimental period.” There were no significant differences in body weight among the groups and no specific adverse events were observed. It is unclear whether the Do et al. (2018) study in dogs reported any adverse effects because the article was in Korean and only the tables were translated to English.

No irritation was observed in an unpublished oral mucosal irritation test of *W. cibaria* CMU in three male Syrian hamsters (KCL Study Report 7, 2021). The strain was administered in the left cheek pouch at 0.3 mL (1.8 × 109 CFU). The control was 0.3 mL of sterile distilled water in the right cheek

pouch. The animals were exposed to the test and control substances for at least 5 minutes, after which they were washed with physiological saline solution.[12] The procedure was repeated every 1 ± 0.1 hr for 4 hr, for a total of 5 applications. At the time of every administration and (24 ± 2) hr after administration, cheek pouches were graded for erythema. At (24 ± 2) hours after the final administration, all animals were euthanized and both cheek pouches were removed. The removed cheek pouches were fixed in 10% formalin solution containing neutral phosphate-buffered saline, sectioned and examined microscopically. No erythema, eschar or abnormal lesions were observed in the cheek pouch at any of the evaluations, and the irritation index was calculated as 0.0.

W. cibaria CMU tested negative for skin sensitization in 40 male Hartley guinea pigs, by the Beuhler method (KCL Study Report 8, 2021). The induction/challenge dose was 40% (w/v) of a preparation containing 3.6 x 10^8 CFU/g suspended in sterile distilled water. The positive control substance (α-hexylcinnamaldehyde) was administered in corn oil vehicle at 90% (w/v) (induction) and 45% (w/v) (challenge). Skin sensitization was evaluated by observing clinical signs and skin reactions 24 and 48 hr after removal of the challenge patches. The test substance showed a sensitization rate of 0% at both evaluation times and was classified as a non-sensitizing substance. The study was valid, as the positive control response was 60% and 70% at the 24 and 48 hr evaluation points, respectively.

10. Clinical Safety Data

A number of clinical studies have been performed with *W. cibaria* strain CMU providing a daily intake of 0.8 x 10^8 – 1.0 x 10^9 CFU per day. While most studies were not specifically designed to assess safety, the relevant parameters are summarized in Table 25. For the purpose of this dossier, we have focused on any discussion of potential adverse effects associated with the intake of strain CMU. In particular, Lee et al. (2020) included several safety parameters that are commonly measured in safety studies. Results of this study showed that daily consumption of 0.8 x 10^8 CFU/day (8 x 10^7 CFU/day) *W. cibaria* strain CMU from OraPharm for 8 weeks was well tolerated in young and middle-aged humans and had no effect on vital signs, clinical chemistry or hematology, except for a significant increase in monocytes (p = 0.005). The increase in monocytes was not considered adverse because it was within normal limits.

Table 25. Results of *W. cibaria* CMU studies in humans

Total Daily Amount	Population Characteristics	Study Design and Duration	Noted Effects Safety parameter Results	Reference
0.8 x 10^8 CFU/day *W. cibaria* strain CMU (OraPharm)	n = 92 without periodontitis; 34/group analyzed Age = 20-39 yrs	Randomized, DB, placebo controlled, 8-week duration. Subjects sucked on tablet containing the test article	14 Dropouts in test article group and 8 dropouts in placebo group. Reasons given for dropouts in each group were withdrawn consent, antibiotic use or <80% compliance.	Kang et al. (2020)

[12] It is unclear whether the cheek pouch was washed after each application.

Total Daily Amount	Population Characteristics	Study Design and Duration	Noted Effects Safety parameter Results	Reference
		or placebo before bed and did not eat or drink afterwards (presumably until morning). Evaluations were obtained prior to eating breakfast	No adverse effects on measured indices of oral health.	
0.8×10^8 CFU/day *W. cibaria* strain CMU (OraPharm)	n = 92 without periodontitis; 34/group analyzed Age = 23.6 (±3.4) yrs in placebo group and 23.4 (±2.9) yrs in test group*	Randomized, DB, placebo controlled, 8-week duration. Subjects were instructed to place powdered test article or placebo in mouth before bed and swallow after melting. Subjects did not eat or drink afterwards (presumably until morning). Evaluations were obtained prior to eating breakfast	14 Dropouts in test article group and 8 dropouts in placebo group. Reasons given for dropouts in each group were withdrawn consent, antibiotic use or <80% compliance. No adverse effect on caries incidence and no increase in acidogenic potential of plaque in test group.	Kang et al. (2021)
1×10^8 CFU/day *W. cibaria* strain CMU (Oradentics Inc.)	n = 60 with halitosis and high breath VSC concentrations; 29/group analyzed Age = 20-30 yrs	Randomized, DB, placebo controlled, 8-week duration. Subjects sucked on tablet containing the test article or placebo before bed and did not eat or drink afterwards (presumably until morning). Evaluations were obtained prior to eating breakfast	1 dropout/group (reason not stated). No adverse effects of test material on indices of halitosis measured.	Kim et al. (2020a)
0.8×10^8 CFU/day *W. cibaria* strain CMU (OraPharm)	n = 92 without periodontitis; 34/group analyzed Age = 20-39 yrs*	Randomized, DB, placebo controlled, 8-week duration. Subjects sucked on tablet containing the test article or placebo before bed and did not eat or drink afterwards (presumably until morning). Evaluations were obtained prior to eating breakfast	14 Dropouts in test article group and 8 dropouts in placebo group. Reasons given for dropouts in each group were withdrawn consent, antibiotic use or <80% compliance. No adverse effects of test material on indices of halitosis measured. No SAE observed. 1 AE per group (mild xerostomia in test group and mild diarrhea in placebo group).	Lee et al. (2020)

Total Daily Amount	Population Characteristics	Study Design and Duration	Noted Effects Safety parameter Results	Reference
			No effect of test material on vital signs, clinical chemistry or hematology except for a significant increase in monocytes (p = 0.005). Value within normal limits.	
0.8×10^8 CFU/day *W. cibaria* strain CMU (OraPharm)	n = 92 college students; 34/test group and 28/placebo group analyzed**	Randomized, DB, placebo controlled, 8-week duration. Subjects sucked on tablet containing the test article or placebo before bed and did not eat or drink afterwards (presumably until morning). Evaluations were obtained prior to eating breakfast	7 Dropouts in test article group and 4 dropouts in placebo group. Reasons given for dropouts in each group were withdrawn consent, antibiotic use or <80% compliance No adverse effects of test material on indices of halitosis measured. No SAE observed. 1 AE per group (mild xerostomia in test group and mild diarrhea in placebo group) considered unelated to intervention	Lee et al. (2021)
1×10^9 CFU/day *W. cibaria* strain CMU (Oradentics Inc.)	n = 50 subjects (25/group) Age not stated	Randomized, DB, placebo controlled, 4-week duration. Subjects sucked on tablet containing the test article or placebo after dinner. Evaluations performed at least 2 hrs after eating or drinking	No mention of any dropouts No adverse effects of test material on growth of the dental caries causing bacteria	Park et al. (2018)

AE – adverse events; CFU – colony forming units; DB – double blind; n – number; SAE – serious adverse events; yrs – years

C. Safety Decision Tree

Pariza et al. (2015) developed a decision tree to assess the safety of microbial cultures for human consumption. This decision tree is commonly used to evaluate safety to a strain level due to the existence of genetic diversity within a genus and species. The safety of *W. cibaria* CMU has been evaluated utilizing the scientific procedures as outlined by Pariza et al. (2015). Based on the outcome of the decision tree for determining the safety of microbial cultures for consumption by humans and animals including strain characterization and genome sequencing, screening for undesirable attributes and metabolites, and experimental evidence of safety in appropriately designed safety evaluation studies, it was concluded that *W. cibaria* CMU is deemed to be safe for human consumption. The decision tree for *W. cibaria* CMU based on Pariza et al. (2015) is provided in Table 26.

Table 26. Safety Decision Tree

Decision Tree Question Based on Pariza et al. (2015)	Conclusion for *W. cibaria* strain CMU
1. Has the strain been characterized for the purpose of assigning an unambiguous genus and species name using currently accepted methodology? (**If YES, go to 2**. If NO, the strain must be characterized and unambiguously identified before proceeding).	Yes. Designation as *W. cibaria* is supported with WGS, 16S rRNA analysis, ANI, phenotypic, and RAPD analysis.
2. Has the strain genome been sequenced? (**If YES, go to 3**. If NO, the genome must be sequenced before proceeding to 3.)	Yes.
3. Is the strain genome free of genetic elements encoding virulence factors and/or toxins associated with pathogenicity? (**If YES, go to 4**. If NO, go to 15.)	Yes, there was no evidence of concern identified. No virulence factors identified from genomic evaluations of strain CMU based on the CGE and Gapped and PSI BLAST, as well as *in vitro* cytotoxicity, biogenic amine, and β-hemolysis analyses.
4. Is the strain genome free of functional and transferable antibiotic resistance gene DNA? (**If YES, go to 5**. If NO, go to 15.)	Yes, there was no evidence of concern identified. Overall MIC results, genomic evaluation of ARGs, and lack of kanamycin and vancomycin resistance transferability indicates that there is no evidence of high risk HGT.
5. Does the strain produce antimicrobial substances? (**If NO, go to 6**. If YES, go to 15.)	No, no evidence of concern identified. Strain CMU does not inhibit growth of *L. acidophilus*, *L. fermentum*, and *L. reuteri in vitro*, and no safety concerns were raised in the animal and human studies.
6. Has the strain been genetically modified using rDNA techniques? (If YES, go to 7. **If NO, go to 8**.)	No. Strain CMU has not been genetically modified.
7. Do the expressed product(s) that are encoded by the introduced DNA have a history of safe use in food? (If YES, go to 8. If NO, the expressed product(s) must be shown to be safe before proceeding to 8.)	--
8. Was the strain isolated from a food that has a history of safe consumption for which the species, to which the strain belongs, is a substantial and characterizing component (not simply an 'incidental isolate')? (If YES, go to 9. **If NO, go to 13**.)	No. Strain CMU was isolated from human saliva. Strain CMU is in a chewing gum product in Korea and this strain has been commercially available in Korea in various products since 2017 without reports of adverse effects.
9. Has the species, to which the strain belongs, undergone a comprehensive peer-reviewed safety evaluation and been affirmed to be safe for food use by an authoritative group of qualified scientific experts? (If YES, go to 10. If NO, go to 13.)	--
10. Do scientific findings published since completion of the comprehensive peer-reviewed safety evaluation cited in question 9a continue to support the conclusion that the species, to which the strain belongs, is safe for use in food?	--

Decision Tree Question Based on Pariza et al. (2015)	Conclusion for *W. cibaria* strain CMU
(If YES, go to 11. If NO, go to 13.)	
11. Will the intended use of the strain expand exposure to the species beyond the group(s) that typically consume the species in "traditional" food(s) in which it is typically found (for example, will a strain that was isolated from a fermented food typically consumed by healthy adults be used in food intended for an 'at risk' group)? (If NO, go to 12. If YES, go to 13.)	–
12. Will the intended use of the strain expand intake of the species (for example, increasing the number of foods beyond the traditional foods in which the species typically found, or using the strain as a probiotic rather than as a fermented food starter culture, which may significantly increase the single dose and/or chronic exposure)? (If NO, go to 14. If YES, go to 13.)	–
13. Does the strain induce undesirable physiological effects in appropriately designed safety evaluation studies? (If YES, go to 15. **If NO, go to 14.**)	No. The strain is not genotoxic and does not produce undesirable effects in safety studies in rodents and a clinical trial that included several but not all clinical chemistry and hematology parameters that are measured in safety studies in rodents.
14. The strain is deemed to be safe for use in the manufacture of food, probiotics, and dietary supplements for human consumption.	Strain CMU meets standards as defined by the Pariza decision tree and is deemed safe for human consumption.
15. The strain is NOT APPROPRIATE for human or animal consumption.	

D. GRAS Criteria

FDA defines "safe" or "safety" as it applies to food ingredients as:

> "…reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."[13]

Amplification is provided in that the conclusion of safety is to include probable consumption of the substance in question, the cumulative effect of the substance and appropriate safety factors. It is FDA's operational definition of safety that serves as the framework against which this evaluation is provided.

Furthermore, in discussing GRAS criteria, FDA notes that[14]:

[13] See 21 CFR 170.3 (e)(i) and 81 FR 54959 Available at: https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe (Accessed on Jan. 04, 2022).
[14] Eligibility for classification as generally recognized as safe (GRAS) pursuant to 21 CFR 170.30. Available at: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-170/subpart-B#170.30 (Accessed Jan. 04, 2022).

> "…General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances directly or indirectly added to food, that there is reasonable certainty that the substance is not harmful under the conditions of its intended use."
>
> "'Common knowledge' can be based on either "scientific procedures" or on experience based on common use of a substance in food prior to January 1, 1958."

FDA discusses in more detail what is meant by the requirement of general knowledge and acceptance of pertinent information within the scientific community, i.e., the so-called "common knowledge element," in terms of the two following component elements:

- Data and information relied upon to establish safety must be generally available, and this is most commonly established by utilizing published, peer-reviewed scientific journals; and
- There must be a basis to conclude that there is consensus (but not unanimity) among qualified scientists about the safety of the substance for its intended use, and this is established by relying upon secondary scientific literature such as published review articles, textbooks, or compendia, or by obtaining opinions of expert panels or opinions from authoritative bodies, such as JECFA and the National Academy of Sciences.

General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive. General recognition of safety through scientific procedures shall be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.

The apparent imprecision of the terms "appreciable," "at the time," and "reasonable certainty" demonstrates that the FDA recognizes the impossibility of providing absolute safety in this or any other area (Lu, 1988; Renwick, 1990; Rulis and Levitt, 2009).

As noted below, this safety assessment to ascertain GRAS status for *Weissella cibaria* strain CMU for the specified food uses meets FDA criteria for reasonable certainty of no harm by considering both the technical and common knowledge elements.

E. Expert Panel Findings on Safety of OraPharm's Weissella cibaria

An evaluation of the safety and GRAS status of the intended use of OraPharm's *Weissella cibaria* strain CMU has been conducted by an Expert Panel convened by GRAS Associates; the Panel consisted of Robert L. Martin, Ph.D; Michael Falk, Ph.D.; and Margitta Dziwenka, DVM, DABT, as Panel Chair. The Expert Panel reviewed OraPharm's dossier as well as other publicly available information available to them. The individuals who served as Expert Panelists are qualified to evaluate the safety of foods and food ingredients by merit of scientific training and experience.

The GRAS Expert Panel report is provided in Appendix 11.

F. Common Knowledge Elements for GRAS Conclusions

The first common knowledge element for a GRAS conclusion requires that data and information relied upon to establish safety must be generally available; this is most commonly established by utilizing studies published in peer-reviewed scientific journals. The second common knowledge element for a GRAS conclusion requires that consensus exists within the broader scientific community.

1. Public Availability of Scientific Information

The key evidence for safety of *Weissella cibaria* strain CMU is publicly available. This includes a complete genome sequence deposited in GenBank and publicly available NCBI data which confirm that the strain is classified as *Weissella cibaria* (NCBI BioSample, 2021; NCBI GenBank, 2021; NCBI Genome Assembly and Annotation, 2021; Kang et al., 2017). Strain CMU is registered as a safe raw material by the Korea Food and Drug Administration (KFDA) and is found in several commercialized oral care live microbial products in Korea (Kang et al., 2019). Results of tests for antibiotic resistance, β-hemolytic activity, potential for virulence, gelatin degradation, production of secondary bile salts or phenylpyruvic acid, and platelet aggregation are reported by Kang et al. (2019). Lim et al. (2018) investigated the antimicrobial activity and metabolite production for the cell-free supernatant (CFS) of strain CMU, reporting the production of organic acids and secreted proteins. Results of genetic toxicity and rodent safety studies and clinical studies using 8×10^7 – 1.0×10^9 CFU *W. cibaria* strain CMU per day have been published. None of the published studies indicate potential safety concerns from *Weissella cibaria* strain CMU.

2. Scientific Consensus

The second common knowledge element for a GRAS conclusion requires that there be a basis to conclude that consensus exists among qualified scientists about the safety of the substance for its intended use.

OraPharm intends to add *W. cibaria* strain CMU to yogurt, frozen desserts (dairy, ices, sorbets and sherbets) and mixes, hard candy and chewing gum with an intended use level of 1×10^8 CFU per serving throughout the shelf life of the products. The 90th percentile intake for all ages is 397 mg/day. Using the specification of not less than 1×10^9 CFU per gram, the EDI in terms of CFU per day is 3.97×10^8. On a body weight basis, intake is 6.24 mg/kg bw/day, or 6.24×10^6 CFU/kg bw/day. Similarly, for male children (6-11 yr), who are estimated to consume the highest amount per kg bw, the EDI is 2.65×10^7 CFU/kg bw/day. These high intake scenarios are unlikely in that they assume that all of the foods consumed contain *W. cibaria* CMU at the highest amount.

W. cibaria strains are commonly found in fermented foods like cassava, meat/fish, kimchi, tarhana, and sourdough, and strain CMU was isolated from human saliva samples. Strain CMU has been identified as *W. cibaria* based on whole genome sequence (WGS) analysis, 16S ribosomal

ribonucleic acid (rRNA) alignment and phylogenetic homology, average nucleotide identity (ANI), and phenotypic evaluations.

OraPharm's *W. cibaria* CMU is produced in accordance with FDA current Good Manufacturing Practices (cGMP). OraPharm affirms that *W. cibaria* CMU is manufactured under cGMP conditions with raw materials and processing aids that meet the appropriate food grade regulations. The manufacturing process includes specific quality control steps to confirm genetic identity and limit genetic drift by confirming the starter strain as *W. cibaria* CMU through 16S ribosomal DNA analysis and maintaining the master stock. OraPharm has established sufficient rigorous product specifications and has demonstrated batch-to-batch consistency against these specifications.

Strain specific data available for *W. cibaria* CMU, based on *in silico/in vitro*, animal and clinical data demonstrate a lack of safety concerns for this strain based on the following:

- OraPharm reports that over 189,585 units of products containing *W. cibaria* CMU were sold from February 17, 2017 to Nov 04, 2021 in Korea and no adverse events have been reported. Available commercialized products provide a daily intake of *W. cibaria* CMU of 1 x 10^9 CFU to 2.4 x 10^{10} CFU per day.

- Results of an EFSA guideline MIC assay for 14 antibiotics, and genomic screening for known antibiotic resistance genes using PCR, ARDB and Resistance Gene Identifier show that *W. cibaria* CMU does not harbor acquired antibiotic resistance.

- *W. cibaria* CMU does not affect growth of other common *Lactobacillus* strains.

- No virulence factors were identified from genomic evaluations based on the CGE and Gapped and PSI BLAST, as well as *in vitro* cytotoxicity, biogenic amine, and β-hemolysis tests. *W. cibaria* does not degrade gelatin, indicating a lack of concern for protein degradation and cell invasion. *W. cibaria* CMU does not produce secondary bile salts (deoxycholic acid and lithocholic acid), D-lactic acid, urease, β-glucuronidase, indole, or nitrate reductase.

- *W. cibaria* CMU colonizes in the mouth, and significantly higher levels of *W. cibaria* are found in the mouths of subjects receiving 28 daily oral doses of 8 x 10^7 CFU *W. cibaria* strain CMU. Continued administration for an additional 28 days does not cause a further increase in *W. cibaria* colonization.

- *W. cibaria* CMU is not genotoxic.

- Results of unpublished studies show that *W. cibaria* CMU is not irritating to the oral mucosa and does not cause skin sensitization.

- The lethal dose of *W. cibaria* CMU in Sprague-Dawley rats is > 5000 mg/kg bw (1.8 x 10^9 CFU/kg bw).

- The NOAEL of *W. cibaria* CMU in a 13-week oral toxicity study in Sprague-Dawley rats is 5,000 mg/kg/day (1.8×10^9 CFU/kg bw/day), the highest dose tested.

- Based on the NOAEL of 1.8×10^9 CFU/kg bw/day in the 13-week toxicity study in rats with *W. cibaria* CMU and a conservative 100-fold safety factor for inter- and intra-species differences, the acceptable daily intake (ADI) of *W. cibaria* CMU in humans is calculated as 1.8×10^7 CFU/kg bw/day. This is considerably higher than the EDI for all ages of 6.24×10^6 CFU/kg bw/day.

- The margins of safety calculated from comparisons of EDI for specific populations to the NOAEL of 1.8×10^9 CFU/kg bw/day in rats are as follows:

    - EDI for all ages: 6.24×10^6 CFU/kg bw/day; margin of safety = 288.4

    - EDI for highest user, male child (6-11 yr) = 2.65×10^7 CFU/kg bw/day; margin of safety = 67.9

- Results of clinical studies suggest that up to 1.0×10^9 CFU per day *W. cibaria* CMU is tolerated.

- Available commercialized products in Korea provide a daily intake of *W. cibaria* CMU of 1×10^9 CFU to 2.4×10^{10} CFU per day, and to date, there are no reports of adverse reactions from distribution and sales of over 189,000 units since 2017.

Overall, the safety data support the conclusion that *W. cibaria* CMU is safe for human consumption at the intended usage level.

OraPharm and the Expert Panel maintain that other well-qualified scientists would conclude that *W. cibaria* CMU is generally recognized as safe for use in food given the regulatory and safety data available and using well accepted toxicological principles.

G. Discussion of Information Inconsistent with GRAS Conclusion

OraPharm is not aware of any information that would be inconsistent with a finding that the proposed use of *W. cibaria* CMU in food is generally recognized as safe.

The regulatory framework for determining whether a substance is generally recognized as safe (GRAS) is in 21 CFR 170.30, which states that GRAS status through scientific procedures shall ordinarily be based upon published studies, which may be corroborated by unpublished studies and other data and information. These criteria have been applied to the existing data for the *W. cibaria* strain CMU.

H. Conclusion

In consideration of the aggregate safety information available, OraPharm concludes that *W. cibaria* strain CMU as defined in the subject notification is safe for use in yogurt, frozen desserts (dairy, ices, sorbets and sherbets) and mixes, hard candy and chewing gum with an intended use level of 1 x 10^8 CFU per serving throughout the shelf life of the products.

The weight of the publicly available evidence from nonclinical and clinical studies with *W. cibaria* strain CMU provides a basis upon which to conclude that the proposed uses of *W. cibaria* strain CMU, as described in this dossier, satisfy the safety standard of Reasonable Certainty of No Harm and are safe. Based on the pivotal, published data and information that are generally available, one may conclude that the proposed uses of *W. cibaria* strain CMU, as produced consistent with current Good Manufactory Practice (cGMP) and meeting the food grade specifications presented above, are Generally Recognized As Safe (GRAS) based on scientific procedures. Support for these conclusions by a consensus of qualified experts in the general scientific community is provided in Appendix 11 (Expert Panel Report).

Accordingly, *Weissella cibaria* strain CMU as produced by OraPharm in accordance with FDA Good Manufacturing Practices and when it meets those specifications declared within the subject notification, meets FDA's definition of safety in that there is "reasonable certainty of no harm under the intended conditions of use" as described herein and, therefore, is generally recognized as safe (GRAS).

PART 7. LIST OF SUPPORTING DATA AND INFORMATION IN THE GRAS NOTICE.

A. References

1. List of Acronyms

µg	Microgram
ADME	Absorption, Distribution, Metabolism and Excretion
ANI	Average nucleotide identity
ANIb	Average nucleotide identity based on BLAST+
ANIm	Average nucleotide identity based on MUMmer
ARG	Antibiotic resistance gene
AST	Antibiotic susceptibility testing
BIOHAZ	EFSA Panel on Biological Hazards
BLAST	Basic Local Alignment Search Tool
CFS	Cell-free supernatant
CGE	Center for Genomic Epidemiology
cGMP	Current Good Manufacturing Practice
EDI	Estimated dietary intake
EFSA	European Food Safety Authority
EPS	Exopolysaccharides
FALCPA	Food Allergen Labeling and Consumer Protection Act of 2004
FALCPA	The Food Allergen Labeling and Consumer Protection Act of 2004
FD&C Act	Federal Food Drug and Cosmetics Act

g	Gram
GA	GRAS Associates
GC	Guanine-cytosine
GRAS	Generally Recognized as Safe
GRN	GRAS Notification
H_2O_2	Hydrogen peroxide
HGT	Horizontal gene transfer
IDF	International Dairy Federation
KFDA	Korea Food and Drug Administration
LAB	Lactic acid bacteria
Mb	Megabases
MBP	Microbial break points
MIC	Minimal inhibitory concentration
mL	Milliliter
N/A	Not available
NCBI	National Center for Biotechnology Information
NR	Not reported
QPS	Qualified Presumption of Safety
RACC	Reference amount customarily consumed
RAPD-PCR	Random amplification of polymorphic DNA-polymerase chain reaction
RGI	Resistance gene identifier
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
TCS	Tetra Correlation Search
tRNA	Transfer ribonucleic acid
U.S.	United States
WGS	Whole genome sequencing

2. References

Abriouel, H., Lerma, L. L., Casado Muñoz, M. D. C., Montoro, B. P., Kabisch, J., Pichner, R., Cho, G.-S., Neve, H., Fusco, V., Franz, C. M. A. P., Gálvez, A. and Benomar, N. (2015) 'The controversial nature of the *Weissella* genus: technological and functional aspects versus whole genome analysis-based pathogenic potential for their application in food and health', *Frontiers in microbiology,* 6, pp. 1197-1197. Available at: https://pubmed.ncbi.nlm.nih.gov/26579103.

Alcock, B. P., Raphenya, A. R., Lau, T. T. Y., Tsang, K. K., Bouchard, M., Edalatmand, A., Huynh, W., Nguyen, A. V., Cheng, A. A., Liu, S., Min, S. Y., Miroshnichenko, A., Tran, H. K., Werfalli, R. E., Nasir, J. A., Oloni, M., Speicher, D. J., Florescu, A., Singh, B., Faltyn, M., Hernandez-Koutoucheva, A., Sharma, A. N., Bordeleau, E., Pawlowski, A. C., Zubyk, H. L., Dooley, D., Griffiths, E., Maguire, F., Winsor, G. L., Beiko, R. G., Brinkman, F. S. L., Hsiao, W. W. L., Domselaar, G. V. and McArthur, A. G. (2020) 'CARD 2020: antibiotic resistome surveillance with the comprehensive antibiotic resistance database', *Nucleic Acids Res,* 48(D1), pp. D517-d525. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7145624/pdf/gkz935.pdf.

Altschul, S. F., Madden, T. L., Schäffer, A. A., Zhang, J., Zhang, Z., Miller, W. and Lipman, D. J. (1997) 'Gapped BLAST and PSI-BLAST: a new generation of protein database search programs', *Nucleic Acids Res,* 25(17), pp. 3389-402.

BIOHAZ (2021) 'Update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA 13: suitability of taxonomic units notified to EFSA until September 2020. European Food Safety Authority Panel on Biological Hazards (BIOHAZ)', *EFSA Journal,* 18(2):5965. Available at: https://www.efsa.europa.eu/en/efsajournal/pub/6377. Accessed June 01, 2021.

Bourdichon, F., Casaregola, S., Farrokh, C., Frisvad, J. C., Gerds, M. L., Hammes, W. P., Harnett, J., Huys, G., Laulund, S., Ouwehand, A., Powell, I. B., Prajapati, J. B., Seto, Y., Ter Schure, E., Van Boven, A., Vankerckhoven, V., Zgoda, A., Tuijtelaars, S. and Hansen, E. B. (2012) 'Food fermentations: microorganisms with technological beneficial use', *Int J Food Microbiol,* 154(3), pp. 87-97.

Bover-Cid, S. and Holzapfel, W. H. (1999) 'Improved screening procedure for biogenic amine production by lactic acid bacteria', *Int J Food Microbiol,* 53(1), pp. 33-41.

CDC (2020) *National Health and Nutrition Examination Survey (NHANES) 2017-2018 Dietary Data*: Centers for Disease Control and Prevention (CDC) National Center for Health Statistics. Available at: https://wwwn.cdc.gov/nchs/nhanes/Search/DataPage.aspx?Component=Dietary&CycleBeginYear=2017.

Chao, S. H., Tomii, Y., Watanabe, K. and Tsai, Y. C. (2008) 'Diversity of lactic acid bacteria in fermented brines used to make stinky tofu', *Int J Food Microbiol,* 123(1-2), pp. 134-41. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0168160507007192?via%3Dihub.

Chao, S. H., Wu, R. J., Watanabe, K. and Tsai, Y. C. (2009) 'Diversity of lactic acid bacteria in suan-tsai and fu-tsai, traditional fermented mustard products of Taiwan', *Int J Food Microbiol,* 135(3), pp. 203-10. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0168160509003778?via%3Dihub.

Chen, Y. S., Wu, H. C., Lo, H. Y., Lin, W. C., Hsu, W. H., Lin, C. W., Lin, P. Y. and Yanagida, F. (2012) 'Isolation and characterisation of lactic acid bacteria from jiang-gua (fermented cucumbers), a traditional fermented food in Taiwan', *J Sci Food Agric,* 92(10), pp. 2069-75. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/jsfa.5583.

Chun, J., Oren, A., Ventosa, A., Christensen, H., Arahal, D. R., da Costa, M. S., Rooney, A. P., Yi, H., Xu, X.-W., De Meyer, S. and Trujillo, M. E. (2018) 'Proposed minimal standards for the use of genome data for the taxonomy of prokaryotes', *International Journal of Systematic and Evolutionary Microbiology,* 68(1), pp. 461-466. Available at: https://www.microbiologyresearch.org/content/journal/ijsem/10.1099/ijsem.0.002516.

Collins, M. D., Samelis, J., Metaxopoulos, J. and Wallbanks, S. (1993) 'Taxonomic studies on some leuconostoc-like organisms from fermented sausages: description of a new genus Weissella for the Leuconostoc paramesenteroides group of species', *J Appl Bacteriol,* 75(6), pp. 595-603. Available at: https://sfamjournals.onlinelibrary.wiley.com/doi/10.1111/j.1365-2672.1993.tb01600.x.

Do, K.-H., Park, H.-E., Kang, M.-S., Kim, J.-T., Yeu, J.-E. and Lee, W.-K. (2018) 'Oral malodor-reducing effects by oral feeding of *Weissella cibaria* CMU in Beagle dogs', *Korean Journal of Veterinary Research,* 58(2), pp. 87-94.

Do, K.-H., Park, H.-E., Kang, M.-S., Kim, J.-T., Yeu, J.-E. and Lee, W.-K. (2019) 'Effects of *Weissella cibaria* CMU on halitosis and calculus, plaque, and gingivitis indices in beagles', *Journal of veterinary dentistry,* 36(2), pp. 135-142.

Dolan, L. C., Arceneaux, B. G., Do, K.-H., Lee, W.-K., Park, G.-Y., Kang, M.-S. and Choi, K.-C. (2022) 'Toxicological and safety evaluations of Weissella cibaria strain CMU in animal toxicity and genotoxicity', *Toxicological Research*. Available at: https://doi.org/10.1007/s43188-021-00119-9.

Eerola, S., Hinkkanen, R., Lindfors, E. and Hirvi, T. (1993) 'Liquid chromatographic determination of biogenic amines in dry sausages', *J AOAC Int,* 76(3), pp. 575-7.

EFSA FEEDAP Panel (2012) 'Guidance on the assessment of bacterial susceptibility to antimicrobials of human and veterinary importance', *EFSA Journal,* 10(6):2740. Available at: https://www.efsa.europa.eu/en/efsajournal/pub/2740. Accessed June 01, 2021.

EFSA FEEDAP Panel (2018a). 'Guidance on the characterisation of microorganisms used as feed additives or as production organisms.' (EFSA Panel on Additives and Products or Substances used in Animal Feed: Rychen, G, Aquilina, G, Azimonti, G, Bampidis, V, Bastos, ML, Bories, G, Chesson, A, Cocconcelli, PS, Flachowsky, G, Gropp, J, Kolar, B, Kouba, M, López-Alonso, M, López Puente, S, Mantovani, A, Mayo, B, Ramos, F, Saarela, M, Villa, RE, Wallace, RJ, Wester, P, Glandorf, B, Herman, L, Kärenlampi, S, Aguilera, J, Anguita, M, Brozzi, R and Galobart, J). *EFSA Journal* 16(3):5206, 24 pp. https://doi.org/10.2903/j.efsa.2018.5206. Available at: https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2018.5206.

EFSA FEEDAP Panel (2018b) 'Guidance on the characterisation of microorganisms used as feed additives or as production organisms. EFSA Panel on additives and products or substances used in animal feed (FEEDAP)', *EFSA Journal,* 16(3):5206. Available at: https://doi.org/10.2903/j.efsa.2018.5206. Accessed June 02, 2021.

Ennahar, S. and Cai, Y. (2004) 'Genetic evidence that Weissella kimchii Choi et al. 2002 is a later heterotypic synonym of Weissella cibaria Björkroth et al. 2002', *Int J Syst Evol Microbiol,* 54(Pt 2), pp. 463-465. Available at: https://www.microbiologyresearch.org/content/journal/ijsem/10.1099/ijs.0.02783-0#tab2.

FDA GRN 936 (2021). GRAS Notification 936. Available online at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=936. Accessed May 28, 2021.

Fessard, A. and Remize, F. (2017) 'Why are Weissella spp. not used as commercial starter cultures for food fermentation?', *Fermentation,* 3(3), pp. 38.

Fusco, V., Quero, G. M., Cho, G.-S., Kabisch, J., Meske, D., Neve, H., Bockelmann, W. and Franz, C. M. A. P. (2015) 'The genus Weissella: taxonomy, ecology and biotechnological potential', *Frontiers in microbiology,* 6, pp. 155-155. Available at: https://pubmed.ncbi.nlm.nih.gov/25852652.

González-Quijano, G. K., Dorantes-Alvarez, L., Hernández-Sánchez, H., Jaramillo-Flores, M. E., de Jesús Perea-Flores, M., Vera-Ponce de León, A. and Hernández-Rodríguez, C. (2014) 'Halotolerance and survival kinetics of lactic acid bacteria isolated from jalapeño pepper (Capsicum annuum L.) fermentation', *J Food Sci,* 79(8), pp. M1545-53. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/1750-3841.12498.

Goris, J., Konstantinidis, K. T., Klappenbach, J. A., Coenye, T., Vandamme, P. and Tiedje, J. M. (2007) 'DNA-DNA hybridization values and their relationship to whole-genome sequence similarities', *Int J Syst Evol Microbiol,* 57(Pt 1), pp. 81-91. Available at: https://www.microbiologyresearch.org/content/journal/ijsem/10.1099/ijs.0.64483-0#tab2.

Hansen, E. B. (2011). Presentation for IDF World Dairy Summit - Microorganisms with technologically beneficial use.

International Dairy Federation (2012) 'Bulletin of the International Dairy Federation No. 455/2012.'. Available at: https://publications.csiro.au/rpr/pub?list=BRO&pid=procite:705420e7-07d1-4761-94dd-62278498c9d7.

International Dairy Federation (2018). Bulletin of the International Dairy Federation No. 495/2018.

Jang, H. J., Kang, M. S., Yi, S. H., Hong, J. Y. and Hong, S. P. (2016) 'Comparative Study on the Characteristics of *Weissella cibaria* CMU and Probiotic Strains for Oral Care', *Molecules,* 21(12).

Jia, B., Raphenya, A. R., Alcock, B., Waglechner, N., Guo, P., Tsang, K. K., Lago, B. A., Dave, B. M., Pereira, S., Sharma, A. N., Doshi, S., Courtot, M., Lo, R., Williams, L. E., Frye, J. G., Elsayegh, T., Sardar, D., Westman, E. L., Pawlowski, A. C., Johnson, T. A., Brinkman, F. S., Wright, G. D. and McArthur, A. G. (2017) 'CARD 2017: expansion and model-centric curation of the comprehensive antibiotic resistance database', *Nucleic Acids Res,* 45(D1), pp. D566-d573. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5210516/pdf/gkw1004.pdf.

Joensen, K. G., Scheutz, F., Lund, O., Hasman, H., Kaas, R. S., Nielsen, E. M. and Aarestrup, F. M. (2014) 'Real-time whole-genome sequencing for routine typing, surveillance, and outbreak detection of verotoxigenic Escherichia coli', *J Clin Microbiol,* 52(5), pp. 1501-10.

Kamboj, K., Vasquez, A. and Balada-Llasat, J.-M. (2015) 'Identification and significance of *Weissella* species infections', *Frontiers in microbiology,* 6, pp. 1204-1204. Available at: https://pubmed.ncbi.nlm.nih.gov/26583007.

Kang, B. K., Cho, M. S. and Park, D. S. (2016) 'Red pepper powder is a crucial factor that influences the ontogeny of *Weissella cibaria* during kimchi fermentation', *Scientific Reports,* 6(1), pp. 28232. Available at: https://doi.org/10.1038/srep28232.

Kang, M.-S., Lee, D.-S., Kim, M., Lee, S.-A. and Nam, S.-H. (2021) 'A Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Acidogenic Potential of Dental Biofilms through a Tablet Containing *Weissella cibaria* CMU', *International Journal of Environmental Research and Public Health,* 18(9), pp. 4674.

Kang, M.-S., Lee, D.-S., Lee, S.-A., Kim, M.-S. and Nam, S.-H. (2020) 'Effects of probiotic bacterium *Weissella cibaria* CMU on periodontal health and microbiota: a randomised, double-blind, placebo-controlled trial', *BMC Oral Health,* 20(1), pp. 243. Available at: https://doi.org/10.1186/s12903-020-01231-2.

Kang, M.-S., Lim, H.-S., Kim, S.-M., Lee, H.-C. and Oh, J.-S. (2011) 'Effect of Weissella cibaria on Fusobacterium nucleatum-induced interleukin-6 and interleukin-8 production in KB cells', *Journal of Bacteriology and Virology,* 41(1), pp. 9-18.

Kang, M.-S., Yeu, J.-E., Oh, J.-S., Shin, B.-A. and Kim, J.-H. (2017) 'Complete Genome Sequences of *Weissella cibaria* Strains CMU, CMS1, CMS2, and CMS3 Isolated from Infant Saliva in South Korea', *Genome announcements,* 5(40), pp. e01103-17. Available at: https://pubmed.ncbi.nlm.nih.gov/28983008.

Kang, M. S., Yeu, J. E. and Hong, S. P. (2019) 'Safety Evaluation of Oral Care Probiotics *Weissella cibaria* CMU and CMS1 by Phenotypic and Genotypic Analysis', *Int J Mol Sci,* 20(11). Available at: https://res.mdpi.com/d_attachment/ijms/ijms-20-02693/article_deploy/ijms-20-02693-v2.pdf.

KCL Study Report 7 (2021) 'Report NT21-00003. Oral Mucosa Irritation Study of *Weissella cibaria* CMU (oraCMU®) in Syrian Hamsters. Sep. 2021'.

KCL Study Report 8 (2021) 'Report GT21-00001. Skin sensitisation Study of *Weissella cibaria* CMU (oraCMU®) in Hartley Guinea Pigs. Aug. 2021'.

Kim, D.-H., Kang, M.-S., Yeu, J.-E., Lee, M.-G. and Cho, J.-W. (2020a) 'Inhibitory effect of the probiotic bacteria, *Weissella cibaria* CMU on halitosis: a randomized placebo-controlled study', *Journal of Korean Academy of Oral Health,* 44(4), pp. 246-252.

Kim, J. W., Jung, B. H., Lee, J. H., Yoo, K. Y., Lee, H., Kang, M. S. and Lee, J. K. (2020b) 'Effect of *Weissella cibaria* on the reduction of periodontal tissue destruction in mice', *Journal of periodontology,* 91(10), pp. 1367-1374.

Kopermsub, P. and Yunchalard, S. (2010) 'Identification of lactic acid bacteria associated with the production of plaa-som, a traditional fermented fish product of Thailand', *Int J Food Microbiol,* 138(3), pp. 200-4.

Lan, W. T., Chen, Y. S. and Yanagida, F. (2009) 'Isolation and characterization of lactic acid bacteria from Yan-dong-gua (fermented wax gourd), a traditional fermented food in Taiwan', *J Biosci Bioeng,* 108(6), pp. 484-7.

Lee, D.-S., Kim, M., Nam, S.-H., Kang, M.-S. and Lee, S.-A. (2021) 'Effects of oral probiotics on subjective halitosis, oral health, and psychosocial health of college students: A randomized, double-blind, placebo-controlled study', *International Journal of Environmental Research and Public Health,* 18(3), pp. 1143.

Lee, D.-S., Lee, S.-A., Kim, M., Nam, S.-H. and Kang, M.-S. (2020) 'Reduction of Halitosis by a Tablet Containing *Weissella cibaria* CMU: A Randomized, Double-Blind, Placebo-Controlled Study', *Journal of medicinal food,* 23(6), pp. 649-657.

Lee, I., Ouk Kim, Y., Park, S. C. and Chun, J. (2016) 'OrthoANI: An improved algorithm and software for calculating average nucleotide identity', *Int J Syst Evol Microbiol,* 66(2), pp. 1100-1103.

Lim, H. S., Yeu, J. E., Hong, S. P. and Kang, M. S. (2018) 'Characterization of Antibacterial Cell-Free Supernatant from Oral Care Probiotic *Weissella cibaria*, CMU', *Molecules,* 23(8). Available at: https://res.mdpi.com/d_attachment/molecules/molecules-23-01984/article_deploy/molecules-23-01984.pdf.

Liu, C. J., Gong, F. M., Li, X. R., Li, H. Y., Zhang, Z. H., Feng, Y. and Nagano, H. (2012) 'Natural populations of lactic acid bacteria in douchi from Yunnan Province, China', *J Zhejiang Univ Sci B,* 13(4), pp. 298-306. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3323945/pdf/JZUSB13-0298.pdf.

Lu, F. C. (1988) 'Acceptable daily intake: inception, evolution, and application', *Regulatory Toxicology and Pharmacology,* 8(1), pp. 45-60.

McArthur, A. G., Waglechner, N., Nizam, F., Yan, A., Azad, M. A., Baylay, A. J., Bhullar, K., Canova, M. J., De Pascale, G., Ejim, L., Kalan, L., King, A. M., Koteva, K., Morar, M., Mulvey, M. R., O'Brien, J. S., Pawlowski, A. C., Piddock, L. J., Spanogiannopoulos, P., Sutherland, A. D., Tang, I., Taylor, P. L., Thaker, M., Wang, W., Yan, M., Yu, T. and Wright, G. D. (2013) 'The comprehensive antibiotic resistance database', *Antimicrob Agents Chemother,* 57(7), pp. 3348-57. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3697360/pdf/zac3348.pdf.

Michalak, M., Gustaw, K., Waśko, A. and Polak-Berecka, M. (2018) 'Composition of lactic acid bacteria during spontaneous curly kale (*Brassica oleracea* var. *sabellica*) fermentation', *Microbiol Res,* 206, pp. 121-130.

Moroni, A. V., Arendt, E. K. and Dal Bello, F. (2011) 'Biodiversity of lactic acid bacteria and yeasts in spontaneously-fermented buckwheat and teff sourdoughs', *Food Microbiol,* 28(3), pp. 497-502.

NCBI BioSample (2021). *Weissella cibaria* CMU - BioSample: SAMN04328351. National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine. Available online at: https://www.ncbi.nlm.nih.gov/biosample/SAMN04328351. Accessed May 11, 2021.

NCBI GenBank (2021). *Weissella cibaria* strain CMU, complete genome. National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine. Available online at: https://www.ncbi.nlm.nih.gov/nuccore/CP013936. Accessed May 11, 2021.

NCBI Genome (2021). *Weissella cibaria.* Organism Overview. National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine. Available online at: https://www.ncbi.nlm.nih.gov/genome/3287. Accessed May 11, 2021.

NCBI Genome Assembly and Annotation (2021). *Weissella cibaria* CMU. Organism Overview. National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine. Available online at: https://www.ncbi.nlm.nih.gov/genome/3287?genome_assembly_id=418159. Accessed May 27, 2021.

NCBI Genome Neighbor Report CMU (2021). *Weissella cibaria* CMU. National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine. Available online at: https://www.ncbi.nlm.nih.gov/genome/neighbors/3287?&genome_assembly_id=418159. Accessed May 27, 2021.

NCBI Genome Tree Report CMU (2021). *Weissella cibaria* CMU. National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine. Available online at: https://www.ncbi.nlm.nih.gov/genome/tree/3287. Accessed Aug 18, 2021.

NCBI Taxonomy (2021). *Weissella cibaria*. Taxonomy Browser. National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine. Available online at: https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=137591. Accessed May 11, 2021.

Ono, H., Nishio, S., Tsurii, J., Kawamoto, T., Sonomoto, K. and Nakayama, J. (2014) 'Monitoring of the microbiota profile in nukadoko, a naturally fermented rice bran bed for pickling vegetables', *J Biosci Bioeng,* 118(5), pp. 520-5.

Pariza, M. W., Gillies, K. O., Kraak-Ripple, S. F., Leyer, G. and Smith, A. B. (2015) 'Determining the safety of microbial cultures for consumption by humans and animals', *Regul Toxicol Pharmacol,* 73(1), pp. 164-71.

Park, H.-R., Kim, H.-J. and Kang, M.-S. (2018) 'Clinical studies on the dental caries prevention effects of the ability of *Weissella cibaria* CMU to adhere to the oral cavity', *Indian J Public Health Res Dev,* 9(9), pp. 755-761.

Quattrini, M., Korcari, D., Ricci, G. and Fortina, M. G. (2020) 'A polyphasic approach to characterize *Weissella cibaria* and *Weissella confusa* strains', *J Appl Microbiol,* 128(2), pp. 500-512. Available at: https://sfamjournals.onlinelibrary.wiley.com/doi/abs/10.1111/jam.14483.

Renwick, A. (1990) 'Acceptable daily intake and the regulation of intense sweeteners', *Food Additives & Contaminants,* 7(4), pp. 463-475.

Richter, M. and Rossello-Mora, R. (2009) 'Shifting the genomic gold standard for the prokaryotic species definition', *Proc Natl Acad Sci U S A,* 106(45), pp. 19126-31. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2776425/pdf/zpq19126.pdf.

Richter, M., Rosselló-Móra, R., Oliver Glöckner, F. and Peplies, J. (2016) 'JSpeciesWS: a web server for prokaryotic species circumscription based on pairwise genome comparison', *Bioinformatics,* 32(6), pp. 929-31.

Rulis, A. M. and Levitt, J. A. (2009) 'FDA'S food ingredient approval process: safety assurance based on scientific assessment', *Regulatory Toxicology and Pharmacology,* 53(1), pp. 20-31. Available at: http://www.sciencedirect.com/science/article/pii/S0273230008002298.

Sanders, M. E., Akkermans, L. M., Haller, D., Hammerman, C., Heimbach, J., Hormannsperger, G., Huys, G., Levy, D. D., Lutgendorff, F., Mack, D., Phothirath, P., Solano-Aguilar, G. and Vaughan, E. (2010) 'Safety assessment of probiotics for human use', *Gut Microbes,* 1(3), pp. 164-85. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3023597/pdf/gmic0103_0164.pdf.

Schäffer, A. A., Aravind, L., Madden, T. L., Shavirin, S., Spouge, J. L., Wolf, Y. I., Koonin, E. V. and Altschul, S. F. (2001) 'Improving the accuracy of PSI-BLAST protein database searches with composition-based statistics and other refinements', *Nucleic Acids Res,* 29(14), pp. 2994-3005.

Scheirlinck, I., Van der Meulen, R., Van Schoor, A., Vancanneyt, M., De Vuyst, L., Vandamme, P. and Huys, G. (2007) 'Influence of geographical origin and flour type on diversity of lactic acid bacteria in traditional Belgian sourdoughs', *Appl Environ Microbiol,* 73(19), pp. 6262-9. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2075033/pdf/0894-07.pdf.

Sengun, I. Y., Nielsen, D. S., Karapinar, M. and Jakobsen, M. (2009) 'Identification of lactic acid bacteria isolated from Tarhana, a traditional Turkish fermented food', *Int J Food Microbiol,* 135(2), pp. 105-11.

UniProt Taxonomy (2021). *Weissella cibaria* Taxonomy. Universal Protein Resource (UniProt). Available online at: https://www.uniprot.org/taxonomy/137591. Accessed May 11, 2021.

Vos, P., Garrity, G., Jones, D., Krieg, N., Ludwig, W., Rainey, F., Schleifer, K. H. and Whitman, W. (2009) *Bergey's Manual of Systematic Bacteriology Second Edition.*

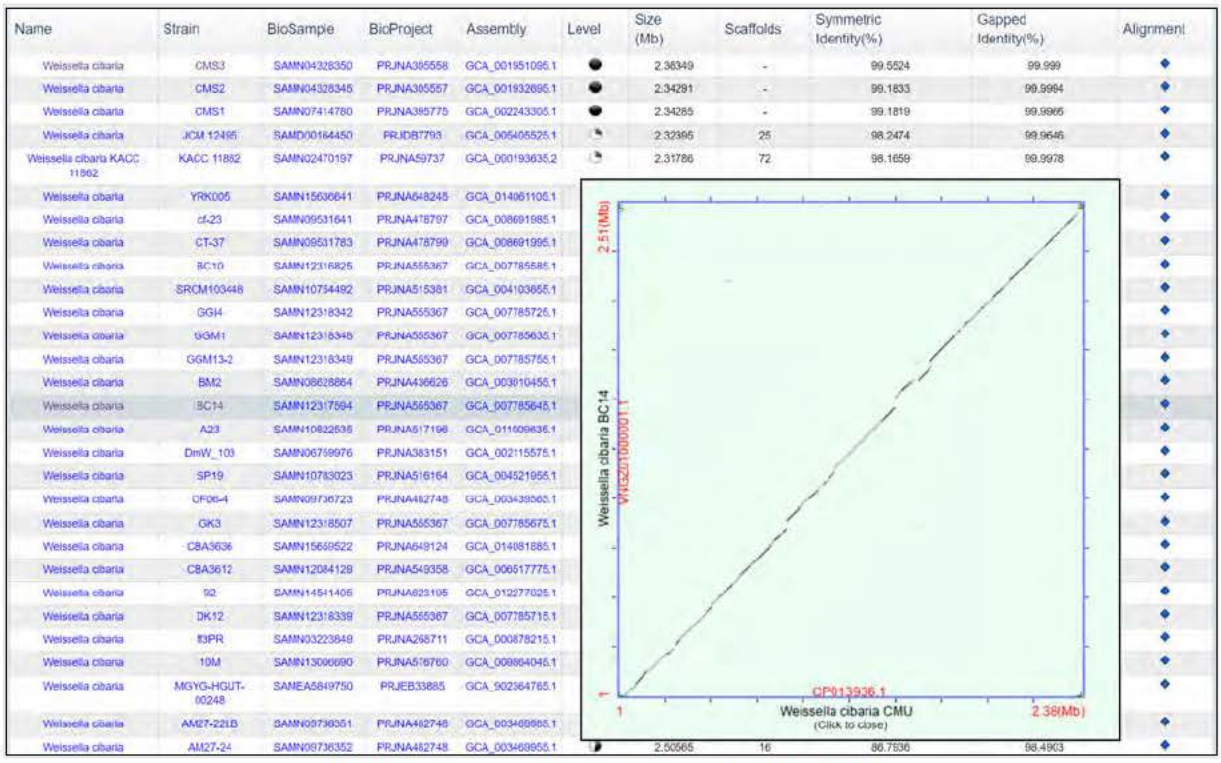
Yoon, S. H., Ha, S. M., Lim, J., Kwon, S. and Chun, J. (2017) 'A large-scale evaluation of algorithms to calculate average nucleotide identity', *Antonie Van Leeuwenhoek,* 110(10), pp. 1281-1286.

Zheng, J., Wittouck, S., Salvetti, E., Franz, C. M. A. P., Harris, H. M. B., Mattarelli, P., O'Toole, P. W., Pot, B., Vandamme, P., Walter, J., Watanabe, K., Wuyts, S., Felis, G. E., Gänzle, M. G. and Lebeer, S. (2020) 'A taxonomic note on the genus *Lactobacillus*: Description of 23 novel genera, emended description of the genus *Lactobacillus* Beijerinck 1901, and union of *Lactobacillaceae* and *Leuconostocaceae*', *International Journal of Systematic and Evolutionary Microbiology*. Available at: https://www.microbiologyresearch.org/content/journal/ijsem/10.1099/ijsem.0.004107.

B. Appendices

Appendix 1 NCBI Genomic Characterization Data

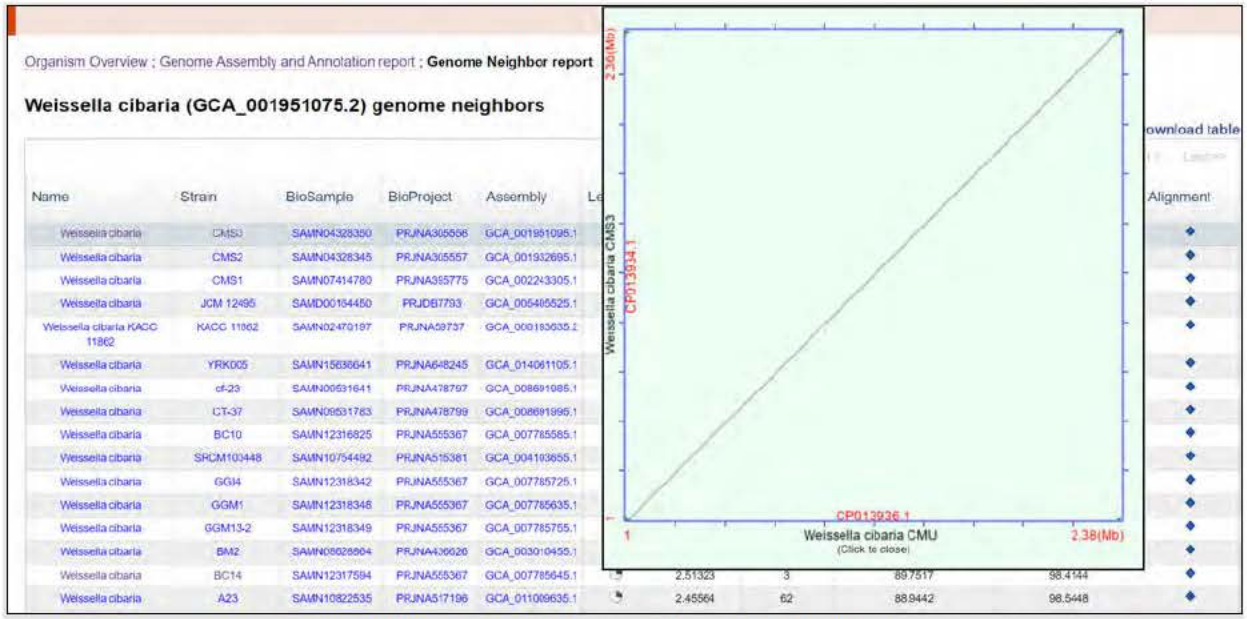
Figure 1.1 NCBI Hit Plot Alignment of Strains CMU and BC14[1]



Name	Strain	BioSample	BioProject	Assembly	Level	Size (Mb)	Scaffolds	Symmetric Identity(%)	Gapped Identity(%)	Alignment
Weissella cibaria	CMS3	SAMN04328350	PRJNA305558	GCA_001951095.1		2.36349	-	99.5524	99.999	
Weissella cibaria	CMS2	SAMN04328345	PRJNA305557	GCA_001932695.1		2.34291	-	99.1833	99.9984	
Weissella cibaria	CMS1	SAMN07414780	PRJNA385775	GCA_002243305.1		2.34285	-	99.1819	99.9986	
Weissella cibaria	JCM 12495	SAMD00164450	PRJDB7793	GCA_005485525.1		2.32395	25	98.2474	99.9646	
Weissella cibaria KACC 11862	KACC 11862	SAMN02470197	PRJNA59737	GCA_000193635.2		2.31786	72	98.1659	99.9978	
Weissella cibaria	YRK005	SAMN15636641	PRJNA648245	GCA_014061105.1						
Weissella cibaria	cf-23	SAMN09531641	PRJNA478797	GCA_008691985.1						
Weissella cibaria	CT-37	SAMN09531783	PRJNA478799	GCA_008691995.1						
Weissella cibaria	BC10	SAMN12316825	PRJNA555367	GCA_007785585.1						
Weissella cibaria	SRCM103448	SAMN10754492	PRJNA515381	GCA_004103655.1						
Weissella cibaria	GGI4	SAMN12318342	PRJNA555367	GCA_007785725.1						
Weissella cibaria	GGM1	SAMN12318348	PRJNA555367	GCA_007785635.1						
Weissella cibaria	GGM13-2	SAMN12318349	PRJNA555367	GCA_007785755.1						
Weissella cibaria	BM2	SAMN08628864	PRJNA436626	GCA_003010455.1						
Weissella cibaria	BC14	SAMN12317594	PRJNA555367	GCA_007785645.1						
Weissella cibaria	A23	SAMN10822535	PRJNA517196	GCA_011009635.1						
Weissella cibaria	DmW_103	SAMN06759976	PRJNA383151	GCA_002115575.1						
Weissella cibaria	SP19	SAMN10783023	PRJNA516164	GCA_004521955.1						
Weissella cibaria	OF06-4	SAMN09736723	PRJNA482748	GCA_003469565.1						
Weissella cibaria	GK3	SAMN12318507	PRJNA555367	GCA_007785675.1						
Weissella cibaria	C8A3636	SAMN15659522	PRJNA648124	GCA_014081885.1						
Weissella cibaria	C8A3612	SAMN12084129	PRJNA549358	GCA_006517775.1						
Weissella cibaria	92	SAMN14541406	PRJNA623105	GCA_012277025.1						
Weissella cibaria	DK12	SAMN12318339	PRJNA555367	GCA_007785715.1						
Weissella cibaria	f3PR	SAMN03223849	PRJNA268711	GCA_000878215.1						
Weissella cibaria	10M	SAMN13066690	PRJNA576760	GCA_009864045.1						
Weissella cibaria	MGYG-HGUT-00248	SAMEA5849750	PRJEB33885	GCA_902364765.1						
Weissella cibaria	AM27-22LB	SAMN09736351	PRJNA482748	GCA_003469885.1						
Weissella cibaria	AM27-24	SAMN09736352	PRJNA482748	GCA_003469955.1		2.50565	16	86.7936	98.4903	

[1]NCBI Genome Neighbor Report CMU (2021)

Figure 1.2 NCBI Hit Plot Alignment of Strains CMU and CMS3[2]



Organism Overview ; Genome Assembly and Annotation report ; **Genome Neighbor report**

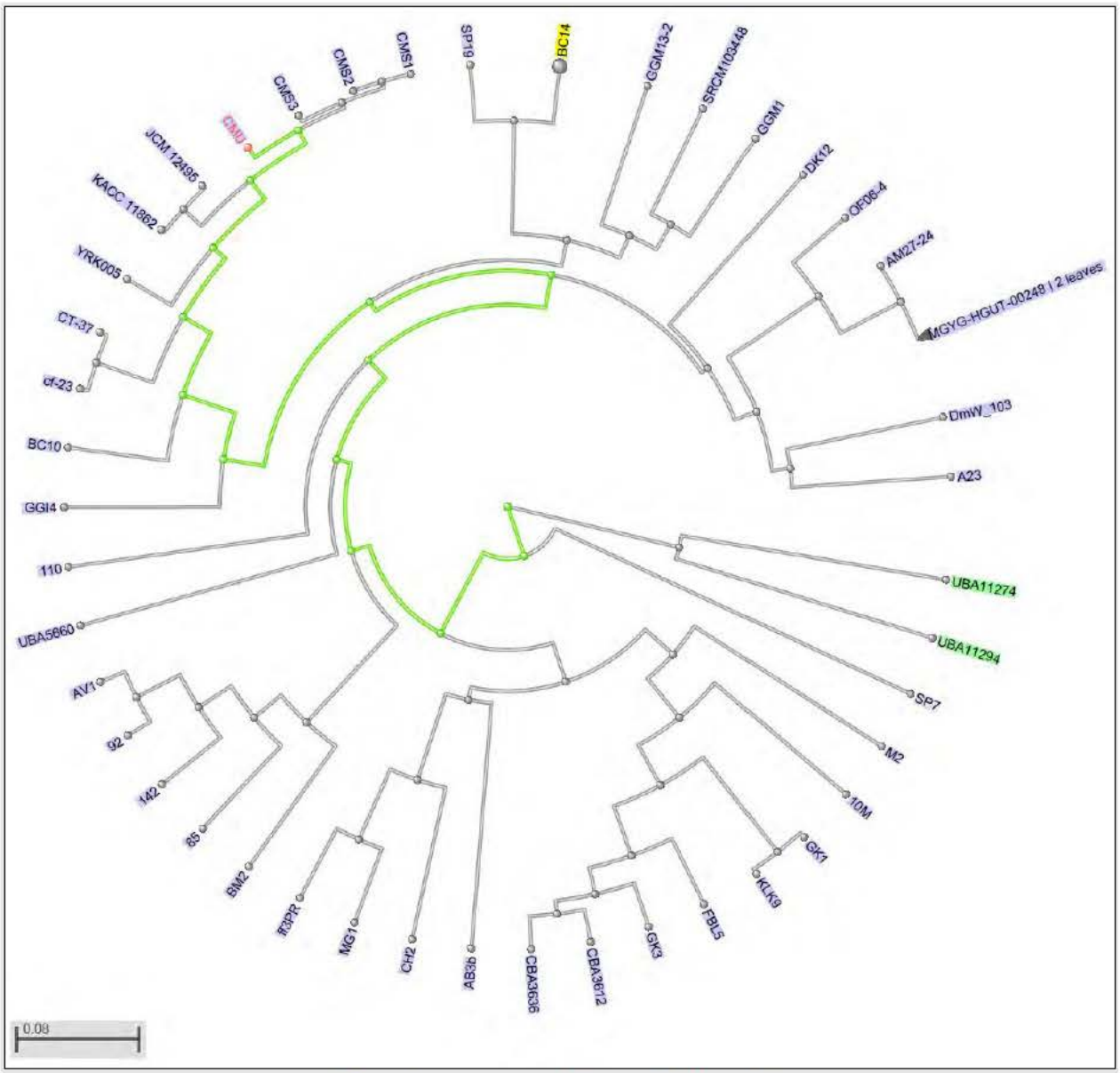
Weissella cibaria (GCA_001951075.2) genome neighbors

Name	Strain	BioSample	BioProject	Assembly	Le	Alignment
Weissella cibaria	CMS3	SAMN04328350	PRJNA305558	GCA_001951095.1		
Weissella cibaria	CMS2	SAMN04328345	PRJNA305557	GCA_001932695.1		
Weissella cibaria	CMS1	SAMN07414780	PRJNA385775	GCA_002243305.1		
Weissella cibaria	JCM 12495	SAMD00164450	PRJDB7793	GCA_005485525.1		
Weissella cibaria KACC 11862	KACC 11862	SAMN02470197	PRJNA59737	GCA_000193635.2		
Weissella cibaria	YRK005	SAMN15636641	PRJNA648245	GCA_014061105.1		
Weissella cibaria	cf-23	SAMN09531641	PRJNA478797	GCA_008691985.1		
Weissella cibaria	CT-37	SAMN09531783	PRJNA478799	GCA_008691995.1		
Weissella cibaria	BC10	SAMN12316825	PRJNA555367	GCA_007785585.1		
Weissella cibaria	SRCM103448	SAMN10754492	PRJNA515381	GCA_004103655.1		
Weissella cibaria	GGI4	SAMN12318342	PRJNA555367	GCA_007785725.1		
Weissella cibaria	GGM1	SAMN12318348	PRJNA555367	GCA_007785635.1		
Weissella cibaria	GGM13-2	SAMN12318349	PRJNA555367	GCA_007785755.1		
Weissella cibaria	BM2	SAMN08628864	PRJNA436626	GCA_003010455.1		
Weissella cibaria	BC14	SAMN12317594	PRJNA555367	GCA_007785645.1		
Weissella cibaria	A23	SAMN10822535	PRJNA517196	GCA_011009635.1		

Weissella cibaria	CMS3	SAMN04328350	PRJNA305558	GCA_001951095.1						
Weissella cibaria	CMS2	SAMN04328345	PRJNA305557	GCA_001932695.1						
Weissella cibaria	CMS1	SAMN07414780	PRJNA385775	GCA_002243305.1						
Weissella cibaria	JCM 12495	SAMD00164450	PRJDB7793	GCA_005485525.1						
Weissella cibaria KACC 11862	KACC 11862	SAMN02470197	PRJNA59737	GCA_000193635.2						
Weissella cibaria	YRK005	SAMN15636641	PRJNA648245	GCA_014061105.1						
Weissella cibaria	cf-23	SAMN09531641	PRJNA478797	GCA_008691985.1						
Weissella cibaria	CT-37	SAMN09531783	PRJNA478799	GCA_008691995.1						
Weissella cibaria	BC10	SAMN12316825	PRJNA555367	GCA_007785585.1						
Weissella cibaria	SRCM103448	SAMN10754492	PRJNA515381	GCA_004103655.1						
Weissella cibaria	GGI4	SAMN12318342	PRJNA555367	GCA_007785725.1						
Weissella cibaria	GGM1	SAMN12318348	PRJNA555367	GCA_007785635.1						
Weissella cibaria	GGM13-2	SAMN12318349	PRJNA555367	GCA_007785755.1						
Weissella cibaria	BM2	SAMN08628864	PRJNA436626	GCA_003010455.1						
Weissella cibaria	BC14	SAMN12317594	PRJNA555367	GCA_007785645.1		2.51323	3	89.7517	98.4144	
Weissella cibaria	A23	SAMN10822535	PRJNA517196	GCA_011009635.1		2.45564	62	88.9442	98.5448	

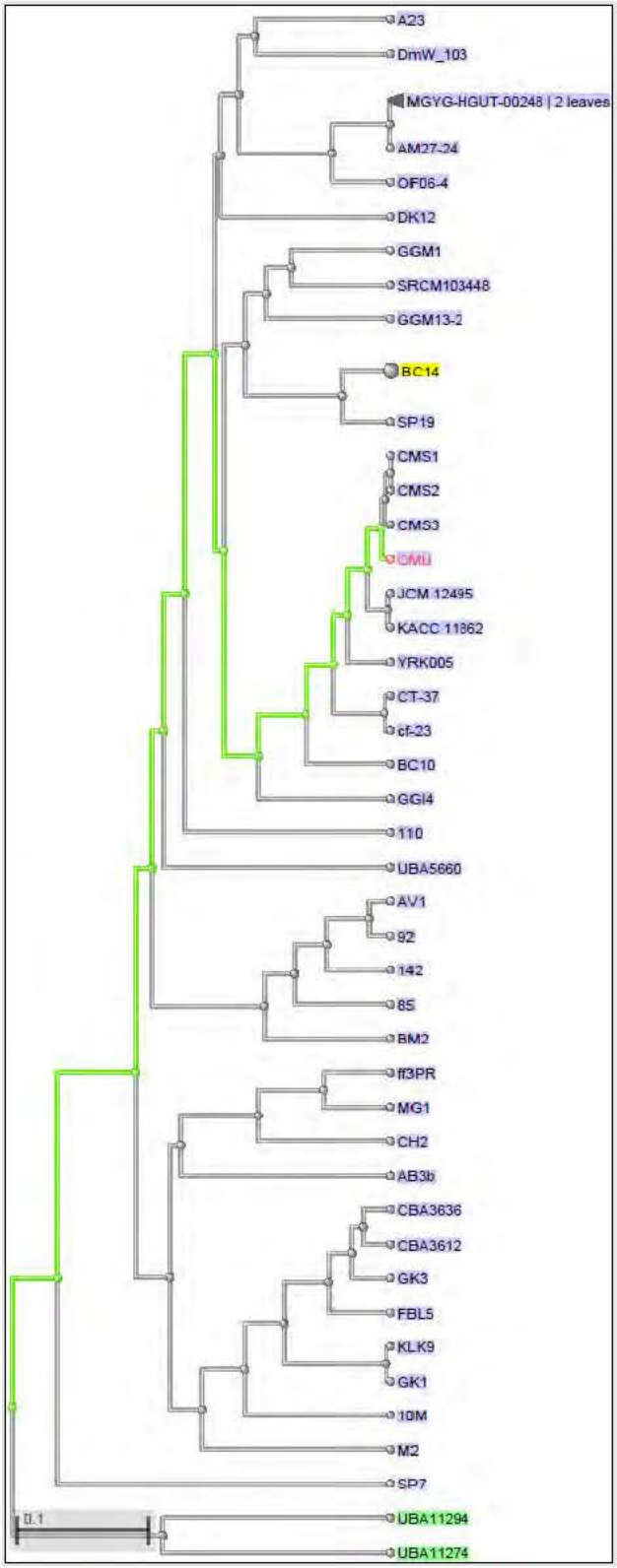
[2]NCBI Genome Neighbor Report CMU (2021)

Figure 1.3 NCBI Genome Report – Circular Tree for Strain CMU[3]



[3] NCBI Genome Tree Report CMU (2021)

Figure 1.4 NCBI Genome Report – Rectangle Cladogram for Strain CMU[4]



[4] NCBI Genome Tree Report CMU (2021)

Appendix 2 Macrogen 16S Reports and Certificates of Analysis for Multiple Lots

Appendix 2.1 *W. cibaria* CMU Lot CI11-0115N

Appendix 2.2 *W. cibaria* CMU Lot CI11-0116N

Appendix 2.3 *W. cibaria* CMU Lot CI11-0117N

Appendix 2.4 *W. cibaria* CMU Lot CI11-0362N

Appendix 2.5 *W. cibaria* CMU Lot CI11-0366N

Appendix 2.1 *W. cibaria* CMU Lot CI11-0115N

Macrogen 16S Report – Lot CI11-0115N

Standard ID

16S rRNA Full Sequencing — Humanizing Genomics macrogen

16S rRNA service report

Order Number : HC00253794
Sample name : Lot_CI11-0115N_contig_1

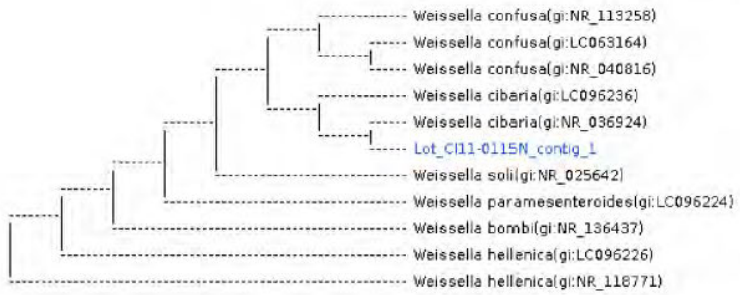
Information

Primer Information

Sequencing Primer Name Primer Sequences	PCR Primer Name Primer Sequences
785F 5' (GGA TTA GAT ACC CTG GTA) 3'	27F 5' (AGA GTT TGA TCM TGG CTC AG) 3
907R 5' (CCG TCA ATT CMT TTR AGT TT) 3'	1492R 5' (TAC GGY TAC CTT GTT ACG ACT T) 3'

Subject						Score		Identities	
Accession	Description	Length	Start	End	Coverage	Bit	E-Value	Match/Total	Pct.(%)
LC096236.1	Weissella cibaria	1516	10	1516	99	2772	0.0	1505/1507	99

Kingdom	Family	Genus	Species
Bacteria	Lactobacillaceae	Weissella	Weissella cibaria



Characterization

Weissella is a genus of Gram-positive bacteria, placed within the family Leuconostocaceae, and formerly considered species of the Leuconostoc paramesenteroides group. The morphology of Weissella species varies from spherical or lenticular cells to irregular rods.

Weissella cibaria is a species of Gram-positive bacteria, placed within the family of Leuconostocaceae. W.cibaria CMGDEX3 was reported from Pakistan to produce high molecular weight,linear dextran with predominant (1→6) linkages.

Query				Subject						Score			Identities			Strand
Name	Length	Start	End	Description	Link	AC	Length	Start	End	Bit	Raw	E-value	Match	Total	Pct(%)	
CMU_Lot_CI11-0115N_contig_1	1541	29	1534	Weissella cibaria gene for 16S ribosomal RNA, partial sequence, strain: JCM 12495	https://www.ncbi.nlm.nih.gov/nucleotide/LC09623	LC096236.1	1516	10	1516	2772	1501	0	1505	1507	99	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	29	1537	Weissella cibaria strain II-I-59 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_0369	NR_036924.1	1529	1	1511	2767	1498	0	1506	1511	99	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	29	1537	Weissella confusa gene for 16S ribosomal RNA, partial sequence, strain: JCM 1093	https://www.ncbi.nlm.nih.gov/nucleotide/LC09316	LC063164.1	1538	21	1531	2734	1480	0	1501	1511	99	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	29	1526	Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_1132	NR_113258.1	1499	1	1499	2717	1471	0	1490	1499	99	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	38	1514	Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_0408	NR_040816.1	1477	1	1477	2684	1453	0	1469	1477	99	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	29	1534	Weissella hellenica gene for 16S ribosomal RNA, partial sequence, strain: JCM 10103	https://www.ncbi.nlm.nih.gov/nucleotide/LC09622	LC096226.1	1512	7	1512	2449	1326	0	1448	1508	96	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	29	1535	Weissella paramesenteroides gene for 16S ribosomal RNA, partial sequence, strain: JCM 9890	https://www.ncbi.nlm.nih.gov/nucleotide/LC09622	LC096224.1	1518	13	1518	2446	1324	0	1452	1513	96	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	29	1537	Weissella hellenica strain NCFB 2973 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_1187	NR_118771.1	1527	11	1519	2444	1323	0	1450	1512	96	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	29	1537	Weissella bombi strain R-53094 16S ribosomal RNA, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_1364	NR_136437.1	1528	1	1510	2436	1319	0	1448	1512	96	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	29	1537	Weissella soli strain MI268 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_0256	NR_025642.1	1558	13	1523	2433	1317	0	1450	1515	96	Plus/Plus

Certificate of Analysis – Lot CI11-0115N

No. : D2021040318 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-04-02	Date of Manufacturg : 2021-02-15
No. of Sample : D2021040318	Expiration Date : 2023-02-14
Lot No. : CI11-0115N	
Inspection Purpose : For official use	
Commodity : Weissella cibaria CMU	
Applicant	Name : OraPharm Inc. Eun-sup Yoon
	Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea

Analytical Result

Test Item	Result
Sensory attribute	Yellowish white powder
Probiotics(CFU/g)	120 000 000 000 CFU/g (124 000 000 000, 109 000 000 000, 137 000 000 000)

End.

Apr . 9 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

한국식품과학연구원
Korea Advanced Food Research Institute

Korea Advanced Food Research Institute
50, Botdeul-ro, Uiwang-si, Gyeonggi-do, Republic of Korea
TEL : 82-2-3470-8200 FAX : 82-2-523-2072 http://www.kafri.or.kr

KAFRI

Certificate of Laboratory Testing(Reference)

Receipt No. (Reissue)	2021-11-003980	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company Name	OraPharm Inc.		
Client Address	905-ho 9-16, Yeommujang 5-gil, Seongdong-gu, Seoul, Republic of Korea		
Client Name	Eun-sup Yoon	Client Tel / Fax	02-2138-2573
Lot No.	CI11-0115N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
Test Purpose	For submission (MFDS)	Date of Issue	2021.03.08

Test Items and Results

Appearance.....Acceptable
Calorie(kcal).....385.4(per 100g)
Carbohydrate(%).....89.4
Moisture(%).....3.8
Ash(%).....0.6
Crude protein(%).....5.6(N factor 6.25)
Crude fat(%).....0.6
Sodium(mg/100g).....21.66

* The above test items and results complied with the test method notified by MFDS.

Note: 1. The above merchandise was submitted and identified by the client.
2. The results shown in this certificate refer only to sample tested and it does not cover the quality of all products.
3. No one can use this certificate for the purpose of test, advertisement and litigation without KAFRI's consent.
4. This certificate has no legal effect.

This certificate does not comply with the Act on Testing and inspection of Food and Drugs of Ministry of Food and Drug Safe.

[redacted]

Testing Personnel

[redacted]

Testing Manager

Korea Advanced Food Research Institute

한국식품고분연구원
Korea Advanced Food Research Institute

Korea Advanced Food Research Institute 50, Botdeul-ro, Uiwang-si, Gyeonggi-do, Republic of Korea TEL : 82-2-3470-8200 FAX : 82-2-523-2072 http://www.kafri.or.kr	KAFRI

Certificate of Laboratory Testing(Reference)

Receipt No. (Reissue)	2021-11-003981	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company Name	OraPharm Inc.		
Client Address	905-ho 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea		
Client Name	Eun-sup Yoon	Client Tel / Fax	02-2138-2573
Lot No.	C111-0115N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
Test Purpose	For submission (MFDS)	Date of Issue	2021.03.02

Test Items and Results

Lead(mg/kg).....0.01
Cadmium(mg/kg).....0.04
Arsenic(mg/kg).....0.00
Mercury(mg/kg).....Not Detected

* The above test items and results complied with the test method notified by MFDS.

Note: 1. The above merchandise was submitted and identified by the client.
2. The results shown in this certificate refer only to sample tested and it does not cover the quality of all products.
3. No one can use this certificate for the purpose of test, advertisement and litigation without KAFRI's consent.
4. This certificate has no legal effect.

This certificate does not comply with the Act on Testing and inspection of Food and Drugs of Ministry of Food and Drug Safe.

[redacted]

Testing Personnel

[redacted]

Testing Manager

Korea Advanced Food Research Institute

한국식품과학연구원
Korea Advanced Food Research Institute

Korea Advanced Food Research Institute 50, Botdeul-ro, Uiwang-si, Gyeonggi-do, Republic of Korea TEL : 82-2-3470-8200 FAX : 82-2-523-2072 http://www.kafri.or.kr	KAFRI

Certificate of Laboratory Testing(Reference)

Receipt No. (Reissue)	2021-11-003987	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company Name	OraPharm Inc.		
Client Address	905-ho 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea		
Client Name	Eun-sup Yoon	Client Tel / Fax	02-2138-2573
Lot No.	CI11-0115N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
Test Purpose	For submission (MFDS)	Date of Issue	2021.03.10

Test Items and Results

Coliforms.....Negative

* The above test items and results complied with the test method notified by MFDS.

Note: 1. The above merchandise was submitted and identified by the client.
2. The results shown in this certificate refer only to sample tested and it does not cover the quality of all products.
3. No one can use this certificate for the purpose of test, advertisement and litigation without KAFRI's consent.
4. This certificate has no legal effect.

This certificate does not comply with the Act on Testing and inspection of Food and Dr[redacted]Drug Safe.

[redacted]

Testing Personnel Testing

Korea Advanced Food Research Inst[redacted]

No. D2021063336 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-02-15
No. of Sample : D2021063336	Expiration Date : 2023-02-14
Lot No. : C111-0115N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Mold & Yeast plate count(/g)	0(Yeast 0, Mold 0)

End.

Jul . 6 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-701, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021063341 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-02-15
No. of Sample : D2021063341	Expiration Date : 2023-02-14
Lot No. : CI11-0115N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-1ê, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Escherichia coli(/g)	0
Salmonella spp.	Negative
Listeria monocytogenes	Negative
Staphylococcus aureus(/g)	0

End.

Jul . 6 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong Dr. j. h. yang

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

한국식품과학연구원
Korea Advanced Food Research Institute

Korea Advanced Food Research Institute 50, Botdeul-ro, Uiwang-si, Gyeonggi-do, Republic of Korea TEL : 82-2-3470-8200 FAX : 82-2-523-2072 http://www.kafri.or.kr	KAFRI

Certificate of Laboratory Testing(Reference)

Receipt No. (Reissue)	2021-11-003979	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company Name	OraPharm Inc.		
Client Address	905-ho 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea		
Client Name	Eun-sup Yoon	Client Tel / Fax	02-2138-2573
Lot No.	CI11-0115N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
Test Purpose	For submission (MFDS)	Date of Issue	2021.03.03

Test Items and Results

BHC(mg/kg).....Not Detected
DDT(mg/kg).....Not Detected
Aldrin(mg/kg).....Not Detected
Dieldrin(mg/kg).....Not Detected
Endrin(mg/kg).....Not Detected

* The above test items and results complied with the test method notified by MFDS.

Note: 1. The above merchandise was submitted and identified by the client.
2. The results shown in this certificate refer only to sample tested and it does not cover the quality of all products.
3. No one can use this certificate for the purpose of test, advertisement and litigation without KAFRI's consent.
4. This certificate has no legal effect.

This certificate does not comply with the Act on Testing and inspection of Food and Drugs of Ministry of Food and Drug Safe.

Jeon jun ho

Testing Personnel

Testing Manager

Korea Advanced Food Research Institute

Appendix 2.2 *W. cibaria* CMU Lot CI11-0116N

Macrogen 16S Report – Lot CI11-0116N

Standard ID

16S rRNA Full Sequencing — Humanizing Genomics macrogen

16S rRNA service report

Order Number : HC00253794
Sample name : Lot_CI11-0116N_contig_1

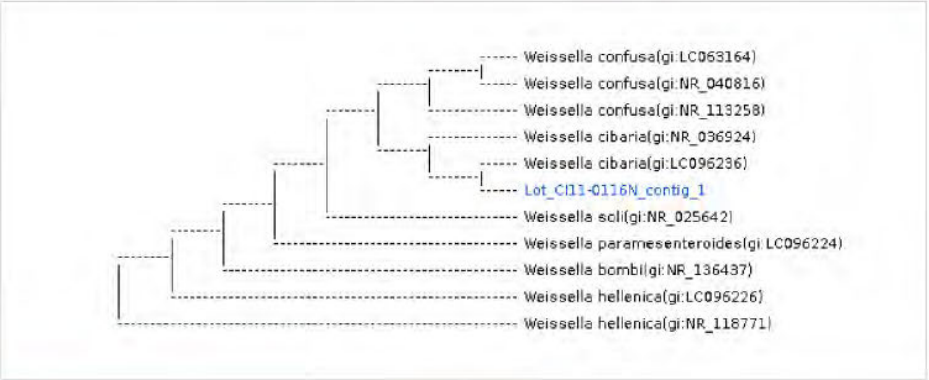
Information

Primer Information

Sequencing Primer Name Primer Sequences	PCR Primer Name Primer Sequences
785F 5' (GGA TTA GAT ACC CTG GTA) 3'	27F 5' (AGA GTT TGA TCM TGG CTC AG) 3
907R 5' (CCG TCA ATT CMT TTR AGT TT) 3'	1492R 5' (TAC GGY TAC CTT GTT ACG ACT T) 3'

Subject						Score		Identities	
Accession	Description	Length	Start	End	Coverage	Bit	E-Value	Match/Total	Pct.(%)
LC096236.1	Weissella cibaria	1516	6	1516	99	2787	0.0	1510/1511	99

Kingdom	Family	Genus	Species
Bacteria	Lactobacillaceae	Weissella	Weissella cibaria



Characterization

Weissella is a genus of Gram-positive bacteria, placed within the family Leuconostocaceae, and formerly considered species of the Leuconostoc paramesenteroides group. The morphology of Weissella species varies from spherical or lenticular cells to irregular rods.

Weissella cibaria is a species of Gram-positive bacteria, placed within the family of Leuconostocaceae. W.cibaria CMGDEX3 was reported from Pakistan to produce high molecular weight,linear dextran with predominant (1→6) linkages.

Query				Subject						Score			Identities			Strand
Name	Length	Start	End	Description	Link	AC	Length	Start	End	Bit	Raw	E-value	Match	Total	Pct(%)	
CMU_Lot_CI11-0116N_contig_1	1539	22	1532	Weissella cibaria gene for 16S ribosomal RNA, partial sequence, strain: JCM 12496	https://www.ncbi.nlm.nih.gov/nucleotide/LC096236	LC096236.1	1516	6	1516	2787	1509	0	1510	1511	99	Plus/Plus
CMU_Lot_CI11-0116N_contig_1	1539	26	1535	Weissella cibaria strain II-1-59 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_036	NR_036924.1	1529	1	1511	2772	1501	0	1507	1511	99	Plus/Plus
CMU_Lot_CI11-0116N_contig_1	1539	22	1535	Weissella confusa gene for 16S ribosomal RNA, partial sequence, strain: JCM 1093	https://www.ncbi.nlm.nih.gov/nucleotide/LC063	LC063164.1	1538	17	1531	2747	1487	0	1508	1515	99	Plus/Plus
CMU_Lot_CI11-0116N_contig_1	1539	26	1524	Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_113	NR_113258.1	1499	1	1499	2724	1475	0	1491	1499	99	Plus/Plus
CMU_Lot_CI11-0116N_contig_1	1539	36	1512	Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_040	NR_040816.1	1477	1	1477	2684	1453	0	1469	1477	99	Plus/Plus
CMU_Lot_CI11-0116N_contig_1	1539	22	1532	Weissella hellenica gene for 16S ribosomal RNA, partial sequence, strain: JCM 10103	https://www.ncbi.nlm.nih.gov/nucleotide/LC096226	LC096226.1	1512	3	1512	2462	1333	0	1453	1512	96	Plus/Plus
CMU_Lot_CI11-0116N_contig_1	1539	22	1533	Weissella paramesenteroides gene for 16S ribosomal RNA, partial sequence, strain: JCM 9890	https://www.ncbi.nlm.nih.gov/nucleotide/LC096224	LC096224.1	1518	9	1518	2460	1332	0	1457	1517	96	Plus/Plus
CMU_Lot_CI11-0116N_contig_1	1539	22	1535	Weissella hellenica strain NCFB 2973 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_118	NR_118771.1	1527	7	1519	2457	1330	0	1455	1516	96	Plus/Plus
CMU_Lot_CI11-0116N_contig_1	1539	22	1535	Weissella soli strain MI268 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_025	NR_025642.1	1558	9	1523	2446	1324	0	1455	1519	96	Plus/Plus
CMU_Lot_CI11-0116N_contig_1	1539	26	1535	Weissella bombi strain R-53094 16S ribosomal RNA, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_136	NR_136437.1	1528	1	1510	2444	1323	0	1449	1512	96	Plus/Plus

Certificate of Analysis – Lot CI11-0116N

No. : D2021040319 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-04-02	Date of Manufacture : 2021-02-15
No. of Sample : D2021040319	Expiration Date : 2023-02-14
Lot No. : CI11-0116N	
Inspection Purpose : For official use	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Sensory attribute	Yellowish white powder
Probiotics(CFU/g)	150 000 000 000 CFU/g (156 000 000 000, 138 000 000 000, 150 000 000 000)

End.

Apr . 9 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong Dr. J. H. yang

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021063334 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-02-15
No. of Sample : D2021063334	Expiration Date : 2023-02-14
Lot No. : C111-0116N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Ash(%)	1.30 %
Moisture(%)	2.85 %

End.

Jul . 7 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

한국식품과학연구원
Korea Advanced Food Research Institute

50, Botdeul-ro, Uiwang-si, Gyeonggi-do, Republic of Korea
TEL : 82-2-3470-8200 FAX : 82-2-523-2072 http://www.kafri.or.kr

KAFRI

Certificate of Laboratory Testing(Reference)

Receipt No. (Reissue)	2021-11-003982	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company Name	OraPharm Inc.		
Client Address	905-ho 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea		
Client Name	Eun-sup Yoon	Client Tel / Fax	02-2138-2573
Lot No.	C111-0116N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
Test Purpose	For submission (MFDS)	Date of Issue	2021.03.02

Test Items and Results

Lead(mg/kg).....0.01
Cadmium(mg/kg).....0.05
Arsenic(mg/kg).....0.00
Mercury(mg/kg).....Not Detected

* The above test items and results complied with the test method notified by MFDS.

Note: 1. The above merchandise was submitted and identified by the client.
2. The results shown in this certificate refer only to sample tested and it does not cover the quality of all products.
3. No one can use this certificate for the purpose of test, advertisement and litigation without KAFRI's consent.
4. This certificate has no legal effect.

This certificate does not comply with the Act on Testing and inspection of Food and Drugs of Ministry of Food and Drug Safe.

[redacted] [redacted]

Testing Personnel Testing Manager

Korea Advanced Food Research Institute

한국식품과학연구원

Korea Advanced Food Research Institute 50, Botdeul-ro, Uiwang-si, Gyeonggi-do, Republic of Korea TEL : 82-2-3470-8200 FAX : 82-2-523-2072 http://www.kafri.or.kr	KAFRI

Certificate of Laboratory Testing(Reference)

Receipt No. (Reissue)	2021-11-003988	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company Name	OraPharm Inc.		
Client Address	905-ho 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea		
Client Name	Eun-sup Yoon	Client Tel / Fax	02-2138-2573
Lot No.	C111-0116N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
Test Purpose	For submission (MFDS)	Date of Issue	2021.03.10

Test Items and Results

Coliforms.....Negative

* The above test items and results complied with the test method notified by MFDS.

Note: 1. The above merchandise was submitted and identified by the client.
2. The results shown in this certificate refer only to sample tested and it does not cover the quality of all products.
3. No one can use this certificate for the purpose of test, advertisement and litigation without KAFRI's consent.
4. This certificate has no legal effect.

This certificate does not comply with the Act on Testing and inspection of Food and Drugs of Ministry of Food and Drug Safety.

[redacted]

Testing Personnel [redacted] Testing Manager

Korea Advanced Food Research Institute

No. : D2021063337 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-02-15
No. of Sample : D2021063337	Expiration Date : 2023-02-14
Lot No. : CIII-0116N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant	Name : OraPharm Inc. Eun-sup Yoon
	Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea

Analytical Result

Test Item	Result
Mold & Yeast plate count(/g)	0(Yeast 0, Mold 0)

End.

Jul . 6 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewanggyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021063342 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-02-15
No. of Sample : D2021063342	Expiration Date : 2023-02-14
Lot No. : C111-0116N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Escherichia coli(/g)	0
Salmonella spp.	Negative
Listeria monocytogenes	Negative
Staphylococcus aureus(/g)	0

End.

Jul . 6 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

Appendix 2.3 *W. cibaria* CMU Lot CI11-0117N

Macrogen 16S Report – Lot CI11-0117N

Standard ID

16S rRNA Full Sequencing — Humanizing Genomics macrogen

16S rRNA service report

Order Number : HC00253794
Sample name : Lot_CI11-0117N_contig_1

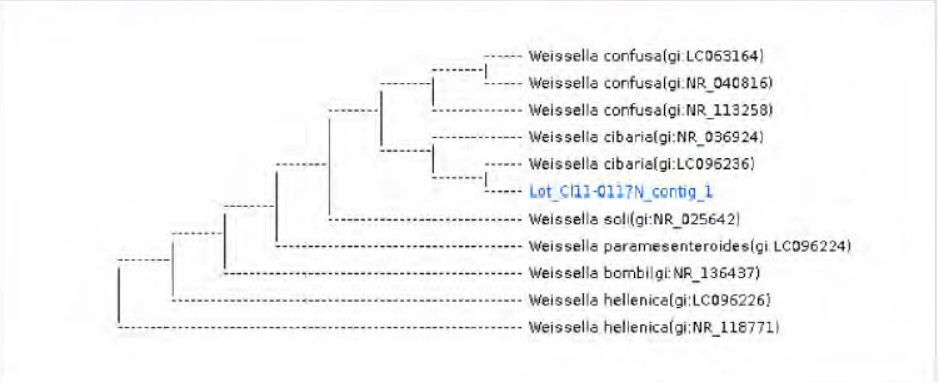
Information

Primer Information

Sequencing Primer Name Primer Sequences	PCR Primer Name Primer Sequences
785F 5' (GGA TTA GAT ACC CTG GTA) 3'	27F 5' (AGA GTT TGA TCM TGG CTC AG) 3
907R 5' (CCG TCA ATT CMT TTR AGT TT) 3'	1492R 5' (TAC GGY TAC CTT GTT ACG ACT T) 3'

Subject						Score		Identities	
Accession	Description	Length	Start	End	Coverage	Bit	E-Value	Match/Total	Pct.(%)
LC096236.1	Weissella cibaria	1516	6	1516	99	2787	0.0	1510/1511	99

Kingdom	Family	Genus	Species
Bacteria	Lactobacillaceae	Weissella	Weissella cibaria



Characterization

Weissella is a genus of Gram-positive bacteria, placed within the family Leuconostocaceae, and formerly considered species of the Leuconostoc paramesenteroides group. The morphology of Weissella species varies from spherical or lenticular cells to irregular rods.

Weissella cibaria is a species of Gram-positive bacteria, placed within the family of Leuconostocaceae. W.cibaria CMGDEX3 was reported from Pakistan to produce high molecular weight,linear dextran with predominant (1→6) linkages.

Query				Subject					Score			Identities			Strand
Name	Length	Start	End	Description	Link	AC	Length	Start	End	Bit	Raw	E-value	Match	Total	Pct(%)	
CMU_Lot_CI11-0117N_contig_1	1542	23	1533	Weissella cibaria gene for 16S ribosomal RNA, partial sequence, strain: JCM 12495	https://www.ncbi.nlm.nih.gov/nuccore/LC096236.1	LC096236.1	1516	6	1516	2787	1509	0	1510	1511	99	Plus/Plus
CMU_Lot_CI11-0117N_contig_1	1542	27	1537	Weissella cibaria strain II-1-59 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_036924.1	NR_036924.1	1529	1	1512	2774	1502	0	1508	1512	99	Plus/Plus
CMU_Lot_CI11-0117N_contig_1	1542	23	1537	Weissella confusa gene for 16S ribosomal RNA, partial sequence, strain: JCM 1093	https://www.ncbi.nlm.nih.gov/nuccore/LC063164.1	LC063164.1	1538	17	1532	2748	1488	0	1507	1516	99	Plus/Plus
CMU_Lot_CI11-0117N_contig_1	1542	27	1525	Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_113258.1	NR_113258.1	1499	1	1499	2724	1475	0	1491	1499	99	Plus/Plus
CMU_Lot_CI11-0117N_contig_1	1542	37	1513	Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_040816.1	NR_040816.1	1477	1	1477	2694	1453	0	1469	1477	99	Plus/Plus
CMU_Lot_CI11-0117N_contig_1	1542	23	1533	Weissella hellenica gene for 16S ribosomal RNA, partial sequence, strain: JCM 10103	https://www.ncbi.nlm.nih.gov/nuccore/LC096226.1	LC096226.1	1512	3	1512	2462	1333	0	1453	1512	96	Plus/Plus
CMU_Lot_CI11-0117N_contig_1	1542	23	1534	Weissella paramesenteroides gene for 16S ribosomal RNA, partial sequence, strain: JCM 9890	https://www.ncbi.nlm.nih.gov/nuccore/LC096224.1	LC096224.1	1518	9	1518	2460	1332	0	1457	1517	96	Plus/Plus
CMU_Lot_CI11-0117N_contig_1	1542	23	1537	Weissella hellenica strain NCFB 2973 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_118771.1	NR_118771.1	1527	7	1520	2459	1331	0	1456	1517	96	Plus/Plus
CMU_Lot_CI11-0117N_contig_1	1542	23	1537	Weissella soli strain Mi268 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_025642.1	NR_025642.1	1558	9	1524	2447	1325	0	1456	1520	96	Plus/Plus
CMU_Lot_CI11-0117N_contig_1	1542	27	1537	Weissella bombi strain R-53094 16S ribosomal RNA, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_136437.1	NR_136437.1	1528	1	1511	2446	1324	0	1450	1513	96	Plus/Plus

Certificate of Analysis – Lot CI11-0117N

RE[illegible]

No. : D2021040320 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-04-02	Date of Manufacture : 2021-02-15
No. of Sample : D2021040320	Expiration Date : 2023-02-14
Lot No. : CI11-0117N	
Inspection Purpose : For official use	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Sensory attribute	Yellowish white powder
Probiotics(CFU/g)	150 000 000 000 CFU/g (112 000 000 000, 160 000 000 000, 167 000 000 000)

End.

Apr . 9 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park,, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021063335 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-02-15
No. of Sample : D2021063335	Expiration Date : 2023-02-14
Lot No. : CIII-0117N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Ash(%)	1.16 %
Moisture(%)	3.05 %

End.

Jul . 7 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

한국식품과학연구원
Korea Advanced Food Research Institute

Korea Advanced Food Research Institute
50, Botdeul-ro, Uiwang-si, Gyeonggi-do, Republic of Korea
TEL : 82-2-3470-8200 FAX : 82-2-523-2072 http://www.kafri.or.kr

KAFRI

Certificate of Laboratory Testing(Reference)

Receipt No. (Reissue)	2021-11-003983	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company Name	OraPharm Inc.		
Client Address	905-ho 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea		
Client Name	Eun-sup Yoon	Client Tel / Fax	02-2138-2573
Lot No.	CI11-0117N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
Test Purpose	For submission (MFDS)	Date of Issue	2021.03.02

Test Items and Results

Lead(mg/kg).....0.02
Cadmium(mg/kg).....0.04
Arsenic(mg/kg).....0.01
Mercury(mg/kg).....Not Detected

* The above test items and results complied with the test method notified by MFDS.

Note: 1. The above merchandise was submitted and identified by the client.
2. The results shown in this certificate refer only to sample tested and it does not cover the quality of all products.
3. No one can use this certificate for the purpose of test, advertisement and litigation without KAFRI's consent.
4. This certificate has no legal effect.

This certificate does not comply with the Act on Testing and Inspection of Food and Drugs of Ministry of Food and Drug Safe.

[redacted]

Testing Personnel

[redacted]

Testing Manager

Korea Advanced Food Research Institute

한국식품과학연구원
Korea Advanced Food Research Institute

Korea Advanced Food Research Institute	KAFRI
50, Botdeul-ro, Uiwang-si, Gyeonggi-do, Republic of Korea TEL : 82-2-3470-8200 FAX : 82-2-523-2072 http://www.kafri.or.kr	

Certificate of Laboratory Testing(Reference)

Receipt No. (Reissue)	2021-11-003989	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company Name	OraPharm Inc.		
Client Address	905-ho 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea		
Client Name	Eun-sup Yoon	Client Tel / Fax	02-2138-2573
Lot No.	CI11-0117N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
Test Purpose	For submission (MFDS)	Date of Issue	2021.03.10

Test Items and Results

Coliforms.....Negative

* The above test items and results complied with the test method notified by MFDS.

Note: 1. The above merchandise was submitted and identified by the client.
2. The results shown in this certificate refer only to sample tested and it does not cover the quality of all products.
3. No one can use this certificate for the purpose of test, advertisement and litigation without KAFRI's consent.
4. This certificate has no legal effect.

This certificate does not comply with the Act on Testing and inspection of Food and Drugs of Ministry of Food and Drug Safe

[redacted] [redacted]

Testing Personnel Testing Manager

Korea Advanced Food Research Institute

No. : D2021063338 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-02-15
No. of Sample : D2021063338	Expiration Date : 2023-02-14
Lot No. : CI11-0117N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Mold & Yeast plate count(/g)	0(Yeast 0, Mold 0)

End.

Jul . 6 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-103, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021063343 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-02-15
No. of Sample : D2021063343	Expiration Date : 2023-02-14
Lot No. : CIII-0117N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Escherichia coli(/g)	0
Salmonella spp.	Negative
Listeria monocytogenes	Negative
Staphylococcus aureus(/g)	0

End.

Jul . 6 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong Dr. J. H. yang

B-101, Korea Bio Park., 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

Appendix 2.4 *W. cibaria* CMU Lot CI11-0362N

Macrogen 16S Report – Lot CI11-0362N

Standard ID

16S rRNA Full Sequencing — Humanizing Genomics macrogen

16S rRNA service report

Order Number : HC00277065
Sample name : CI11-0362N_contig_1

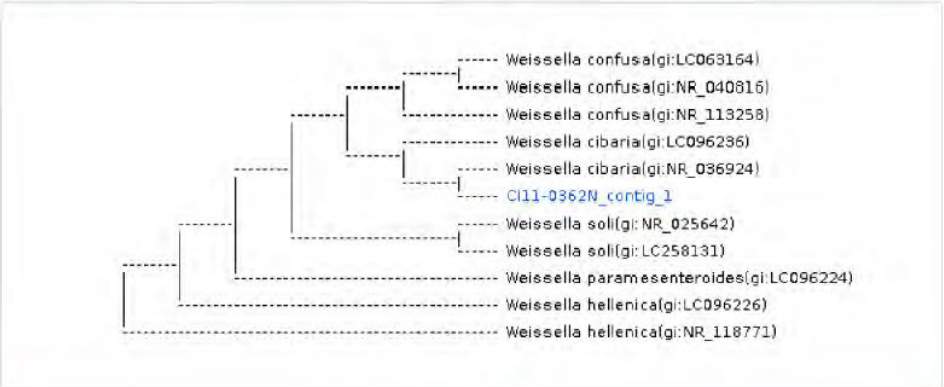
Information

Primer Information

Sequencing Primer Name Primer Sequences	PCR Primer Name Primer Sequences
785F 5' (GGA TTA GAT ACC CTG GTA) 3'	27F 5' (AGA GTT TGA TCM TGG CTC AG) 3
907R 5' (CCG TCA ATT CMT TTR AGT TT) 3'	1492R 5' (TAC GGY TAC CTT GTT ACG ACT T) 3'

Subject						Score		Identities	
Accession	Description	Length	Start	End	Coverage	Bit	E-Value	Match/Total	Pct.(%)
LC096236.1	Weissella cibaria	1516	4	1513	99	2780	0.0	1509/1511	99

Kingdom	Family	Genus	Species
Bacteria	Lactobacillaceae	Weissella	Weissella cibaria



Characterization

Weissella is a genus of Gram-positive bacteria, placed within the family Leuconostocaceae, and formerly considered species of the Leuconostoc paramesenteroides group. The morphology of Weissella species varies from spherical or lenticular cells to irregular rods.

Weissella cibaria is a species of Gram-positive bacteria, placed within the family of Leuconostocaceae. W.cibaria CMGDEX3 was reported from Pakistan to produce high molecular weight,linear dextran with predominant (1→6) linkages.

Query				Subject						Score			Identities			Strand
Name	Length	Start	End	Description	Link	AC	Length	Start	End	Bit	Raw	E-value	Match	Total	Pct(%)	
CMU_CI11-0362N_contig_1	1512	2	1512	Weissella cibaria gene for 16S ribosomal RNA, partial sequence, strain: JCM 12495	https://www.ncbi.nlm.nih.gov/nuccore/LC096236.1	LC096236.1	1516	4	1513	2780	1505	0	1509	1511	99	Plus/Plus
CMU_CI11-0362N_contig_1	1512	8	1512	Weissella cibaria strain II-I-59 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_036924.1	NR_036924.1	1529	1	1504	2761	1495	0	1501	1505	99	Plus/Plus
CMU_CI11-0362N_contig_1	1512	2	1512	Weissella confusa gene for 16S ribosomal RNA, partial sequence, strain: JCM 1093	https://www.ncbi.nlm.nih.gov/nuccore/LC063164.1	LC063164.1	1538	15	1524	2739	1483	0	1502	1511	99	Plus/Plus
CMU_CI11-0362N_contig_1	1512	8	1507	Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_113258.1	NR_113258.1	1499	1	1499	2719	1472	0	1491	1500	99	Plus/Plus
CMU_CI11-0362N_contig_1	1512	18	1495	Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_040816.1	NR_040816.1	1477	1	1477	2678	1450	0	1469	1478	99	Plus/Plus
CMU_CI11-0362N_contig_1	1512	2	1512	Weissella hellenica gene for 16S ribosomal RNA, partial sequence, strain: JCM 10103	https://www.ncbi.nlm.nih.gov/nuccore/LC096226.1	LC096226.1	1512	1	1509	2457	1330	0	1452	1512	96	Plus/Plus
CMU_CI11-0362N_contig_1	1512	2	1512	Weissella paramesenteroides gene for 16S ribosomal RNA, partial sequence, strain: JCM 9890	https://www.ncbi.nlm.nih.gov/nuccore/LC096224.1	LC096224.1	1516	7	1514	2451	1327	0	1455	1516	96	Plus/Plus
CMU_CI11-0362N_contig_1	1512	2	1512	Weissella hellenica strain NCFB 2973 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_118771.1	NR_118771.1	1527	5	1512	2449	1326	0	1451	1512	96	Plus/Plus
CMU_CI11-0362N_contig_1	1512	2	1512	Weissella soli strain Mi268 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nuccore/NR_025642.1	NR_025642.1	1558	7	1516	2438	1320	0	1451	1515	96	Plus/Plus
CMU_CI11-0362N_contig_1	1512	2	1512	Weissella soli gene for 16S ribosomal RNA, partial sequence, strain: JCM 12536	https://www.ncbi.nlm.nih.gov/nuccore/LC258131.1	LC258131.1	1518	7	1516	2435	1318	0	1450	1515	96	Plus/Plus

Certificate of Analysis – Lot CI11-0362N

No. : D2021060278 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-02	Date of Manufacture : 2021-05-18
No. of Sample : D2021060278	Expiration Date : 2023-05-17
Lot No. : CI11-0362N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Sensory attribute	yellowish white powder
Probiotics(CFU/g)	150 000 000 000 CFU/g (134 000 000 000, 173 000 000 000, 141 000 000 000)

End.

Jun . 10 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong Dr. J. H. yang

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021060280 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-02	Date of Manufacture : 2021-05-18
No. of Sample : D2021060280	Expiration Date : 2023-05-17
Lot No. : C111-0362N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : DraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Sensory attribute	yellowish white powder
Calorie(Kcal/100g)	382.82 Kcal/100g
Carbohydrate(%)	89.49 %
Crude protein(%)	6.17 %
Crude fat(%)	0.02 %
Moisture(%)	3.03 %
Ash(%)	1.29 %
Sodium(mg/100g)	27.00 mg/100g

End.

Jun . 14 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong Dr. J. H. yang

8-101, Korea Bio Park,, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

No. : D2021060286 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-02	Date of Manufacture : 2021-05-18
No. of Sample : D2021060286	Expiration Date : 2023-05-17
Lot No. : CI11-0362N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant: Name : OraPharm Inc. Eun-sup Yoon	
Applicant: Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Lead(mg/kg)	0.0107 mg/kg
Arsenic(mg/kg)	0.0067 mg/kg
Cadmium(mg/kg)	0.0398 mg/kg
Mercury(mg/kg)	0.0016 mg/kg

End.

Jun . 7 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park., 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021060282 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-02	Date of Manufacture : 2021-05-18
No. of Sample : D2021060282	Expiration Date : 2023-05-17
Lot No. : C111-0362N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeommujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Coliform Group	Negative

End.

Jun . 9 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-104, Korea Bio Park,, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021063339 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-05-18
No. of Sample : D2021063339	Expiration Date : 2023-05-17
Lot No. : C1J1-0382N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Mold & Yeast plate count(/g)	0(Yeast 0, Mold 0)

End.

Jul . 6 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewanggyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021063344 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-05-18
No. of Sample : D2021063344	Expiration Date : 2023-05-17
Lot No. : C111-0362N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Escherichia coli(/g)	0
Salmonella spp.	Negative
Listeria monocytogenes	Negative
Staphylococcus aureus(/g)	0

End.

Jul 6 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021060284 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-02	Date of Manufacture : 2021-05-18
No. of Sample : D2021060284	Expiration Date : 2023-05-17
Lot No. : C111-0362N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
BHC(mg/kg)	Not detected
DDT(mg/kg)	Not detected
Aldrin(mg/kg)	Not detected
Dieldrin(mg/kg)	Not detected
Endrin(mg/kg)	Not detected

End.

Jun . 10 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101 Korea Bio Park, 700 DAewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

Appendix 2.5 *W. cibaria* CMU Lot CI11-0366N

Macrogen 16S Report – Lot CI11-0366N

Standard ID

16S rRNA Full Sequencing — Humanizing Genomics macrogen

16S rRNA service report

Order Number : HC00277065
Sample name : CI11-0366N_contig_1

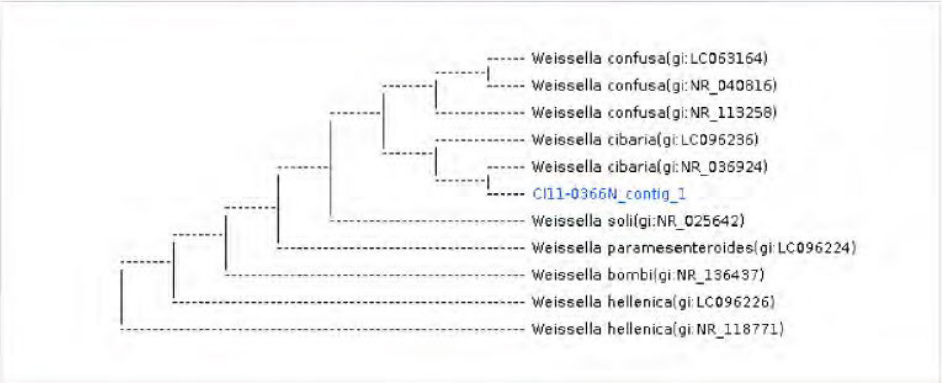
Information

Primer Information

Sequencing Primer Name Primer Sequences	PCR Primer Name Primer Sequences
785F 5' (GGA TTA GAT ACC CTG GTA) 3'	27F 5' (AGA GTT TGA TCM TGG CTC AG) 3
907R 5' (CCG TCA ATT CMT TTR AGT TT) 3'	1492R 5' (TAC GGY TAC CTT GTT ACG ACT T) 3'

Subject						Score		Identities	
Accession	Description	Length	Start	End	Coverage	Bit	E-Value	Match/Total	Pct.(%)
LC096236.1	Weissella cibaria	1516	6	1514	99	2776	0.0	1507/1509	99

Kingdom	Family	Genus	Species
Bacteria	Lactobacillaceae	Weissella	Weissella cibaria



Characterization

Weissella is a genus of Gram-positive bacteria, placed within the family Leuconostocaceae, and formerly considered species of the Leuconostoc paramesenteroides group. The morphology of Weissella species varies from spherical or lenticular cells to irregular rods.

Weissella cibaria is a species of Gram-positive bacteria, placed within the family of Leuconostocaceae. W.cibaria CMGDEX3 was reported from Pakistan to produce high molecular weight,linear dextran with predominant (1→6) linkages.

Query				Subject							Score			Identities			Strand
Name	Length	Start	End	Description	Link	AC	Length	Start	End	Bit	Raw	E-value	Match	Total	Pct(%)	
CMU_CI11-0366N_contig_1	1544	28	1535	Weissella cibaria gene for 16S ribosomal RNA, partial sequence, strain: JCM 12495	https://www.ncbi.nlm.nih.gov/nucleotide/LC096236.1	LC096236.1	1516	6	1514	2776	1503	0	1507	1509	99	Plus/Plus
CMU_CI11-0366N_contig_1	1544	31	1541	Weissella cibaria strain II-I-59 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_036924.1	NR_036924.1	1529	1	1513	2771	1500	0	1508	1513	99	Plus/Plus
CMU_CI11-0366N_contig_1	1544	22	1541	Weissella confusa gene for 16S ribosomal RNA, partial sequence, strain: JCM 1093	https://www.ncbi.nlm.nih.gov/nucleotide/LC063164.1	LC063164.1	1538	10	1533	2739	1483	0	1511	1524	99	Plus/Plus
CMU_CI11-0366N_contig_1	1544	31	1529	Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_113258.1	NR_113258.1	1499	1	1499	2724	1475	0	1491	1499	99	Plus/Plus
CMU_CI11-0366N_contig_1	1544	41	1517	Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_040816.1	NR_040816.1	1477	1	1477	2684	1453	0	1469	1477	99	Plus/Plus
CMU_CI11-0366N_contig_1	1544	28	1535	Weissella hellenica gene for 16S ribosomal RNA, partial sequence, strain: JCM 10103	https://www.ncbi.nlm.nih.gov/nucleotide/LC096226.1	LC096226.1	1512	3	1510	2453	1326	0	1450	1510	96	Plus/Plus
CMU_CI11-0366N_contig_1	1544	22	1535	Weissella paramesenteroides gene for 16S ribosomal RNA, partial sequence, strain: JCM 9890	https://www.ncbi.nlm.nih.gov/nucleotide/LC096224.1	LC096224.1	1518	2	1515	2449	1326	0	1458	1521	96	Plus/Plus
CMU_CI11-0366N_contig_1	1544	28	1535	Weissella hellenica strain NCFB 2973 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_118771.1	NR_118771.1	1527	7	1513	2446	1324	0	1449	1510	96	Plus/Plus
CMU_CI11-0366N_contig_1	1544	31	1541	Weissella bombi strain R-53094 16S ribosomal RNA, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_136437.1	NR_136437.1	1528	1	1512	2440	1321	0	1450	1514	96	Plus/Plus
CMU_CI11-0366N_contig_1	1544	22	1541	Weissella soli strain Mi268 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_025642.1	NR_025642.1	1558	2	1525	2430	1320	0	1460	1528	96	Plus/Plus

Certificate of Analysis – Lot CI11-0366N

No. : D2021060279 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-02	Date of Manufacture : 2021-05-20
No. of Sample : D2021060279	Expiration Date : 2023-05-19
Lot No. : CI11-0366N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Sensory attribute	yellowish white powder
Probiotics(CFU/g)	110 000 000 000 CFU/g (104 000 000 000, 108 000 000 000, 123 000 000 000)

End.

Jun . 10 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021060281 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-02	Date of Manufacture : 2021-05-20
No. of Sample : D2021060281	Expiration Date : 2023-05-19
Lot No. : C111-0366N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Sensory attribute	yellowish white powder
Calorie(Kcal/100g)	381.53 Kcal/100g
Carbohydrate(%)	89.35 %
Crude protein(%)	6.01 %
Crude fat(%)	0.01 %
Moisture(%)	3.34 %
Ash(%)	1.29 %
Sodium(mg/100g)	44.76 mg/100g

End.

Jun . 14 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021060287 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-02	Date of Manufacture : 2021-05-20
No. of Sample : D2021060287	Expiration Date : 2023-05-19
Lot No. : CIL1-0366N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Lead(mg/kg)	0.0096 mg/kg
Arsenic(mg/kg)	0.0048 mg/kg
Cadmium(mg/kg)	0.0383 mg/kg
Mercury(mg/kg)	0.0022 mg/kg

End.

Jun . 7 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park , 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021060283 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-02	Date of Manufacture : 2021-05-20
No. of Sample : D2021060283	Expiration Date : 2023-05-19
Lot No. : C11-0366N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant: Name : OraPharm Inc. Eun-sup Yoon	
Applicant: Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Coliform Group	Negative

End.

Jun 9 , 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021063340 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-05-20
No. of Sample : D2021063340	Expiration Date : 2023-05-19
Lot No. : C111-0366N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Mold & Yeast plate count(/g)	0(Yeast 0, Mold 0)

End.

Jul . 6 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021063345 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-28	Date of Manufacture : 2021-05-20
No. of Sample : D2021063345	Expiration Date : 2023-05-19
Lot No. : C111-0366N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
Escherichia coli(/g)	0
Salmonella spp.	Negative
Listeria monocytogenes	Negative
Staphylococcus aureus(/g)	0

End.

Jul . 6 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101 Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

No. : D2021060285 Page (1) / Pages (1)

Certificate of Analysis

Date of Application : 2021-06-02	Date of Manufacture : 2021-05-20
No. of Sample : D2021060285	Expiration Date : 2023-05-19
Lot No. : CIli-0366N	
Inspection Purpose : Export	
Commodity : Weissella cibaria CMU	
Applicant — Name : OraPharm Inc. Eun-sup Yoon	
Applicant — Company address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea	

Analytical Result

Test Item	Result
BHC(mg/kg)	Not detected
DDT(mg/kg)	Not detected
Aldrin(mg/kg)	Not detected
Dieldrin(mg/kg)	Not detected
Endrin(mg/kg)	Not detected

End.

Jun . 10 . 2021

We hereby certify that the above are correct.

Korea Health Supplements Association Sub. Korea Health Supplements Institute

Director : Yang, Joo-Hong [redacted]

B-101, Korea Bio Park, 700, Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea

KHSI

Appendix 3 Average Nucleotide Identity and Strain Specific PCR Results

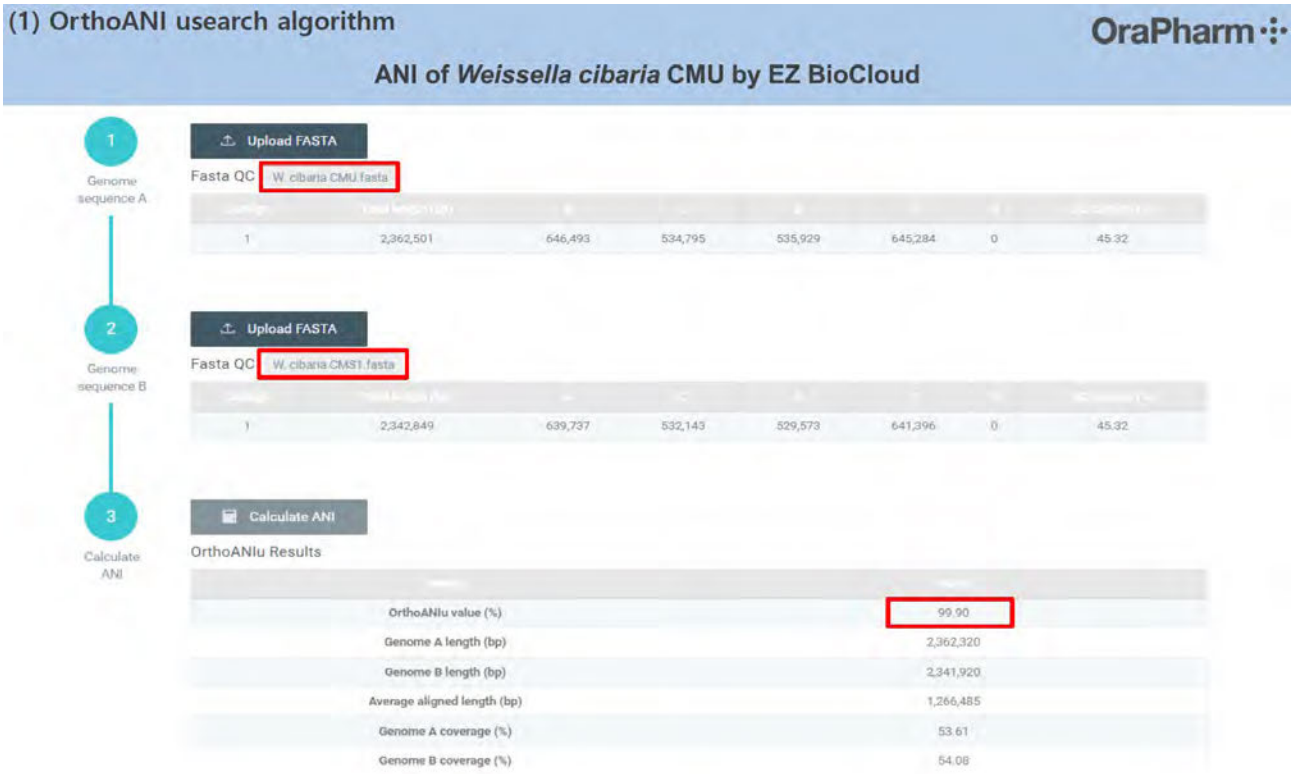
Appendix 3.1 OrthoANI usearch Algorithm

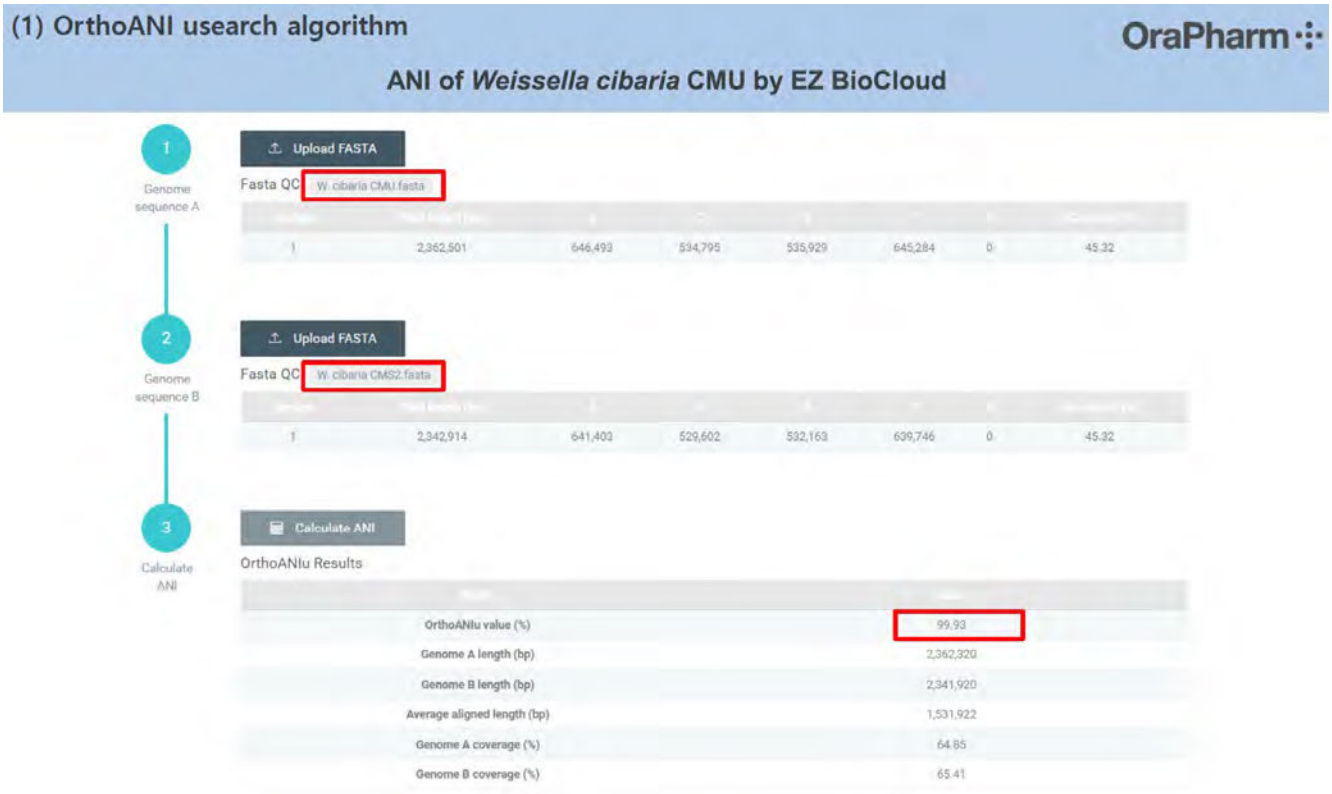
Appendix 3.2 JSpeciesWS Algorithm

Appendix 3.3 ANI Calculator Algorithm

Appendix 3.4 Strain Specific PCR Results

Appendix 3.1 OrthoANI usearch Algorithm





(1) OrthoANI usearch algorithm

OraPharm

ANI of *Weissella cibaria* CMU by EZ BioCloud

1 Genome sequence A

Upload FASTA

Fasta QC W. cibaria CMU.fasta

1	2,362,501	646,493	534,795	535,929	645,284	0	45.32

2 Genome sequence B

Upload FASTA

Fasta QC W. cibaria CMS3.fasta

1	2,342,907	641,401	529,601	532,163	639,742	0	45.32

3 Calculate ANI

Calculate ANI

OrthoANIu Results

OrthoANIu value (%)	99.92
Genome A length (bp)	2,362,320
Genome B length (bp)	2,341,920
Average aligned length (bp)	1,679,193
Genome A coverage (%)	71.08
Genome B coverage (%)	71.70

(1) OrthoANI usearch algorithm

OraPharm

ANI of *Weissella cibaria* CMU by EZ BioCloud

1 Genome sequence A

Upload FASTA

Fasta QC W. cibaria CMU.fasta

1	2,362,501	646,493	534,795	535,929	645,284	0	45.32

2 Genome sequence B

Upload FASTA

Fasta QC W. cibaria JCM 12495.fasta

1	406,515	107,274	105,100	80,931	113,210	0	45.76

3 Calculate ANI

Calculate ANI

OrthoANIu Results

OrthoANIu value (%)	99.94
Genome A length (bp)	2,362,320
Genome B length (bp)	405,960
Average aligned length (bp)	270,773
Genome A coverage (%)	11.46
Genome B coverage (%)	66.70

(1) OrthoANI usearch algorithm

OraPharm

ANI of *Weissella cibaria* CMU by EZ BioCloud

1 Genome sequence A

Upload FASTA

Fasta QC W. cibaria CMU.fasta

1	2,362,501	646,493	534,795	535,929	645,284	0	45.32

2 Genome sequence B

Upload FASTA

Fasta QC W. cibaria BC14.fasta

1	2,473,048	677,691	559,095	555,425	680,837	0	45.07

3 Calculate ANI

Calculate ANI

OrthoANIu Results

OrthoANIu value (%)	98.45
Genome A length (bp)	2,362,320
Genome B length (bp)	2,472,480
Average aligned length (bp)	1,644,774
Genome A coverage (%)	69.63
Genome B coverage (%)	66.52

(1) OrthoANI usearch algorithm

OraPharm

ANI of *Weissella cibaria* CMU by EZ BioCloud

1 Genome sequence A

Upload FASTA

Fasta QC W. cibaria CMU.fasta

1	2,362,501	646,493	534,795	535,929	645,284	0	45.32

2 Genome sequence B

Upload FASTA

Fasta QC W. cibaria CH2.fasta

1	2,466,961	680,613	553,286	558,949	674,113	0	45.09

3 Calculate ANI

Calculate ANI

OrthoANIu Results

OrthoANIu value (%)	96.90
Genome A length (bp)	2,362,320
Genome B length (bp)	2,466,360
Average aligned length (bp)	1,526,677
Genome A coverage (%)	64.63
Genome B coverage (%)	61.90

(1) OrthoANI usearch algorithm

OraPharm

ANI of *Weissella cibaria* CMU by EZ BioCloud

1 Genome sequence A

Upload FASTA

Fasta QC W. cibaria CMU.fasta

1	2,362,501	646,493	534,795	535,929	645,284	0	45.32

2 Genome sequence B

Upload FASTA

Fasta QC W. confusa VTT E-133279.fasta

1	2,212,145	604,915	495,769	501,367	610,094	0	45.08

3 Calculate ANI

Calculate ANI

OrthoANIu Results

OrthoANIu value (%)	79.01
Genome A length (bp)	2,362,320
Genome B length (bp)	2,211,360
Average aligned length (bp)	957,212
Genome A coverage (%)	40.52
Genome B coverage (%)	43.29

(1) OrthoANI usearch algorithm

OraPharm

ANI of *Weissella cibaria* CMU by EZ BioCloud

1 Genome sequence A

Upload FASTA

Fasta QC W. cibaria CMU.fasta

1	2,362,501	646,493	534,795	535,929	645,284	0	45.32

2 Genome sequence B

Upload FASTA

Fasta QC W. hellenica CCUG 33494.fasta

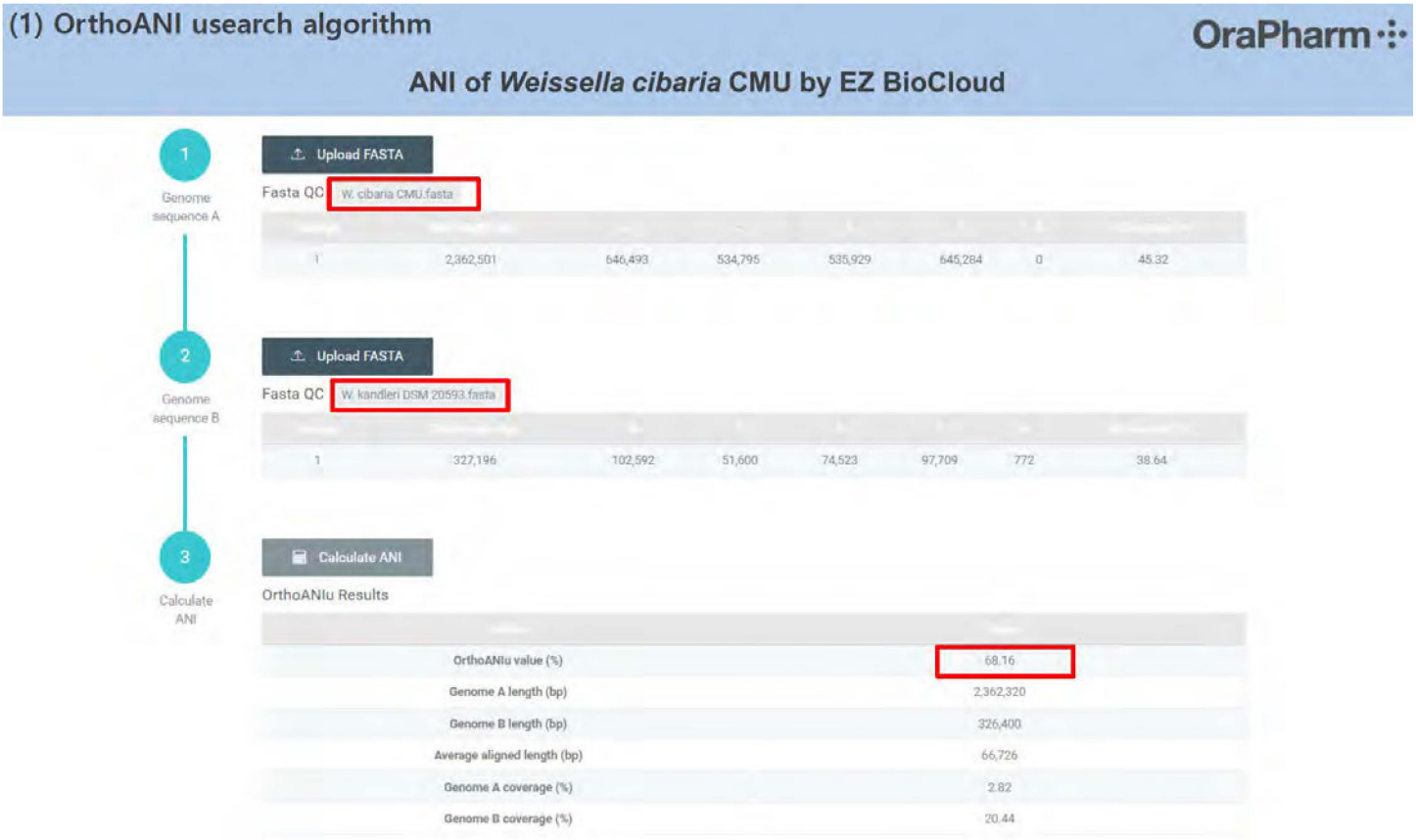
1	380,413	118,663	81,507	60,801	119,442	0	37.41

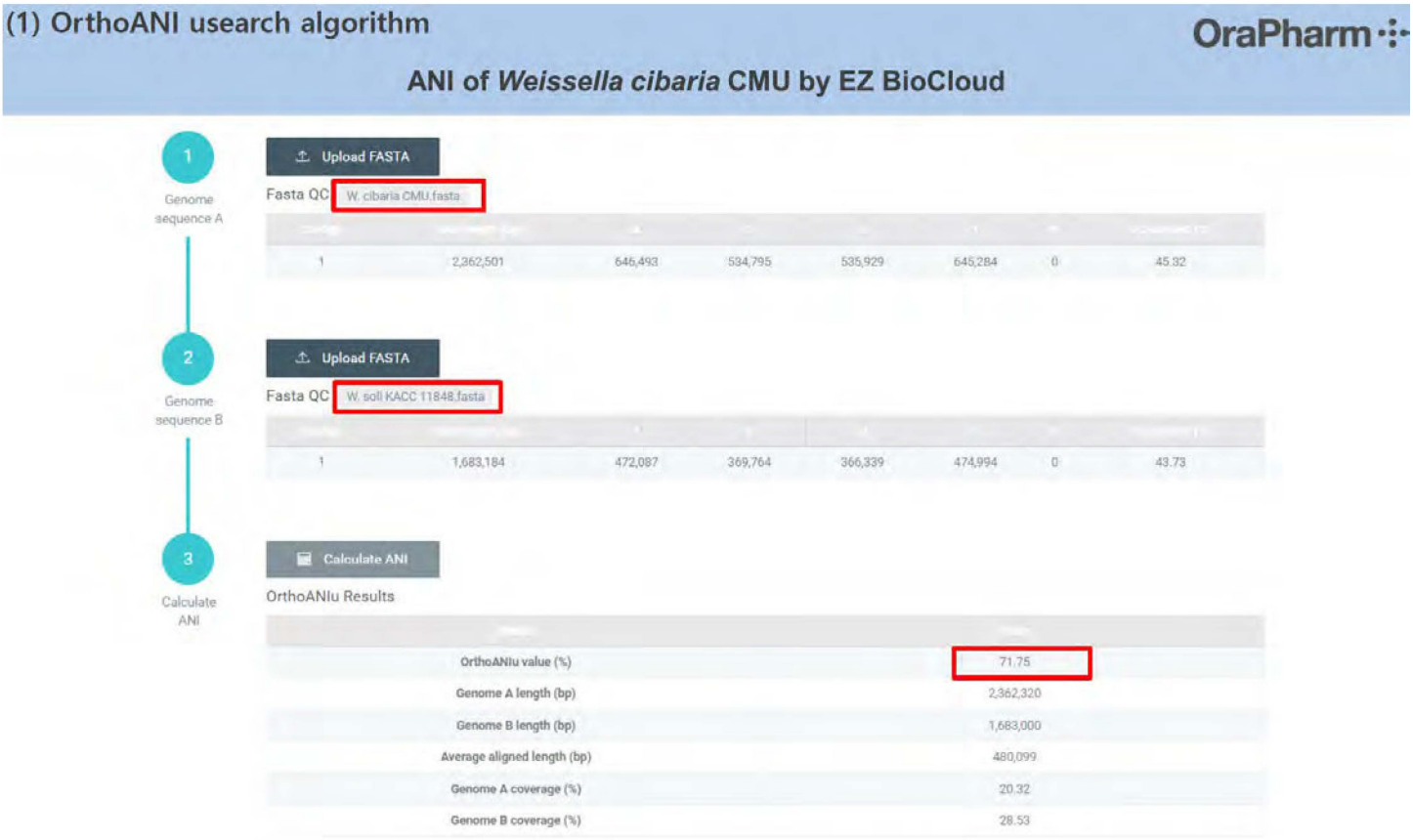
3 Calculate ANI

Calculate ANI

OrthoANIu Results

OrthoANIu value (%)	74.05
Genome A length (bp)	2,362,320
Genome B length (bp)	379,440
Average aligned length (bp)	127,025
Genome A coverage (%)	5.38
Genome B coverage (%)	33.48


(1) OrthoANI usearch algorithm
OraPharm
ANI of Weissella cibaria CMU by EZ BioCloud
1
Genome sequence A
Upload FASTA
Fasta QC
W. cibaria CMU.fasta
1 2,362,501 646,493 534,795 535,929 645,284 0 45.32
2
Genome sequence B
Upload FASTA
Fasta QC
W. kandleri DSM 20593.fasta
1 327,196 102,592 51,600 74,523 97,709 772 38.64
3
Calculate ANI
Calculate ANI
OrthoANIu Results
OrthoANIu value (%) 68.16
Genome A length (bp) 2,362,320
Genome B length (bp) 326,400
Average aligned length (bp) 66,726
Genome A coverage (%) 2.82
Genome B coverage (%) 20.44


(1) OrthoANI usearch algorithm
OraPharm
ANI of Weissella cibaria CMU by EZ BioCloud
1
Genome sequence A
Upload FASTA
Fasta QC
W. cibaria CMU.fasta
1 2,362,501 646,493 534,795 535,929 645,284 0 45.32
2
Genome sequence B
Upload FASTA
Fasta QC
W. soli KACC 11848.fasta
1 1,683,184 472,087 369,764 366,339 474,994 0 43.73
3
Calculate ANI
Calculate ANI
OrthoANIu Results
OrthoANIu value (%) 71.75
Genome A length (bp) 2,362,320
Genome B length (bp) 1,683,000
Average aligned length (bp) 480,099
Genome A coverage (%) 20.32
Genome B coverage (%) 28.53

(1) OrthoANI usearch algorithm

OraPharm

ANI of *Weissella cibaria* CMU by EZ BioCloud

1 Genome sequence A

Upload FASTA

Fasta QC W. cibaria CMU.fasta

1	2,362,501	646,493	534,795	535,929	645,284	0	45.32

2 Genome sequence B

Upload FASTA

Fasta QC W. thailandensis JCM 10695.fasta

1	198,590	63,115	35,858	39,652	59,866	99	38.04

3 Calculate ANI

Calculate ANI

OrthoANIu Results

OrthoANIu value (%)	69.79
Genome A length (bp)	2,362,320
Genome B length (bp)	197,880
Average aligned length (bp)	30,349
Genome A coverage (%)	1.28
Genome B coverage (%)	15.34

Appendix 3.2 JSpeciesWS Algorithm

(2) JSpeciesWS algorithm

OraPharm

ANI based on BLAST+ (ANIb) of *Weissella cibaria* CMU by JSpeciesWS

Show ANIb and [aligned nucleotides] [%] ▾ Download as .csv

Legend: Above cutoff (> 95%) Below cutoff (< 95%) Suspicious alignment!

	W. cibaria CMU.fasta	W. cibaria CMS1.fasta	W. cibaria CMS2.fasta	W. cibaria CMS3.fasta	W. cibaria BC14.fasta	W. cibaria CH2.fasta	W. cibaria JCM 12495.fasta	W. confusa VTT E-133279.fasta	W. hellenica CCUG 33494.fasta	W. kandleri DSM 20593.fasta	W. paramesenteroides FDAARGOS 414.fasta	W. soli KACC 11848.fasta	W. thailandensis JCM 10695.fasta
W. cibaria CMU.fasta	-	99.99 (99.91)	99.99 (99.94)	99.99 (99.95)	98.29 (93.94)	96.72 (91.75)	98.01 (17.84)	78.23 (63.61)	71.75 (8.50)	67.32 (4.42)	72.22 (43.07)	71.28 (35.65)	68.45 (2.24)
W. cibaria CMS1.fasta	100.00 (99.85)	-	-	-	-	-	-	-	-	-	-	-	-
W. cibaria CMS2.fasta	100.00 (99.84)	-	-	-	-	-	-	-	-	-	-	-	-
W. cibaria CMS3.fasta	100.00 (99.89)	-	-	-	-	-	-	-	-	-	-	-	-
W. cibaria BC14.fasta	98.20 (89.17)	-	-	-	-	-	-	-	-	-	-	-	-
W. cibaria CH2.fasta	96.58 (87.76)	-	-	-	-	-	-	-	-	-	-	-	-
W. cibaria JCM 12495.fasta	100.00 (99.84)	-	-	-	-	-	-	-	-	-	-	-	-
W. confusa VTT E-133279.fasta	77.39 (67.43)	-	-	-	-	-	-	-	-	-	-	-	-
W. hellenica CCUG 33494.fasta	73.52 (46.30)	-	-	-	-	-	-	-	-	-	-	-	-
W. kandleri DSM 20593.fasta	67.64 (30.07)	-	-	-	-	-	-	-	-	-	-	-	-
W. paramesenteroides FDAARGOS 414.fasta	72.32 (49.26)	-	-	-	-	-	-	-	-	-	-	-	-
W. soli KACC 11848.fasta	70.86 (47.52)	-	-	-	-	-	-	-	-	-	-	-	-
W. thailandensis JCM 10695.fasta	59.02 (26.30)	-	-	-	-	-	-	-	-	-	-	-	-

(2) JSpeciesWS algorithm

OraPharm

ANI based on BLAST+ (ANIb) of *Weissella cibaria* CMU by JSpeciesWS

ANIb Matrix | ANIb Result by Genome

W_cibaria_CMU.fasta ▾ Download as .csv

Legend: Above cutoff (> 95%) Below cutoff (< 95%) Suspicious alignment!

Genome	ANIb [%]	Aligned [%]	Aligned [bp]	Total [bp]
W_cibaria_CMS1.fasta	99.99	99.91	2360306	2362501
W_cibaria_CMS2.fasta	99.99	99.94	2360990	2362501
W_cibaria_CMS3.fasta	99.99	99.95	2361358	2362501
W_cibaria_BC14.fasta	98.29	93.94	2219251	2362501
W_cibaria_JCM_12495.fasta	98.01	17.84	421460	2362501
W_cibaria_CH2.fasta	96.72	91.75	2167678	2362501
W_confusa_VTT_E-133279.fasta	78.23	63.61	1502901	2362501
W_paramesenteroides_FDAARGOS_414.fasta	72.22	43.07	1017454	2362501
W_hellenica_CCUG_33494.fasta	71.75	8.50	200719	2362501
W_soli_KACC_11848.fasta	71.28	35.65	842158	2362501
W_thailandensis_JCM_10695.fasta	68.45	2.24	52935	2362501
W_kandleri_DSM_20593.fasta	67.32	4.42	104393	2362501

(2) JSpeciesWS algorithm

OraPharm

ANI based on MUMmer (ANIm) of *Weissella cibaria* CMU by JSpeciesWS

Show ANIm and [aligned nucleotides] [%] ▾ | Download as .csv

Legend: Above cutoff (> 95%) | Below cutoff (< 95%) | Suspicious alignment!

	W. cibaria CMU.fasta	W. cibaria CMS1.fasta	W. cibaria CMS2.fasta	W. cibaria CMS3.fasta	W. cibaria BC14.fasta	W. cibaria CH2.fasta	W. cibaria JCM 12495.fasta	W. confusa VTT E-133279.fasta	W. hellenica CCUG 33494.fasta	W. kandleri DSM 20593.fasta	W. paramesenteroides FDAARGOS 414.fasta	W. soli KACC 11848.fasta	W. thailandensis JCM 10695.fasta
W. cibaria CMU.fasta	-	99.98 (100.00)	99.99 (100.00)	99.99 (100.00)	98.48 (94.79)	96.93 (93.14)	99.99 (17.54)	87.36 (28.14)	87.39 (1.39)	84.86 (0.12)	88.26 (6.11)	86.41 (5.56)	85.65 (0.02)
W. cibaria CMS1.fasta	99.98 (100.00)	-	-	-	-	-	-	-	-	-	-	-	-
W. cibaria CMS2.fasta	99.99 (100.00)	-	-	-	-	-	-	-	-	-	-	-	-
W. cibaria CMS3.fasta	99.99 (100.00)	-	-	-	-	-	-	-	-	-	-	-	-
W. cibaria BC14.fasta	98.50 (89.69)	-	-	-	-	-	-	-	-	-	-	-	-
W. cibaria CH2.fasta	96.93 (88.81)	-	-	-	-	-	-	-	-	-	-	-	-
W. cibaria JCM 12495.fasta	99.99 (100.00)	-	-	-	-	-	-	-	-	-	-	-	-
W. confusa VTT E-133279.fasta	87.35 (29.45)	-	-	-	-	-	-	-	-	-	-	-	-
W. hellenica CCUG 33494.fasta	87.39 (8.64)	-	-	-	-	-	-	-	-	-	-	-	-
W. kandleri DSM 20593.fasta	84.86 (0.81)	-	-	-	-	-	-	-	-	-	-	-	-
W. paramesenteroides FDAARGOS 414.fasta	88.58 (6.48)	-	-	-	-	-	-	-	-	-	-	-	-
W. soli KACC 11848.fasta	86.39 (6.29)	-	-	-	-	-	-	-	-	-	-	-	-
W. thailandensis JCM 10695.fasta	85.65 (0.24)	-	-	-	-	-	-	-	-	-	-	-	-

(2) JSpeciesWS algorithm

OraPharm

ANI based on MUMmer (ANIm) of *Weissella cibaria* CMU by JSpeciesWS

ANIm Result Matrix | ANIm Result by Genome

W._cibaria_CMU.fasta ▾ | Download as .csv

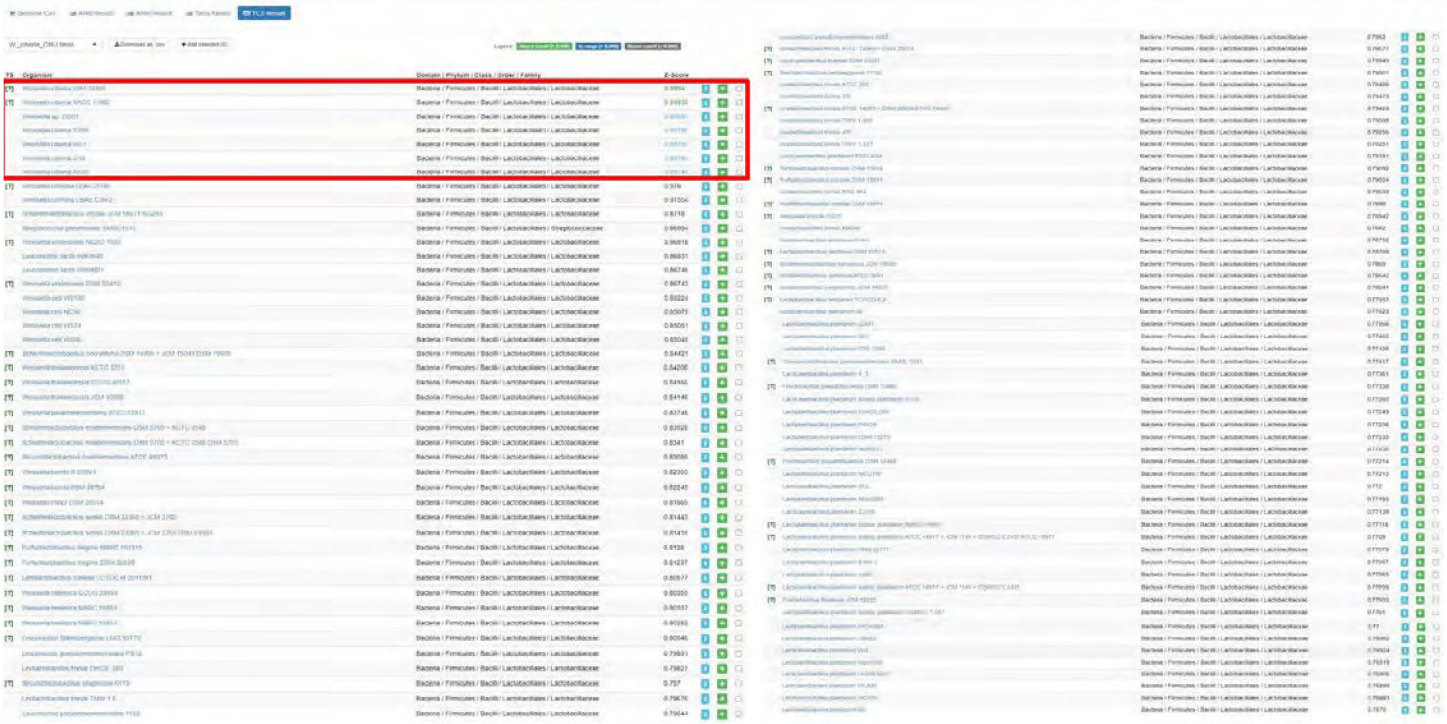
Legend: Above cutoff (> 95%) | Below cutoff (< 95%) | Suspicious alignment!

Genome	ANIm [%]	Aligned [%]	Aligned [bp]	Total [bp]
W._cibaria_CMS2.fasta	99.99	100.00	2362501	2362501
W._cibaria_CMS3.fasta	99.99	100.00	2362500	2362501
W._cibaria_JCM_12495.fasta	99.99	17.54	414378	2362501
W._cibaria_CMS1.fasta	99.98	100.00	2362501	2362501
W._cibaria_BC14.fasta	98.48	94.79	2239482	2362501
W._cibaria_CH2.fasta	96.93	93.14	2200403	2362501
W._paramesenteroides_FDAARGOS_414.fasta	88.26	6.11	144336	2362501
W._hellenica_CCUG_33494.fasta	87.39	1.39	32954	2362501
W._confusa_VTT_E-133279.fasta	87.36	28.14	664875	2362501
W._soli_KACC_11848.fasta	86.41	5.56	131443	2362501
W._thailandensis_JCM_10695.fasta	85.65	0.02	476	2362501
W._kandleri_DSM_20593.fasta	84.86	0.12	2797	2362501

(2) JSpeciesWS algorithm

OraPharm

Tetra Correlation Search (TCS) of *Weissella cibaria* CMU by JSpeciesWS



(2) JSpeciesWS algorithm

OraPharm

Tetra-nucleotide signature correlation index (Tetra) of *Weissella cibaria* CMU by JSpeciesWS

Tetra Results Matrix | Tetra Result by Genome

Download as .csv

Legend: Above cutoff (> 0.999) | In range (> 0.989) | Below cutoff (< 0.989)

	W. cibaria CMU.fasta	W. cibaria CMS1.fasta	W. cibaria CMS2.fasta	W. cibaria CMS3.fasta	W. cibaria BC14.fasta	W. cibaria CH2.fasta	W. cibaria JCM 12495.fasta	W. confusa VTT E-133279.fasta	W. hellenica CCUG 33494.fasta	W. kandleri DSM 20593.fasta	W. paramesenteroides FDAARGOS 414.fasta	W. soli KACC 11848.fasta	W. thailandensis JCM 10695.fasta
W. cibaria CMU.fasta	*	0.99998	0.99998	0.99998	0.9991	0.99851	0.97501	0.97469	0.81143	0.67592	0.83494	0.9047	0.76344
W. cibaria CMS1.fasta	0.99998	*	—	—	—	—	—	—	—	—	—	—	—
W. cibaria CMS2.fasta	0.99998	—	*	—	—	—	—	—	—	—	—	—	—
W. cibaria CMS3.fasta	0.99998	—	—	*	—	—	—	—	—	—	—	—	—
W. cibaria BC14.fasta	0.9991	—	—	—	*	—	—	—	—	—	—	—	—
W. cibaria CH2.fasta	0.99851	—	—	—	—	*	—	—	—	—	—	—	—
W. cibaria JCM 12495.fasta	0.97501	—	—	—	—	—	*	—	—	—	—	—	—
W. confusa VTT E-133279.fasta	0.97469	—	—	—	—	—	—	*	—	—	—	—	—
W. hellenica CCUG 33494.fasta	0.81143	—	—	—	—	—	—	—	*	—	—	—	—
W. kandleri DSM 20593.fasta	0.67592	—	—	—	—	—	—	—	—	*	—	—	—
W. paramesenteroides FDAARGOS 414.fasta	0.83494	—	—	—	—	—	—	—	—	—	*	—	—
W. soli KACC 11848.fasta	0.9047	—	—	—	—	—	—	—	—	—	—	*	—
W. thailandensis JCM 10695.fasta	0.76344	—	—	—	—	—	—	—	—	—	—	—	*

(2) JSpeciesWS algorithm

OraPharm

Tetra-nucleotide signature correlation index (Tetra) of *Weissella cibaria* CMU by JSpeciesWS

Tetra Results Matrix | Tetra Result by Genome

W._cibaria_CMU.fasta ▾ Download as .csv

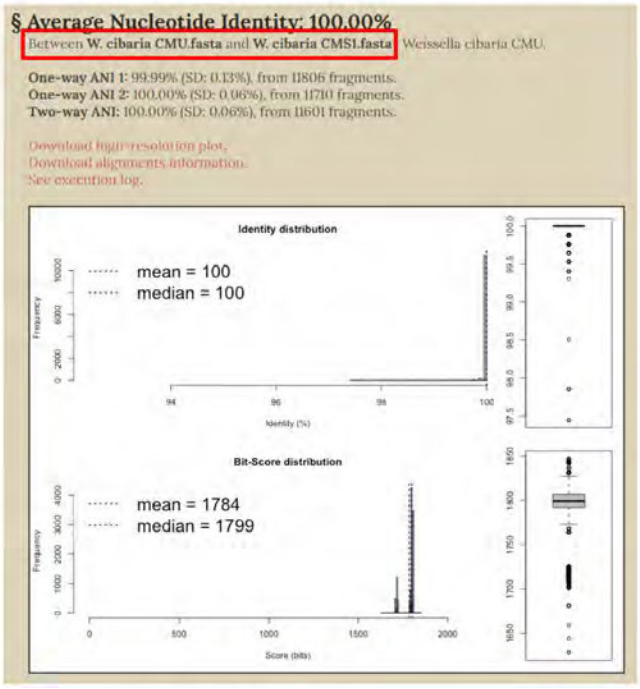
Legend: Above cutoff (> 0.999) | In range (> 0.989) | Below cutoff (< 0.989)

Genome	PCC
W._cibaria_CMS1.fasta	0.99998
W._cibaria_CMS2.fasta	0.99998
W._cibaria_CMS3.fasta	0.99998
W._cibaria_BC14.fasta	0.9991
W._cibaria_CH2.fasta	0.99891
W._cibaria_JCM_12495.fasta	0.97501
W._confusa_VTT_E-133279.fasta	0.97489
W._soli_KACC_11848.fasta	0.9047
W._paramesenteroides_FDAARGOS_414.fasta	0.83494
W._hellenica_CCUG_33494.fasta	0.81143
W._thailandensis_JCM_10695.fasta	0.76344
W._kandleri_DSM_20593.fasta	0.67592

Appendix 3.3 ANI Calculator Algorithm

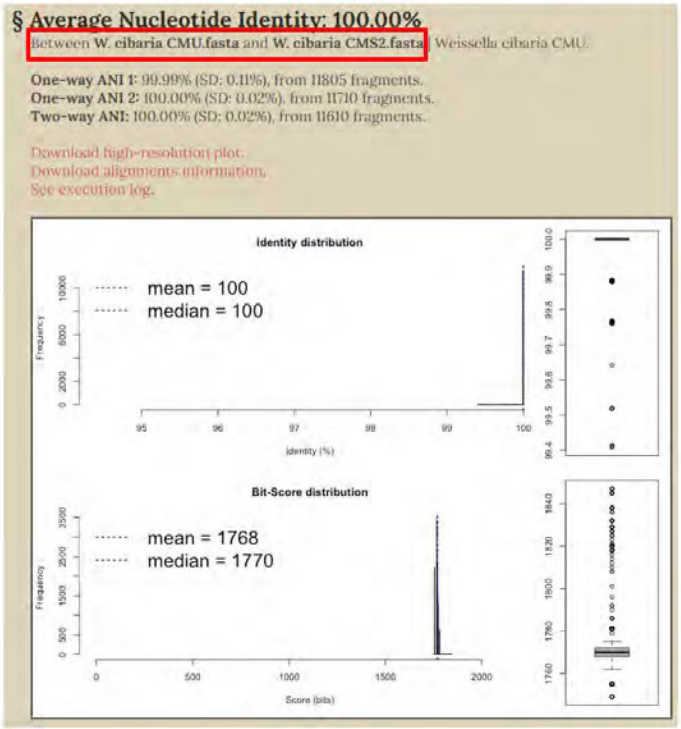
(3) ANI calculator algorithm

ANI of *Weissella cibaria* CMU by ANI calculator



(3) ANI calculator algorithm

ANI of *Weissella cibaria* CMU by ANI calculator



(3) ANI calculator algorithm

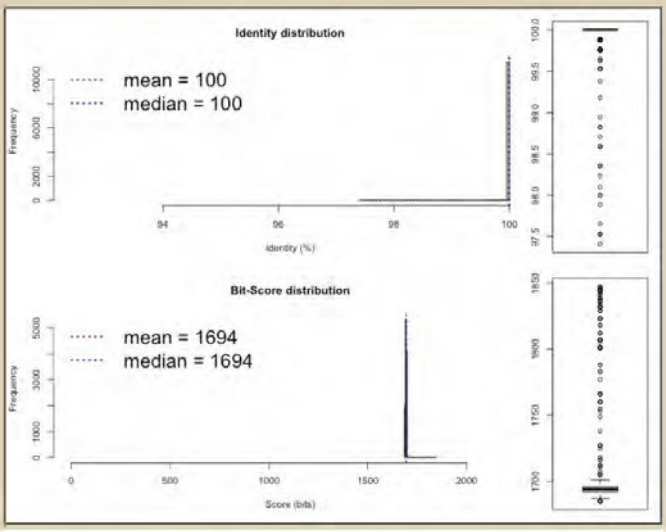
ANI of *Weissella cibaria* CMU by ANI calculator

§ Average Nucleotide Identity: 100.00%

Between **W. cibaria CMU.fasta** and **W. cibaria CMS3.fasta** | Weissella cibaria CMU.

One-way ANI 1: 99.99% (SD: 0.14%), from 11808 fragments.
One-way ANI 2: 99.99% (SD: 0.01%), from 11710 fragments.
Two-way ANI: 100.00% (SD: 0.08%), from 11557 fragments.

Download high-resolution plot.
Download alignments information.
See execution log.



(3) ANI calculator algorithm

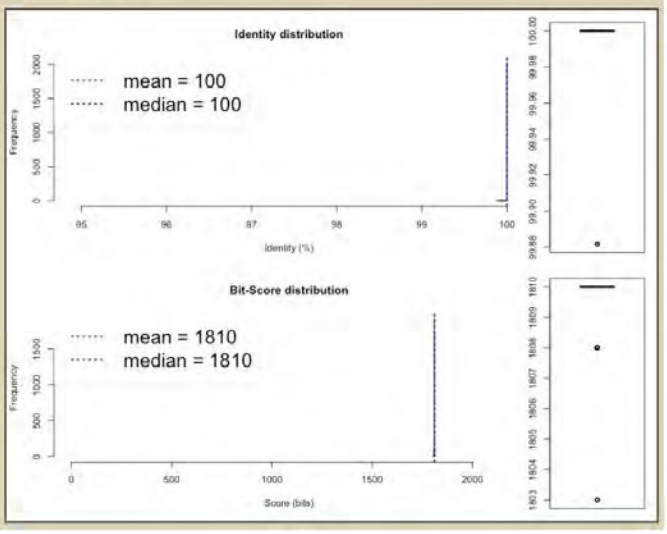
ANI of *Weissella cibaria* CMU by ANI calculator

§ Average Nucleotide Identity: 100.00%

Between **W. cibaria CMU.fasta** and **W. cibaria JCM 12495.fasta** | Weissella cibaria CMU.

One-way ANI 1: 99.93% (SD: 1.34%), from 2036 fragments.
One-way ANI 2: 100.00% (SD: 0.01%), from 2028 fragments.
Two-way ANI: 100.00% (SD: 0.01%), from 2028 fragments.

Download high-resolution plot.
Download alignments information.
See execution log.



(3) ANI calculator algorithm

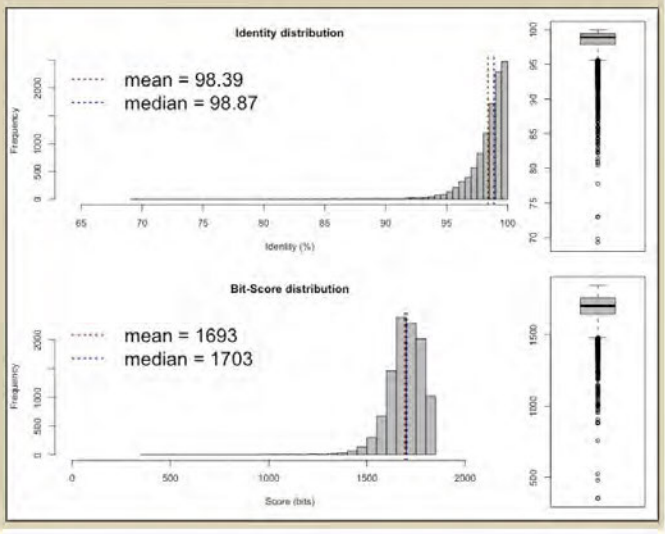
ANI of *Weissella cibaria* CMU by ANI calculator

§ Average Nucleotide Identity: 98.39%

Between **W. cibaria CMU.fasta** and **W. cibaria BC14.fasta** (Weissella cibaria CMU.

One-way ANI 1: 98.29% (SD: 2.12%), from 11009 fragments.
One-way ANI 2: 98.30% (SD: 2.08%), from 10904 fragments.
Two-way ANI: 98.39% (SD: 1.80%), from 10481 fragments.

Download high-resolution plot.
Download alignments information.
See execution log.



(3) ANI calculator algorithm

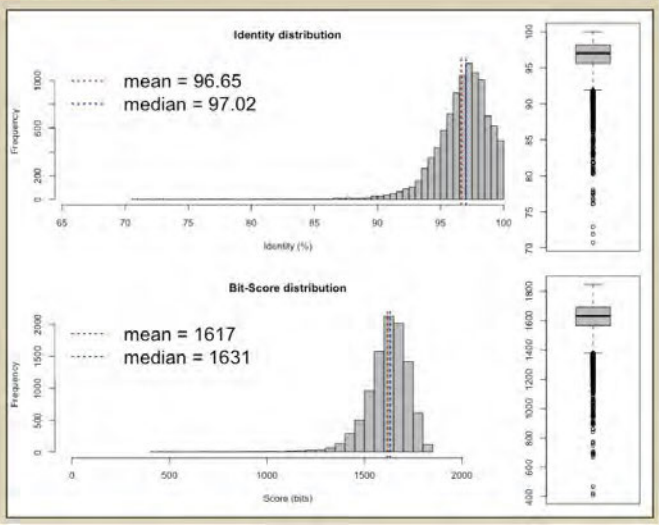
ANI of *Weissella cibaria* CMU by ANI calculator

§ Average Nucleotide Identity: 96.65%

Between **W. cibaria CMU.fasta** and **W. cibaria CH2.fasta** (Weissella cibaria CMU.

One-way ANI 1: 96.57% (SD: 2.57%), from 10682 fragments.
One-way ANI 2: 96.56% (SD: 2.52%), from 10643 fragments.
Two-way ANI: 96.65% (SD: 2.35%), from 9991 fragments.

Download high-resolution plot.
Download alignments information.
See execution log.



(3) ANI calculator algorithm

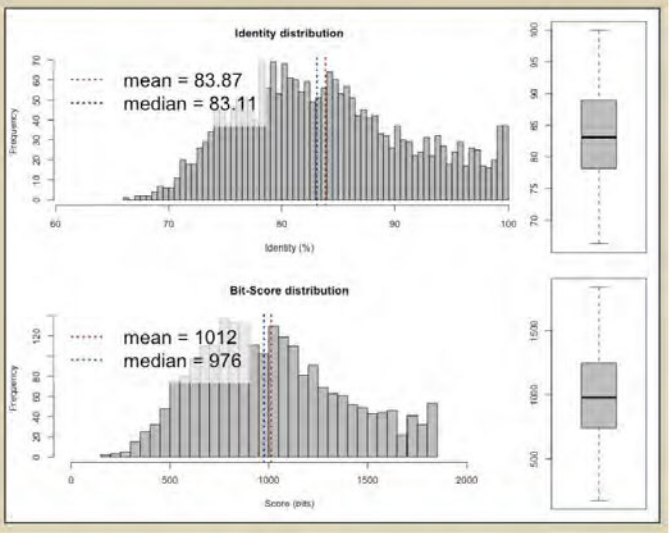
ANI of *Weissella cibaria* CMU by ANI calculator

§ Average Nucleotide Identity: 83.87%

Between **W. cibaria CMU.fasta** and **W. confusa VTT E-133279.fasta** (Weissella cibaria CMU, Weissella confusa VTT E-133279)

One-way ANI 1: 83.91% (SD: 7.85%), from 3382 fragments.
One-way ANI 2: 83.75% (SD: 7.77%), from 3311 fragments.
Two-way ANI: 83.87% (SD: 7.52%), from 2324 fragments.

Download high-resolution plot.
Download alignments information.
See execution log.



(3) ANI calculator algorithm

ANI of *Weissella cibaria* CMU by ANI calculator

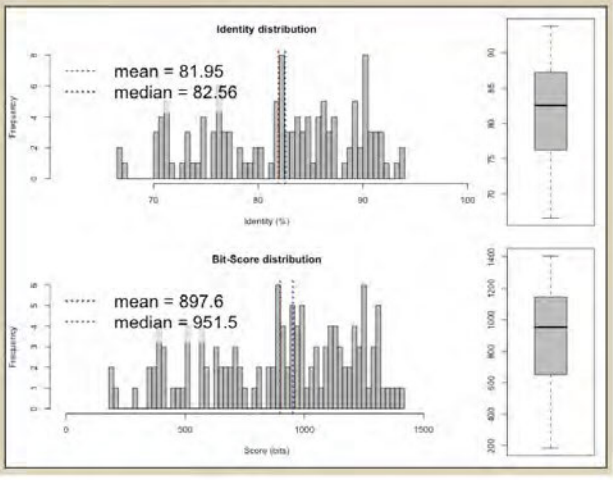
§ Average Nucleotide Identity: 81.95%

Between **W. cibaria CMU.fasta** and **W. hellenica CCUG 33494.fasta** (Weissella cibaria CMU, Weissella hellenica CCUG 33494)

One-way ANI 1: 82.07% (SD: 6.81%), from 196 fragments.
One-way ANI 2: 82.27% (SD: 6.68%), from 194 fragments.
Two-way ANI: 81.95% (SD: 6.95%), from 128 fragments.

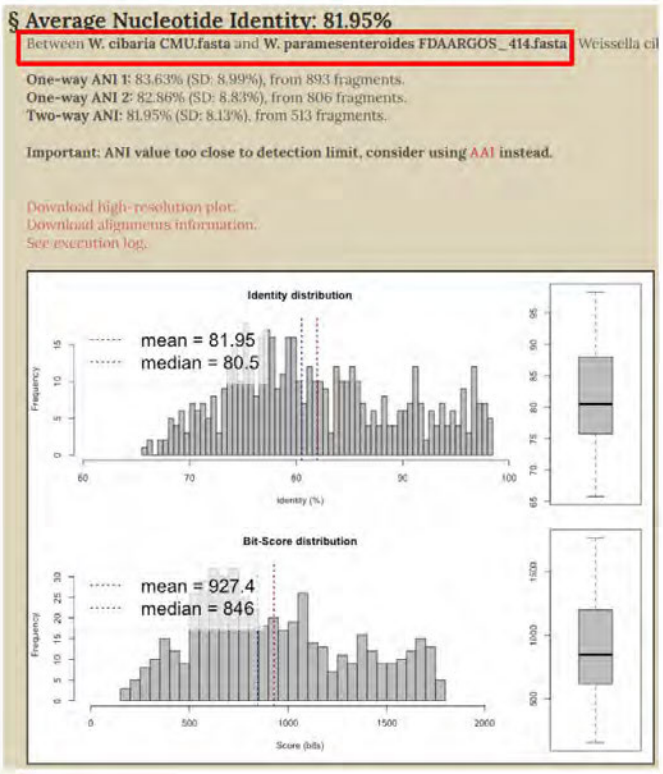
Important: ANI value too close to detection limit, consider using AAI instead.

Download high-resolution plot.
Download alignments information.
See execution log.



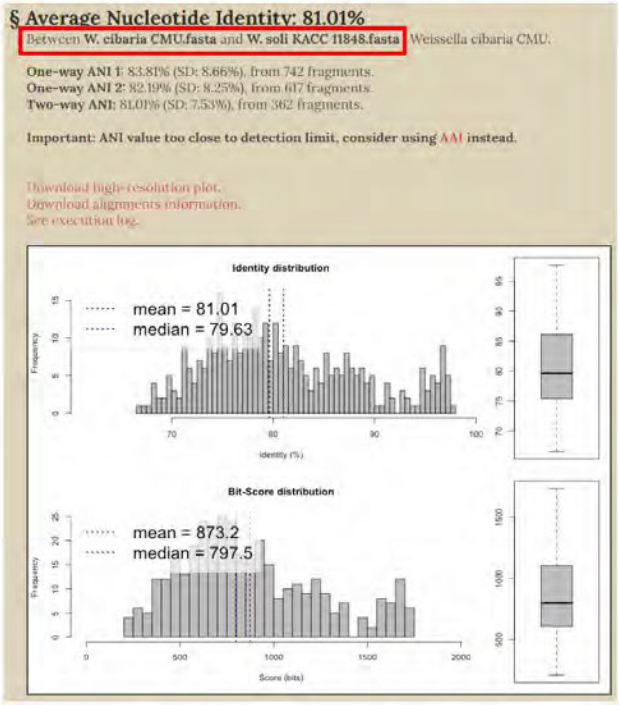
(3) ANI calculator algorithm

ANI of *Weissella cibaria* CMU by ANI calculator



(3) ANI calculator algorithm

ANI of *Weissella cibaria* CMU by ANI calculator



(3) ANI calculator algorithm

ANI of *Weissella cibaria* CMU by ANI calculator

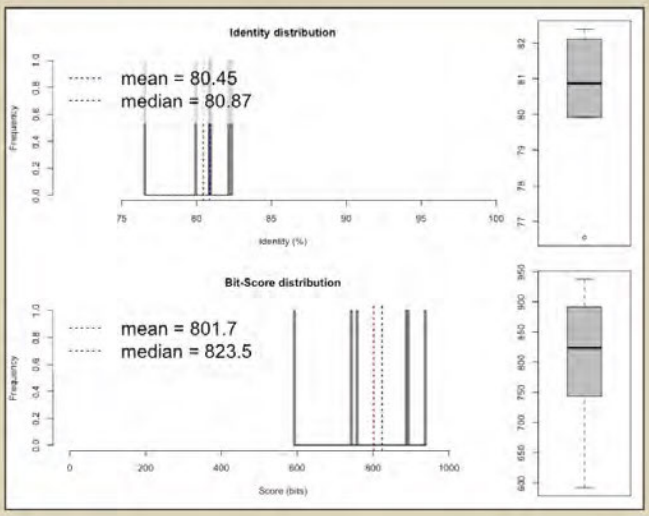
§ Average Nucleotide Identity:

Between **W. cibaria CMU.fasta** and **W. kandleri DSM 20593.fasta** Weissella cibaria CMU.

Insufficient hits to estimate one-way ANI: 9 Insufficient hits to estimate one-way ANI: 11 Insufficient hits to estimate two-way ANI: 6

Important: ANI value too close to detection limit, consider using AAI instead.

Download high-resolution plot.
Download alignments information.
See execution log.



(3) ANI calculator algorithm

ANI of *Weissella cibaria* CMU by ANI calculator

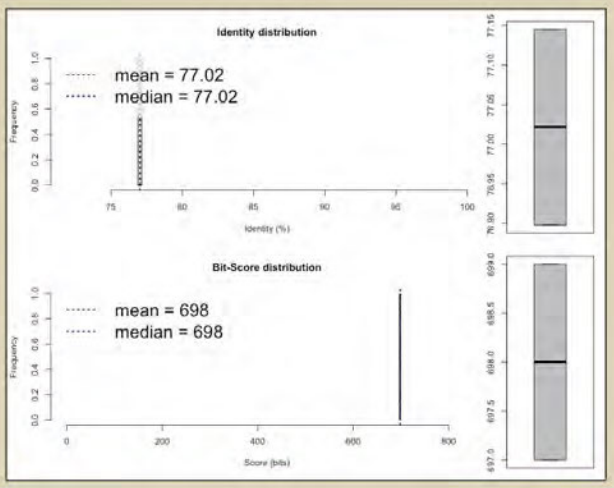
§ Average Nucleotide Identity:

Between **W. cibaria CMU.fasta** and **W. thailandensis JCM 10695.fasta** Weissella cibaria CMU.

Insufficient hits to estimate one-way ANI: 3 Insufficient hits to estimate one-way ANI: 3 Insufficient hits to estimate two-way ANI: 2

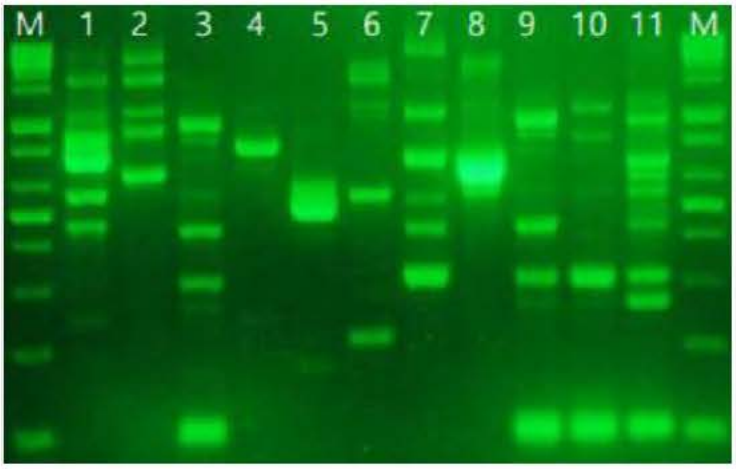
Important: ANI value too close to detection limit, consider using AAI instead.

Download high-resolution plot.
Download alignments information.
See execution log.



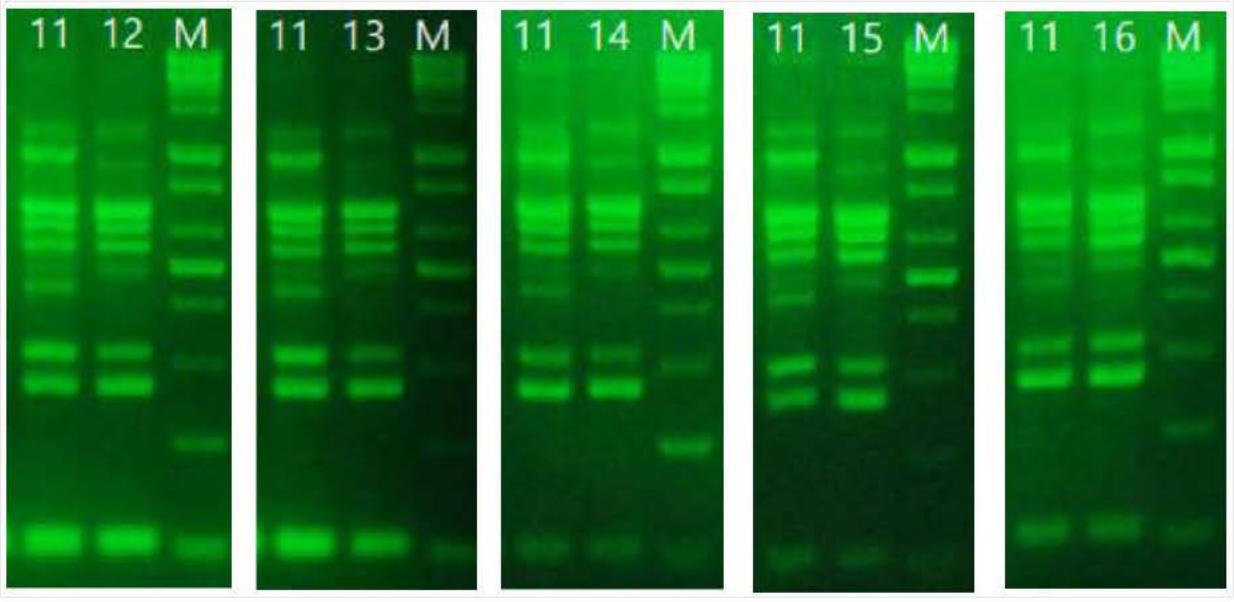
Appendix 3.4 Strain specific PCR results

RAPD-PCR Patterns of Multiple *Weissella* Species Compared to *W. cibaria* CMU



M = 1 kb Plus DNA Ladder; 1 = *W. thailandensis* KCTC 3551; 2 = *W. viridescens* KCTC 3504; 3 = *W. soli* KCTC 3789; 4 = *W. paramesenteroides* KCTC 3531; 5 = *W. minor* KCTC 3604; 6 = *W. kandleri* KCTC 3610; 7 = *W. halotolerans* KCTC 3595; 8 = *W. confusa* KCTC 3499 (ATCC 10881); 9 = *W. cibaria* KCTC 3807; 10 = *W. cibaria* KCTC 3746; 11 = *W. cibaria* CMU reference stock

RAPD-PCR Patterns of *W. cibaria* CMU Reference Stock Compared to Five Strain CMU Production Lots



M = 1 kb Plus DNA Ladder; 11 = *W. cibaria* CMU reference stock; 12 = *W. cibaria* CMU Production Lot No. CI11-0115N; 13 = *W. cibaria* CMU Production Lot No. CI11-0116N; 14 = *W. cibaria* CMU Production Lot No. CI11-0117N; 15 = *W. cibaria* CMU Production Lot No. CI11-0366N; 16 = *W. cibaria* CMU Production Lot No. CI11-0362N

Appendix 4 Manufacturing Documentation

발급번호 : 11H9-QJO7-8B47-XNZR-DXBZ

식품의약품안전처

#11 JayuPyeonghwa-Ro, Busanjin-Gu, Busan, 614-720, Republic of Korea,
Tel:+82-51-602-6111, Fax:+82-51-602-6245

Certificate No. : MFDS FID - 2017060033

CERTIFICATE GOOD MANUFACTURING PRACTICES APPLIED ESTABLISHMENT

MM/DD/YY : 11/09/17

This is to certify that the following is designated as GMP applied establishment in accordance with the Article 22.2 of the Health Functional Food Act and the Article 26 the Enforcement Rule of the Health Functional Food Act.

- Name of Manufacturer : LACTOMASON CO., Ltd.
- Address : 13-10, Worasanro 950 beon-gil, Munsan-eup, Jinju-si, Gyeongsangnam-do, Republic of Korea
- Name of Representative : Minn Sohn
- Name of registered Production Manager : Jonglin Yoon
- Name of registered Quality Control Manager : Chunho Park
- Notice : This certificate is valid only for Health Fuctional Food manufactured by Good Manufacturing Practices Applied Manufacturers.
- Approval Date : 20171109
- Remarks : Purpose of [redacted]

Signature : [redacted]

Director of General Services Division
Busan Regional Food & Drug Administration
Republic of Korea

[redacted]

This certificate was issued by internet and can be verified at Food Safety Korea Site(http://www.foodsafetykorea.go.kr)

Appendix 5 Representative Allergen Testing Reports

Appendix 5.1 *W. cibaria* CMU Lot CI11-0116N

Appendix 5.2 *W. cibaria* CMU Lot CI11-0117N

Appendix 5.3 *W. cibaria* CMU Lot CI11-0366N

Appendix 5.1 *W. cibaria* CMU Lot CI11-0116N

Milk and Soy – Lot CI11-0116N

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31115 Issued Date 2021. 08. 12 Page 1 of 1

ORAPHARM INC.
905-ho 9-16, yeonmujang 5-gil
seongdong-gu, seoul
korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-

This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No : AYFN21-31115
Product Name : Weissella cibaria CMU
Item No./Lot No. : MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0116N
Testing Period : 2021. 08. 04 to 2021. 08. 12
Purpose of Test Report : Reference

Test Results

Test Item	Unit	Method	MDL	Result
Milk	ng/uL	In-house method(FQW-25-12)	1	Detected
Soybean	ng/uL	Korea Food Code	1	Not Detected

Note) (1)** = Qualitative analysis (No Unit)
(2) The test results are limited to the requested product(sample name, item no.), and the sample don't have food Labeling information of Korea regulation.
(3) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025.
(4) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx
(5) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

*** End of Report***

[redacted]

Conard Lee
Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. #301, 57, Malgeumnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 689 3600 f +82 (0)70 4332 1659 http://www.sgsgroup.kr

Gluten – Lot CI11-0116N

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31116 Issued Date 2021. 08. 12 Page 1 of 1

ORAPHARM INC.
905-ho 9-16, yeonmujang 5-gil
seongdong-gu, seoul
korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-

This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No.	:	AYFN21-31116
Product Name	:	Weissella cibaria CMU
Item No./Lot No.	:	MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0116N
Test Period	:	2021. 08. 04 to 2021. 08. 12
Purpose of Test Report :		Reference

Test Results

Test Items	Unit	Test Method	LOQ	Results
Allergen Gluten	mg/kg	Veratox for Gliadin R5 Allergen, Neogen No. 8510	5	<5.0

NOTE: (1) Not detected = ≤ LOQ, g/100g = %(w/w), - = No regulation, ** = Qualitative analysis (No Unit)
(2) LOQ = Limit Of Quantitation
(3) The test results are limited to the requested product(sample name, item no.), and the sample don`t have food Labeling information of Korea regulation.
(4) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025.
(5) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx.
(6) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

*** End of Report ***

[redacted]

ConardLee

Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. #301, 67, Maligeumnae-gil, Uiwang-si, Gyeonggi-do, Korea #16007
t +82 (0)31 689 8600 f +82 (0)70 4332 1669 http://www.sgsgroup.kr
Member of the SGS Group (Société Générale de Surveillance)

Appendix 5.2 *W. cibaria* CMU Lot CI11-0117N

Milk and Soy – Lot CI11-0117N

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31118 Issued Date 2021. 08. 12 Page 1 of 1

ORAPHARM INC.
905-ho 9-16, yeonmujang 5-gil
seongdong-gu, seoul
korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-

This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No : AYFN21-31118
Product Name : Weissella cibaria CMU
Item No./Lot No. : MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0117N
Testing Period : 2021. 08. 04 to 2021. 08. 12
Purpose of Test Report : Reference

Test Results

Test Item	Unit	Method	MDL	Result
Milk	ng/uL	In-house method(FQW-25-12)	1	Detected
Soybean	ng/uL	Korea Food Code	1	Not Detected

Note) (1)** = Qualitative analysis (No Unit)
(2) The test results are limited to the requested product(sample name, item no.), and the sample don't have food Labeling information of Korea regulation.
(3) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025.
(4) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx
(5) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

*** End of Report***

[redacted]
ConanLee
Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. #301, 67, Malgeunnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 689 8600 f +82 (0)70 4332 1659 http://www.sgsgroup.kr
Member of the SGS Group (Société Générale de Surveillance)

Gluten – Lot CI11-0117N

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31119 Issued Date 2021. 08. 12 Page 1 of 1

ORAPHARM INC.
905-ho 9-16, yeonmujang 5-gil
seongdong-gu, seoul
korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-
This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No. : AYFN21-31119
Product Name : Weissella cibaria CMU
Item No./Lot No. : MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0117N
Test Period : 2021. 08. 04 to 2021. 08. 12
Purpose of Test Report : Reference
Test Results

Test Items	Unit	Test Method	LOQ	Results
Allergen Gluten	mg/kg	Veratox for Gliadin R5 Allergen, Neogen No. 8510	5	<5.0

NOTE: (1) Not detected = ≤ LOQ, g/100g = %(w/w), - = No regulation, ** = Qualitative analysis (No Unit)
(2) LOQ = Limit Of Quantitation
(3) The test results are limited to the requested product(sample name, item no.), and the sample don't have food Labeling information of Korea regulation.
(4) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025.
(5) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx.
(6) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

*** End of Report ***

[redacted]

Conard Lee
Technical Manager / SGS KOREA

FQP-32-F2 (3)

SGS Korea Co.,Ltd. #301, 67, Malgeunnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 689 5500 f +82 (0)70 4332 1659 http://www.sgsgroup.kr
Member of the SGS Group (Société Générale de Surveillance)

Appendix 5.3 *W. cibaria* CMU Lot CI11-0366N

Milk and Soy – Lot CI11-0366N

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31121 Issued Date 2021. 08. 12 Page 1 of 1

ORAPHARM INC.
905-ho 9-16, yeonmujang 5-gil
seongdong-gu, seoul
korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-

This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No : AYFN21-31121
Product Name : Weissella cibaria CMU
Item No./Lot No. : MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0366N
Testing Period : 2021. 08. 04 to 2021. 08. 12
Purpose of Test Report : Reference

Test Results

Test Item	Unit	Method	MDL	Result
Milk	ng/uL	In-house method(FQW-25-12)	1	Detected
Soybean	ng/uL	Korea Food Code	1	Not Detected

Note) (1)** = Qualitative analysis (No Unit)
(2) The test results are limited to the requested product(sample name, item no.), and the sample don't have food Labeling information of Korea regulation.
(3) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025.
(4) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx
(5) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

*** End of Report***

[redacted]

Gerard Lee

Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. 9301, 67, Malgeunnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 659 8600 f +82 (0)70 4332 1658 http://www.sgsgroup.kr
Member of the SGS Group (Société Générale de Surveillance)

Gluten – Lot CI11-0366N

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31122 Issued Date 2021. 08. 12 Page 1 of 1

ORAPHARM INC.
905-ho 9-16, yeonmujang 5-gil
seongdong-gu, seoul
korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-
This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No. : AYFN21-31122
Product Name : Weissella cibaria CMU
Item No./Lot No. : MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0366N
Test Period : 2021. 08. 04 to 2021. 08. 12
Purpose of Test Report : Reference
Test Results

Test Items	Unit	Test Method	LOQ	Results
Allergen Gluten	mg/kg	Veratox for Gliadin R5 Allergen, Neogen No. 8510	5	<5.0

NOTE: (1) Not detected = ≤ LOQ, g/100g = %(w/w), - = No regulation, ** = Qualitative analysis (No Unit)
(2) LOQ = Limit Of Quantitation
(3) The test results are limited to the requested product(sample name, item no.), and the sample don`t have food Labeling information of Korea regulation.
(4) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025.
(5) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx.
(6) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

*** End of Report ***

[redacted]

Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. #321, 67, Mageumnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 689 9600 f +82 (0)70 4332 1689 http://www.sgsgroup.kr
Member of the SGS Group (Societe Generale de Surveillance)

Appendix 6 Representative Pesticide Testing Reports

Appendix 6.1 *W. cibaria* CMU Lot CI11-0116N

Appendix 6.2 *W. cibaria* CMU Lot CI11-0117N

Appendix 6.3 *W. cibaria* CMU Lot CI11-0366N

Appendix 6.1 *W. cibaria* CMU Lot CI11-0116N

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31117 Issued Date : 2021. 08. 12 Page 1 of 2

ORAPHARM INC.
905-ho 9-16,yeonmujang 5-gil
seongdong-gu,seoul
korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-
This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No.	: AYFN21-31117
Product Name	: Weissella cibaria CMU
Item No./Lot No.	: MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0116N
Testing Period	: 2021. 08. 04 - 2021. 08. 10
Purpose of Test Report	: Reference
Test Items	: Pesticide 245. For the items, please refer to following page(s)
Test Method	: Analysis of hazardous substances in agricultural, GC and LC
Test Results	: 245 Not Detected

Notes
1) Not detected = ≤LOQ (0.01mg/kg), LOQ= Limit of quantitation
2) The test results are limited to the requested product(sample name, item no.), and the sample don't have food Labeling information of Korea regulation..
3) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025..
4) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx.
5) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

[redacted]
Kwangsoo Jeon
Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. #301, 67, Malgeunnae-gil, Uiwang-si, Gyeonggi-do, Korea 16071
t +82 (0)31 689 8600 f +82 (0)70 4332 1659 http://www.sgsgroup.kr
Member of the SGS Group (Société Générale de Surveillance)

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31117 Issued Date : 2021. 08. 12 Page 2 of 2

SGS File No. : AYFN21-31117

Product Name : Weissella cibaria CMU

Pesticide 245 items

Acetamiprid, Acrinathrin, Alachlor, Aldicarb, Aldrin, Amisulbrom, Anilofos, Azinphos-methyl, Azoxystrobin, Bendiocarb, Benthiavalicarb-isopropyl, Benzoximate, BHC, Bifenox, Bifenthrin, Biteranol, Boscalid, Bromobutide, Bromopropylate, Buprofezin, Butachlor, Cadusafos, Captan, Carbaryl(NAC), Carbendazim, Carbofuran, Carbophenothion, Chinomethionat(Oxythioquinox), Chlorantraniliprole, Chlordane, Chlorfenapyr, Chlorfenvinphos, Chlorfluazuron, Chlorobenzilate, Chlorothalonil, Chlorpropham, Chlorpyrifos, Chlorpyrifos-methyl, Chromafenozide, Clofentezine, Clothianidin, Cyazofamid, Cyflufenamid, Cyfluthrin (beta), Cyhalofop-butyl, Cyhalothrin-lambda, Cymoxanil, Cypermethrin, Cyproconazole, Cyprodinil, DDT, Deltamethrin, Diazinon, Dichlofluanid, Dichlorvos/DDVP, Diclofop-methyl, Dicloran, Dicofol, Diethofencarb, Difenoconazole, Diflubenzuron, Dimepiperate, Dimethenamid, Dimethoate, Dimethomorph(E,Z), Dimethylvinphos(Z), Diniconazole, Diphenamid, Diphenylamine, Disulfoton, Dithiopyr, Diuron, Edifenphos, Endosulfan (alpha, bata,sulfate), Endrin(dieldrin), EPN, Esprocarb, Ethaboxam, Ethalfluralin, Ethiofencarb, Ethion, Ethoprophos, Etoxazole, Etofenprox, Etridiazole, Etrimfos, Fenamidone, Fenamiphos, Fenarimol, Fenazaquin, Fenbuconazole, Fenitrothion : MEP, Fenobucarb, Fenothiocarb, Fenoxanil, Fenpropathrin, Fenpyroximate, Fenthion : MPP, Fenvalerate, Ferimzone, Fipronil, Fluacrypyrim, Flubendiamide, Flucythrinate, Fludioxonil, Flufenoxuron, Flumioxazine, Fluopicolide, Fluquinconazole, Flusilazole, Flutolanil, Folpet, Forchlorfenuron, Fosthiazate, Fthalide, Furathiocarb, Halfenprox, Heptachlor, Heptachlor epoxide, Hexaconazole, Hexaflumuron, Hexythiazox, Imazalil, Imibenconazole, Imidacloprid, Indanofan, Indoxacarb, Iprobenfos/IBP, Iprodione, Iprovalicarb, Isofenphos, Isoprocarb : MIPC, Isoprothiolane, Kresoxim-methyl, Lufenuron, Malathion, Mandipropamid, Mecarbam, Mefenacet, Mepanipyrim, Mepronil, Metalaxyl, Metamifop, Metconazole, Methabenzthiazuron, Methidathion, Methiocarb, Methomyl, Methoxychlor, Methoxyfenozide, Metobromuron, Metolachlor, Metolcarb, Metribuzin, Mevinphos, Molinate, Myclobutanil, Napropamide, Novaluron, Nuarimol, Ofurace, Oxadiazon, Oxamyl, Oxaziclomefon, Oxyfluorfen, Paclobutrazole, Parathion, Parathion-methyl, Penconazole, Pencycuron, Pendimethalin, Pentoxazone, Permethrin, Phenthoate:PAP, Phorate, Phosalone, Phosphamidone, Piperophos, Pirimicarb, Pirimiphos-ethyl, Pirimiphos-methyl, Probenazole, Prochloraz, Procymidone, Profenofos, Prometryn, Propanil, Propiconazole, Propoxur, Prothiofos, Pyraclofos, Pyraclostrobin, Pyrazophos, Pyribenzoxim, Pyributicarb, Pyridaben, Pyridalyl, Pyridaphenthion, Pyrimethanil, Pyrimidifen, Pyriminobac-methyl(E,Z), Pyriproxyfen, Pyroquilon, Quinoclamine, Quintozene(pentachloroaniline, Methyl pentachlorophenyl sulfide), Silafluofen, Simazine, Simeconazole, Simetryn, Spirodiclofen, Spiromesifen, Tebuconazole, Tebufenozide, Tebufenpyrad, Tebupirimfos, Teflubenzuron, Tefluthrin, Terbufos, Terbuthylazine, Terbutryn, Tetraconazole, Tetradifon, Thiabendazole, Thiacloprid, Thiamethoxam, Thiazopyr, Thifluzamide, Thiobencarb, Thiodicarb, Thiophanate-methyl, Tiadinil, Tolclofos-methyl, Tolylfluanid, Tralomethrin, Triadimefon, Triadimenol, Triazophos, Tricyclazole, Trifloxystrobin, Triflumizole, Triflumuron, Trifluralin, Uniconazole, Vinclozolin, Zoxamide

*** End of Report ***

SGS Korea Co.,Ltd. #301, 67, Maigeunnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 689 8600 f +82 (0)70 4332 1659 http://www.sgsgroup.kr

Appendix 6.2 *W. cibaria* CMU Lot CI11-0117N

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31120 Issued Date : 2021. 08. 12 Page 1 of 2

ORAPHARM INC.
905-ho 9-16,yeonmujang 5-gil
seongdong-gu,seoul
korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-
This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No.	: AYFN21-31120
Product Name	: Weissella cibaria CMU
Item No./Lot No.	: MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0117N
Testing Period	: 2021. 08. 04 - 2021. 08. 10
Purpose of Test Report	: Reference
Test Items	: Pesticide 245. For the items, please refer to following page(s)
Test Method	: Analysis of hazardous substances in agricultural, GC and LC
Test Results	: 245 Not Detected

Notes
1) Not detected = ≤LOQ (0.01mg/kg), LOQ= Limit of quantitation
2) The test results are limited to the requested product(sample name, item no.), and the sample don't have food Labeling information of Korea regulation..
3) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025..
4) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx.
5) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

[redacted]
Kwangsoo Jeon
Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. #301, 67, Malgeunnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 689 8600 f +82 (0)70 4332 1659 http://www.sgsgroup.kr
Member of the SGS Group (Société Générale de Surveillance)

SGS

Test Report (Reference)No. F690101/LF-CTSAYFN21-31120 Issued Date : 2021. 08. 12 Page 2 of 2

SGS File No. : AYFN21-31120

Product Name : Weissella cibaria CMU

Pesticide 245 items

Acetamiprid, Acrinathrin, Alachlor, Aldicarb, Aldrin, Amisulbrom, Anilofos, Azinphos-methyl, Azoxystrobin, Bendiocarb, Benthiavalicarb-isopropyl, Benzoximate, BHC, Bifenox, Bifenthrin, Biteranol, Boscalid, Bromobutide, Bromopropylate, Buprofezin, Butachlor, Cadusafos, Captan, Carbaryl(NAC), Carbendazim, Carbofuran, Carbophenothion, Chinomethionat(Oxythioquinox), Chlorantraniliprole, Chlordane, Chlorfenapyr, Chlorfenvinphos, Chlorfluazuron, Chlorobenzilate, Chlorothalonil, Chlorpropham, Chlorpyrifos, Chlorpyrifos-methyl, Chromafenozide, Clofentezine, Clothianidin, Cyazofamid, Cyflufenamid, Cyfluthrin (beta), Cyhalofop-butyl, Cyhalothrin-lambda, Cymoxanil, Cypermethrin, Cyproconazole, Cyprodinil, DDT, Deltamethrin, Diazinon, Dichlofluanid, Dichlorvos/DDVP, Diclofop-methyl, Dicloran, Dicofol, Diethofencarb, Difenoconazole, Diflubenzuron, Dimepiperate, Dimethenamid, Dimethoate, Dimethomorph(E,Z), Dimethylvinphos(Z), Diniconazole, Diphenamid, Diphenylamine, Disulfoton, Dithiopyr, Diuron, Edifenphos, Endosulfan (alpha, bata,sulfate), Endrin(dieldrin), EPN, Esprocarb, Ethaboxam, Ethalfluralin, Ethiofencarb, Ethion, Ethoprophos, Etoxazole, Etofenprox, Etridiazole, Etrimfos, Fenamidone, Fenamiphos, Fenarimol, Fenazaquin, Fenbuconazole, Fenitrothion : MEP, Fenobucarb, Fenothiocarb, Fenoxanil, Fenpropathrin, Fenpyroximate, Fenthion : MPP, Fenvalerate, Ferimzone, Fipronil, Fluacrypyrim, Flubendiamide, Flucythrinate, Fludioxonil, Flufenoxuron, Flumioxazine, Fluopicolide, Fluquinconazole, Flusilazole, Flutolanil, Folpet, Forchlorfenuron, Fosthiazate, Fthalide, Furathiocarb, Halfenprox, Heptachlor, Heptachlor epoxide, Hexaconazole, Hexaflumuron, Hexythiazox, Imazalil, Imibenconazole, Imidacloprid, Indanofan, Indoxacarb, Iprobenfos/IBP, Iprodione, Iprovalicarb, Isofenphos, Isoprocarb : MIPC, Isoprothiolane, Kresoxim-methyl, Lufenuron, Malathion, Mandipropamid, Mecarbam, Mefenacet, Mepanipyrim, Mepronil, Metalaxyl, Metamifop, Metconazole, Methabenzthiazuron, Methidathion, Methiocarb, Methomyl, Methoxychlor, Methoxyfenozide, Metobromuron, Metolachlor, Metolcarb, Metribuzin, Mevinphos, Molinate, Myclobutanil, Napropamide, Novaluron, Nuarimol, Ofurace, Oxadiazon, Oxamyl, Oxaziclomefon, Oxyfluorfen, Paclobutrazole, Parathion, Parathion-methyl, Penconazole, Pencycuron, Pendimethalin, Pentoxazone, Permethrin, Phenthoate:PAP, Phorate, Phosalone, Phosphamidone, Piperophos, Pirimicarb, Pirimiphos-ethyl, Pirimiphos-methyl, Probenazole, Prochloraz, Procymidone, Profenofos, Prometryn, Propanil, Propiconazole, Propoxur, Prothiofos, Pyraclofos, Pyraclostrobin, Pyrazophos, Pyribenzoxim, Pyributicarb, Pyridaben, Pyridalyl, Pyridaphenthion, Pyrimethanil, Pyrimidifen, Pyriminobac-methyl(E,Z), Pyriproxyfen, Pyroquilon, Quinoclamine, Quintozene(pentachloroaniline, Methyl pentachlorophenyl sulfide), Silafluofen, Simazine, Simeconazole, Simetryn, Spirodiclofen, Spiromesifen, Tebuconazole, Tebufenozide, Tebufenpyrad, Tebupirimfos, Teflubenzuron, Tefluthrin, Terbufos, Terbuthylazine, Terbutryn, Tetraconazole, Tetradifon, Thiabendazole, Thiacloprid, Thiamethoxam, Thiazopyr, Thifluzamide, Thiobencarb, Thiodicarb, Thiophanate-methyl, Tiadinil, Tolclofos-methyl, Tolylfluanid, Tralomethrin, Triadimefon, Triadimenol, Triazophos, Tricyclazole, Trifloxystrobin, Triflumizole, Triflumuron, Trifluralin, Uniconazole, Vinclozolin, Zoxamide

*** End of Report ***

SGS Korea Co.,Ltd. #301, 67, Malgeunnae-gil, Uiwang-si, Gyeonggi-do, Korea #16007
t +82 (0)31 689 8600 f +82 (0)70 4332 1659 http://www.sgsgroup.kr

Member of the SGS Group (Société Générale de Surveillance)

Appendix 6.3 *W. cibaria* CMU Lot CI11-0366N

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31123 Issued Date : 2021. 08. 12 Page 1 of 2

ORAPHARM INC.
905-ho 9-16,yeonmujang 5-gil
seongdong-gu,seoul
korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-
This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No.	: AYFN21-31123
Product Name	: Weissella cibaria CMU
Item No./Lot No.	: MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0366N
Testing Period	: 2021. 08. 04 - 2021. 08. 10
Purpose of Test Report	: Reference
Test Items	: Pesticide 245. For the items, please refer to following page(s)
Test Method	: Analysis of hazardous substances in agricultural, GC and LC
Test Results	: 245 Not Detected

Notes
1) Not detected = ≤LOQ (0.01mg/kg), LOQ= Limit of quantitation
2) The test results are limited to the requested product(sample name, item no.), and the sample don't have food Labeling information of Korea regulation..
3) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025..
4) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx.
5) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose .

[redacted]
Kwangsoo Jeon
Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. #301, 67, Malgeunnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 689 8600 f +82 (0)70 4332 1659 http://www.sgsgroup.kr
Member of the SGS Group (Société Générale de Surveillance)

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-31123 Issued Date : 2021. 08. 12 Page 2 of 2

SGS File No. : AYFN21-31123

Product Name : Weissella cibaria CMU

Pesticide 245 items

Acetamiprid, Acrinathrin, Alachlor, Aldicarb, Aldrin, Amisulbrom, Anilofos, Azinphos-methyl, Azoxystrobin, Bendiocarb, Benthiavalicarb-isopropyl, Benzoximate, BHC, Bifenox, Bifenthrin, Biteranol, Boscalid, Bromobutide, Bromopropylate, Buprofezin, Butachlor, Cadusafos, Captan, Carbaryl(NAC), Carbendazim, Carbofuran, Carbophenothion, Chinomethionat(Oxythioquinox), Chlorantraniliprole, Chlordane, Chlorfenapyr, Chlorfenvinphos, Chlorfluazuron, Chlorobenzilate, Chlorothalonil, Chlorpropham, Chlorpyrifos, Chlorpyrifos-methyl, Chromafenozide, Clofentezine, Clothianidin, Cyazofamid, Cyflufenamid, Cyfluthrin (beta), Cyhalofop-butyl, Cyhalothrin-lambda, Cymoxanil, Cypermethrin, Cyproconazole, Cyprodinil, DDT, Deltamethrin, Diazinon, Dichlofluanid, Dichlorvos/DDVP, Diclofop-methyl, Dicloran, Dicofol, Diethofencarb, Difenoconazole, Diflubenzuron, Dimepiperate, Dimethenamid, Dimethoate, Dimethomorph(E,Z), Dimethylvinphos(Z), Diniconazole, Diphenamid, Diphenylamine, Disulfoton, Dithiopyr, Diuron, Edifenphos, Endosulfan (alpha, bata,sulfate), Endrin(dieldrin), EPN, Esprocarb, Ethaboxam, Ethalfluralin, Ethiofencarb, Ethion, Ethoprophos, Etoxazole, Etofenprox, Etridiazole, Etrimfos, Fenamidone, Fenamiphos, Fenarimol, Fenazaquin, Fenbuconazole, Fenitrothion : MEP, Fenobucarb, Fenothiocarb, Fenoxanil, Fenpropathrin, Fenpyroximate, Fenthion : MPP, Fenvalerate, Ferimzone, Fipronil, Fluacrypyrim, Flubendiamide, Flucythrinate, Fludioxonil, Flufenoxuron, Flumioxazine, Fluopicolide, Fluquinconazole, Flusilazole, Flutolanil, Folpet, Forchlorfenuron, Fosthiazate, Fthalide, Furathiocarb, Halfenprox, Heptachlor, Heptachlor epoxide, Hexaconazole, Hexaflumuron, Hexythiazox, Imazalil, Imibenconazole, Imidacloprid, Indanofan, Indoxacarb, Iprobenfos/IBP, Iprodione, Iprovalicarb, Isofenphos, Isoprocarb : MIPC, Isoprothiolane, Kresoxim-methyl, Lufenuron, Malathion, Mandipropamid, Mecarbam, Mefenacet, Mepanipyrim, Mepronil, Metalaxyl, Metamifop, Metconazole, Methabenzthiazuron, Methidathion, Methiocarb, Methomyl, Methoxychlor, Methoxyfenozide, Metobromuron, Metolachlor, Metolcarb, Metribuzin, Mevinphos, Molinate, Myclobutanil, Napropamide, Novaluron, Nuarimol, Ofurace, Oxadiazon, Oxamyl, Oxaziclomefon, Oxyfluorfen, Paclobutrazole, Parathion, Parathion-methyl, Penconazole, Pencycuron, Pendimethalin, Pentoxazone, Permethrin, Phenthoate:PAP, Phorate, Phosalone, Phosphamidone, Piperophos, Pirimicarb, Pirimiphos-ethyl, Pirimiphos-methyl, Probenazole, Prochloraz, Procymidone, Profenofos, Prometryn, Propanil, Propiconazole, Propoxur, Prothiofos, Pyraclofos, Pyraclostrobin, Pyrazophos, Pyribenzoxim, Pyributicarb, Pyridaben, Pyridalyl, Pyridaphenthion, Pyrimethanil, Pyrimidifen, Pyriminobac-methyl(E,Z), Pyriproxyfen, Pyroquilon, Quinoclamine, Quintozene(pentachloroaniline, Methyl pentachlorophenyl sulfide), Silafluofen, Simazine, Simeconazole, Simetryn, Spirodiclofen, Spiromesifen, Tebuconazole, Tebufenozide, Tebufenpyrad, Tebupirimfos, Teflubenzuron, Tefluthrin, Terbufos, Terbuthylazine, Terbutryn, Tetraconazole, Tetradifon, Thiabendazole, Thiacloprid, Thiamethoxam, Thiazopyr, Thifluzamide, Thiobencarb, Thiodicarb, Thiophanate-methyl, Tiadinil, Tolclofos-methyl, Tolylfluanid, Tralomethrin, Triadimefon, Triadimenol, Triazophos, Tricyclazole, Trifloxystrobin, Triflumizole, Triflumuron, Trifluralin, Uniconazole, Vinclozolin, Zoxamide

*** End of Report ***

SGS Korea Co.,Ltd. #301, 67, Malgeunnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 689 8600 f +82 (0)70 4332 1659 http://www.sgsgroup.kr

Member of the SGS Group (Société Générale de Surveillance)

Appendix 7 Intake Analysis – Food Codes

Food Codes Utilized for Intake Analysis of *W. cibaria* CMU

Food code	Main food description	WWEIA Category description
	Yogurts	
11400000	Yogurt, NFS	Yogurt, regular
11400010	Yogurt, Greek, NS as to type of milk or flavor	Yogurt, Greek
11410000	Yogurt, NS as to type of milk or flavor	Yogurt, regular
11411010	Yogurt, NS as to type of milk, plain	Yogurt, regular
11411100	Yogurt, whole milk, plain	Yogurt, regular
11411200	Yogurt, low fat milk, plain	Yogurt, regular
11411300	Yogurt, nonfat milk, plain	Yogurt, regular
11411390	Yogurt, Greek, NS as to type of milk, plain	Yogurt, Greek
11411400	Yogurt, Greek, whole milk, plain	Yogurt, Greek
11411410	Yogurt, Greek, low fat milk, plain	Yogurt, Greek
11411420	Yogurt, Greek, nonfat milk, plain	Yogurt, Greek
11430000	Yogurt, NS as to type of milk, fruit	Yogurt, regular
11431000	Yogurt, whole milk, fruit	Yogurt, regular
11432000	Yogurt, low fat milk, fruit	Yogurt, regular
11433000	Yogurt, nonfat milk, fruit	Yogurt, regular
11433990	Yogurt, Greek, NS as to type of milk, fruit	Yogurt, Greek
11434000	Yogurt, Greek, whole milk, fruit	Yogurt, Greek
11434010	Yogurt, Greek, low fat milk, fruit	Yogurt, Greek
11434020	Yogurt, Greek, nonfat milk, fruit	Yogurt, Greek
11434090	Yogurt, NS as to type of milk, flavors other than fruit	Yogurt, regular
11434100	Yogurt, whole milk, flavors other than fruit	Yogurt, regular
11434200	Yogurt, low fat milk, flavors other than fruit	Yogurt, regular
11434300	Yogurt, nonfat milk, flavors other than fruit	Yogurt, regular
11435000	Yogurt, Greek, NS as to type of milk, flavors other than fruit	Yogurt, Greek
11435010	Yogurt, Greek, whole milk, flavors other than fruit	Yogurt, Greek
11435020	Yogurt, Greek, low fat milk, flavors other than fruit	Yogurt, Greek
11435030	Yogurt, Greek, nonfat milk, flavors other than fruit	Yogurt, Greek
11435100	Yogurt, Greek, with oats	Yogurt, Greek
11436000	Yogurt, liquid	Yogurt, regular
11440010	Chipotle dip, yogurt based	Dips, gravies, other sauces
11440020	Dill dip, yogurt based	Dips, gravies, other sauces
11440030	Onion dip, yogurt based	Dips, gravies, other sauces
11440040	Ranch dip, yogurt based	Dips, gravies, other sauces
11440050	Spinach dip, yogurt based	Dips, gravies, other sauces
11440060	Tzatziki dip	Dips, gravies, other sauces
11440070	Vegetable dip, yogurt based	Dips, gravies, other sauces
11446000	Yogurt parfait, low fat, with fruit	Yogurt, regular
11480010	Yogurt, whole milk, baby food	Baby food: yogurt
11480020	Yogurt, whole milk, baby food, with fruit and multigrain cereal puree, NFS	Baby food: yogurt
11480030	Yogurt, whole milk, baby food, with fruit and multigrain cereal puree, plus iron	Baby food: yogurt
11480040	Yogurt, whole milk, baby food, with fruit and multigrain cereal puree, plus DHA	Baby food: yogurt

67250100	Banana juice with lowfat yogurt, baby food	Baby food: yogurt
67250150	Mixed fruit juice with lowfat yogurt, baby food	Baby food: yogurt
67404300	Blueberry yogurt dessert, baby food, strained	Baby food: yogurt
67404500	Mixed fruit yogurt dessert, baby food, strained	Baby food: yogurt
67404070	Apple yogurt dessert, baby food, strained	Baby food: yogurt
67408500	Banana yogurt dessert, baby food, strained	Baby food: yogurt
67413700	Peach yogurt dessert, baby food, strained	Baby food: yogurt
67430500	Yogurt and fruit snack, baby food	Baby food: yogurt
67413700	Peach yogurt dessert, baby food, strained	Baby food: yogurt
67430500	Yogurt and fruit snack, baby food	Baby food: yogurt
41420380	Yogurt, soy	Processed soy products
42401100	Yogurt, coconut milk	Yogurt, regular
Frozen Desserts		
11459990	Frozen yogurt, NFS	Ice cream and frozen dairy desserts
11460000	Frozen yogurt, vanilla	Ice cream and frozen dairy desserts
11460100	Frozen yogurt, chocolate	Ice cream and frozen dairy desserts
11460500	Frozen yogurt, soft serve, vanilla	Ice cream and frozen dairy desserts
11460510	Frozen yogurt, soft serve, chocolate	Ice cream and frozen dairy desserts
11461200	Frozen yogurt sandwich	Ice cream and frozen dairy desserts
11461210	Frozen yogurt bar, vanilla	Ice cream and frozen dairy desserts
11461220	Frozen yogurt bar, chocolate	Ice cream and frozen dairy desserts
11461250	Frozen yogurt cone, chocolate	Ice cream and frozen dairy desserts
11461260	Frozen yogurt cone, vanilla	Ice cream and frozen dairy desserts
11461300	Frozen yogurt cone, vanilla, waffle cone	Ice cream and frozen dairy desserts
11461320	Frozen yogurt cone, chocolate, waffle cone	Ice cream and frozen dairy desserts
13110000	Ice cream, NFS	Ice cream and frozen dairy desserts
13110100	Ice cream, vanilla	Ice cream and frozen dairy desserts
13110102	Ice cream, vanilla, with additional ingredients	Ice cream and frozen dairy desserts
13110110	Ice cream, chocolate	Ice cream and frozen dairy desserts
13110112	Ice cream, chocolate, with additional ingredients	Ice cream and frozen dairy desserts
13110200	Ice cream, soft serve, vanilla	Ice cream and frozen dairy desserts
13110210	Ice cream, soft serve, chocolate	Ice cream and frozen dairy desserts
13110460	Gelato, vanilla	Ice cream and frozen dairy desserts
13110470	Gelato, chocolate	Ice cream and frozen dairy desserts
13120050	Ice cream bar, vanilla	Ice cream and frozen dairy desserts
13120100	Ice cream bar, vanilla, chocolate coated	Ice cream and frozen dairy desserts
13120110	Ice cream candy bar	Ice cream and frozen dairy desserts
13120140	Ice cream bar, chocolate	Ice cream and frozen dairy desserts
13120500	Ice cream sandwich, vanilla	Ice cream and frozen dairy desserts
13120510	Ice cream sandwich, chocolate	Ice cream and frozen dairy desserts
13120550	Ice cream cookie sandwich	Ice cream and frozen dairy desserts
13120730	Ice cream cone, scooped, vanilla	Ice cream and frozen dairy desserts
13120735	Ice cream cone, scooped, vanilla, waffle cone	Ice cream and frozen dairy desserts
13120740	Ice cream cone, NFS	Ice cream and frozen dairy desserts
13120770	Ice cream cone, scooped, chocolate	Ice cream and frozen dairy desserts
13120775	Ice cream cone, scooped, chocolate, waffle cone	Ice cream and frozen dairy desserts
13120782	Ice cream cone, soft serve, vanilla	Ice cream and frozen dairy desserts
13120784	Ice cream cone, soft serve, chocolate	Ice cream and frozen dairy desserts
13120786	Ice cream cone, soft serve, vanilla, waffle cone	Ice cream and frozen dairy desserts
13120788	Ice cream cone, soft serve, chocolate, waffle cone	Ice cream and frozen dairy desserts

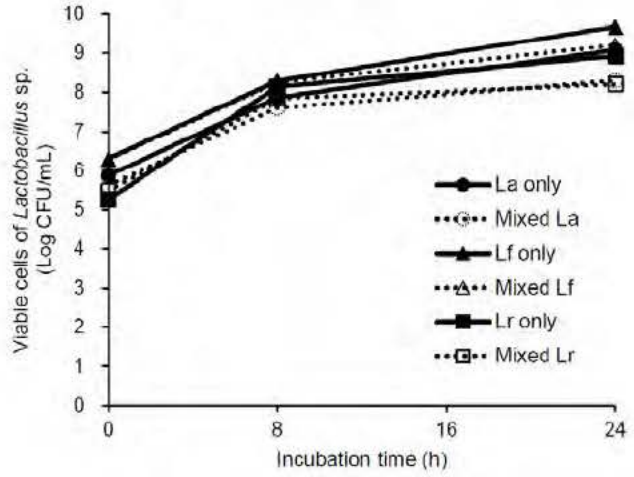
13120790	Ice cream cone, vanilla, prepackaged	Ice cream and frozen dairy desserts
13120792	Ice cream cone, chocolate, prepackaged	Ice cream and frozen dairy desserts
13121000	Ice cream sundae, NFS	Ice cream and frozen dairy desserts
13121100	Ice cream sundae, fruit topping	Ice cream and frozen dairy desserts
13121120	Banana split	Ice cream and frozen dairy desserts
13121300	Ice cream sundae, hot fudge topping	Ice cream and frozen dairy desserts
13121400	Ice cream sundae, caramel topping	Ice cream and frozen dairy desserts
13126000	Ice cream, fried	Ice cream and frozen dairy desserts
13130100	Light ice cream, NFS	Ice cream and frozen dairy desserts
13130300	Light ice cream, vanilla	Ice cream and frozen dairy desserts
13130310	Light ice cream, chocolate	Ice cream and frozen dairy desserts
13130700	Soft serve, blended with candy or cookies, from fast food	Ice cream and frozen dairy desserts
13135000	Light ice cream sandwich, vanilla	Ice cream and frozen dairy desserts
13135010	Light ice cream sandwich, chocolate	Ice cream and frozen dairy desserts
13140000	Light ice cream bar, vanilla	Ice cream and frozen dairy desserts
13140100	Light ice cream bar, vanilla, chocolate coated	Ice cream and frozen dairy desserts
13140115	Light ice cream bar, chocolate	Ice cream and frozen dairy desserts
13140700	Creamsicle	Ice cream and frozen dairy desserts
13140710	Creamsicle, light	Ice cream and frozen dairy desserts
13140900	Fudgesicle	Ice cream and frozen dairy desserts
13142100	Light ice cream cone, vanilla, prepackaged	Ice cream and frozen dairy desserts
13142110	Light ice cream cone, chocolate, prepackaged	Ice cream and frozen dairy desserts
13150000	Sherbet, all flavors	Ice cream and frozen dairy desserts
13161600	Fudgesicle, light	Ice cream and frozen dairy desserts
63420105	Frozen fruit juice bar	Gelatins, ices, sorbets
63420205	Frozen fruit juice bar, no sugar added	Gelatins, ices, sorbets
63430150	Sorbet	Gelatins, ices, sorbets
91501010	Gelatin dessert	Gelatins, ices, sorbets
91501020	Gelatin dessert with fruit	Gelatins, ices, sorbets
91501100	Gelatin salad with vegetables	Gelatins, ices, sorbets
91511010	Gelatin dessert, sugar free	Gelatins, ices, sorbets
91511020	Gelatin dessert, sugar free, with fruit	Gelatins, ices, sorbets
91520100	Yokan	Gelatins, ices, sorbets
91601000	Italian Ice	Gelatins, ices, sorbets
91601010	Italian Ice, no sugar added	Gelatins, ices, sorbets
91610900	Popsicle, NFS	Gelatins, ices, sorbets
91611000	Popsicle	Gelatins, ices, sorbets
91611100	Popsicle, no sugar added	Gelatins, ices, sorbets
91612000	Freezer pop	Gelatins, ices, sorbets
91621000	Snow cone	Gelatins, ices, sorbets
91621050	Snow cone, no sugar added	Gelatins, ices, sorbets
Hard Candy, Mints, Chewing Gum		
91745020	Hard candy	Candy not containing chocolate
91770020	Dietetic or low calorie hard candy	Candy not containing chocolate
91770050	Dietetic or low calorie mints	Candy not containing chocolate
91800100	Chewing gum, NFS	Candy not containing chocolate
91801000	Chewing gum, regular	Candy not containing chocolate
91802000	Chewing gum, sugar free	Candy not containing chocolate
91770000	Dietetic or low calorie candy, NFS	Candy not containing chocolate
91745020	Hard candy	Candy not containing chocolate

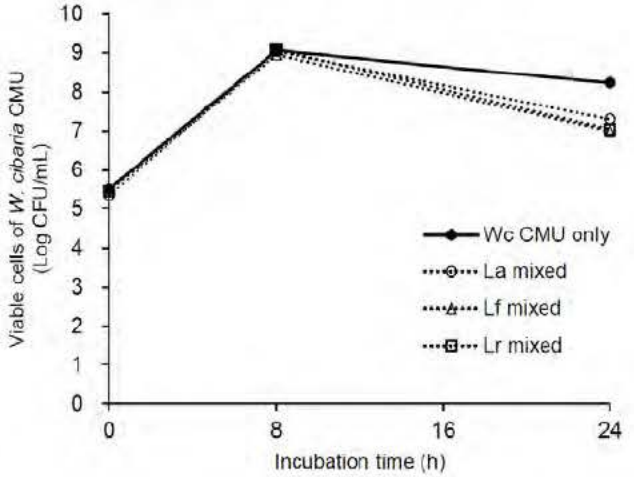
Appendix 8 Effects of *W. cibaria* CMU on the Growth of *Lactobacilli* Over Time

h	0	8	24
La only	5.87	7.87	9.08
Mixed La	5.62	7.60	8.30
Lf only	6.30	8.29	9.67
Mixed Lf	6.28	8.26	9.20
Lr only	5.26	8.14	8.92
Mixed Lr	5.48	7.85	8.20

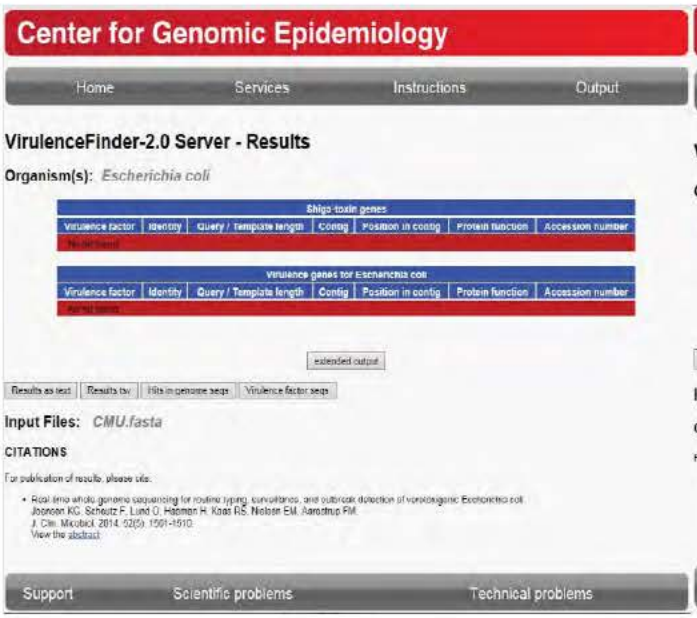
h	0	8	24
Wc CMU only	5.51	9.06	8.23
La mixed	5.34	9.03	7.30
Lf mixed	5.45	8.94	7.00
Lr mixed	5.45	9.08	7.04

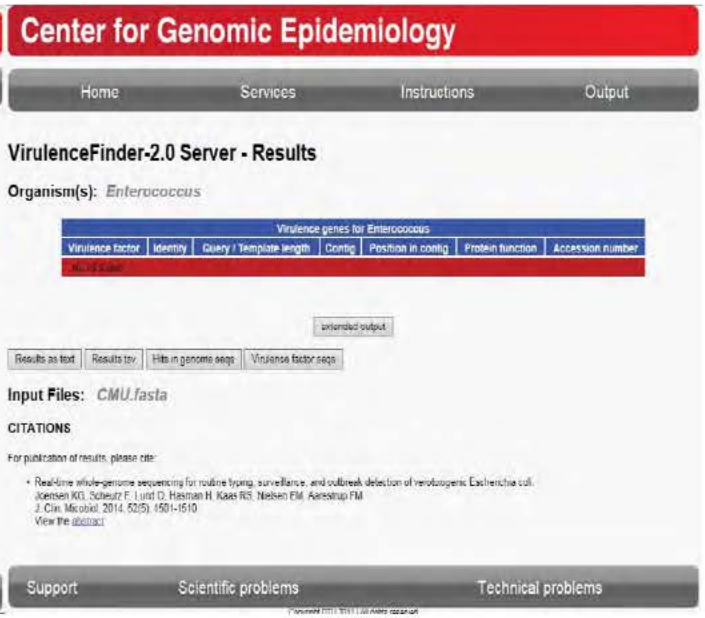
La, *Lactobacillus acidophilus* ATCC 4356; Lf, *Lactobacillus fermentum* ATCC 14931; Lr, *Lactobacillus reuteri* KCTC 3594; Wc CMU, *Weissella cibaria* CMU

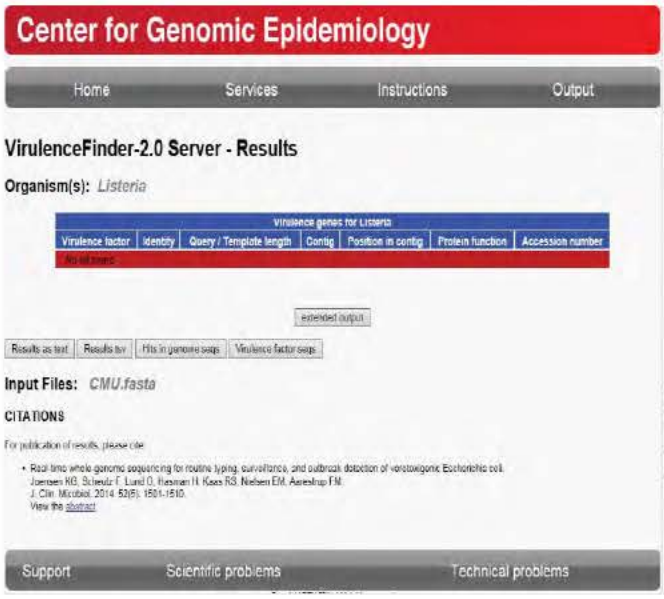


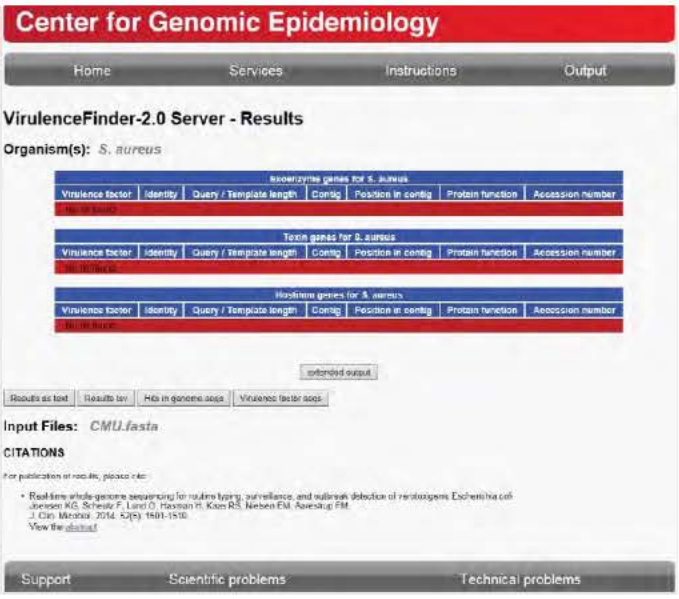


Appendix 9 Center for Genomic Epidemiology – VirulenceFinder 2.0 Results









Appendix 10 Biogenic Amine Analysis

Appendix 10.1 *W. cibaria* CMU Lot CI11-0116N

Appendix 10.2 *W. cibaria* CMU Lot CI11-0117N

Appendix 10.3 *W. cibaria* CMU Lot CI11-0366N

Appendix 10.1 *W. cibaria* CMU Lot CI11-0116N

Certificate of Analysis

No. of Sample : Weissella cibaria CMU Lot No. CI11-0116N

Inspection Purpose : Reference only | Date of Application : 2021-11-17

Applicant
Name : OraPharm Inc, Eun-Sup Yoon
Company address : 04782, 905-ho, 9-16, Yeonmujang-5-gil, Seongdong-gu, Seoul, Republic of Korea

Analytical Result

Biogenic amines	Concentration (mg/kg)
Tryptamine	0.00
β-phenylethylamine	0.00
Putrescine	0.00
Cadaverine	0.00
Histamine	0.00
Tyramine	0.00
Spermidine	0.00
Spermine	0.00

Analysis of biogenic amines using chromatographic AOAC 1993, 76(3) method[1].

[1]Eerola S, Hinkkanen R, Lindfors E, Hirvi T, 1993. Liquid chromatographic determination of biogenic amines in dry sausages. Journal of AOAC International, 76(3), 575-577.

2021. 11. 17.

We hereby certify that the above are correct.

Korea University, College of Science and Technology, Department of Food and Biotechnology

Director : Jae-Hyung, Mah

Korea University Sejong Campus, 2511 Sejong-ro, Sejong City, 30019, Korea

KOREA UNIVERSITY SEJONG CAMPUS

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-43146

Issued Date 2021. 10. 29 Page 1 of 1

ORAPHARM INC.
905-ho 9-16, Yeonmujang 5-gil
Seongdong-gu, Seoul
Republic of Korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-

This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No. : AYFN21-43146
Product Name : Weissella cibaria CMU
Item No./Lot No. : MFG:2021.02.15, EXP:2023.02.14 Lot NO: CI11-0116N
Test Period : 2021. 10. 21 to 2021. 10. 28
Purpose of Test Report : Reference

Test Results

Test Items	Unit	Test Method	LOQ	Results
Histamine	mg/kg	Korea Food Code, HPLC/PDA	5	Not Detected

NOTE: (1) Not detected = ≤ LOQ, g/100g = %(w/w), - = No regulation, ** = Qualitative analysis (No Unit)
(2) LOQ = Limit Of Quantitation
(3) The test results are limited to the requested product(sample name, item no.), and the sample don't have food Labeling information of Korea regulation.
(4) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025.
(5) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx.
(6) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

*** End of Report ***

[redacted]

Jungsub Shim

Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. 3F, 67, Malgeunmae-gil, Uiwang-si, Gyeonggi-do, Korea 16071
t +82 (0)31 689 3600 f +82 (0)70 4332 1699 http://www.sgsgroup.kr

Member of the SGS Group (Société Générale de Surveillance)

Appendix 10.2 *W. cibaria* CMU Lot CI11-0117N

Certificate of Analysis

No. of Sample : Weissella cibaria CMU Lot No. CI11-0117N

Inspection Purpose : Reference only | Date of Application : 2021-11-17

Applicant
Name : OraPharm Inc, Eun-Sup Yoon
Company address : 04782, 905-ho, 9-16, Yeonmujang-5-gil, Seongdong-gu, Seoul, Republic of Korea

Analytical Result

Biogenic amines	Concentration (mg/kg)
Tryptamine	0.00
β-phenylethylamine	0.00
Putrescine	0.00
Cadaverine	0.00
Histamine	0.00
Tyramine	0.00
Spermidine	0.00
Spermine	0.00

Analysis of biogenic amines using chromatographic AOAC 1993, 76(3) method[1].

[1]Eerola S, Hinkkanen R, Lindfors E, Hirvi T, 1993. Liquid chromatographic determination of biogenic amines in dry sausages. Journal of AOAC International, 76(3), 575-577.

2021. 11. 17.

We hereby certify that the above are correct.

Korea University, College of Science and Technology, Department of Food and Biotechnology

Director : Jae-Hyung, Mah

Korea University Sejong Campus, 2511 Sejong-ro, Sejong City, 30019, Korea

KOREA UNIVERSITY SEJONG CAMPUS

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-43147

Issued Date 2021. 10. 29 Page 1 of 1

ORAPHARM INC.
905-ho 9-16, Yeonmujang 5-gil
Seongdong-gu, Seoul
Republic of Korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-

This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No.	:	AYFN21-43147
Product Name	:	Weissella cibaria CMU
Item No./Lot No.	:	MFG:2021.02.15, EXP:2023.02.14 Lot NO: CI11-0117N
Test Period	:	2021. 10. 21 to 2021. 10. 28
Purpose of Test Report :		Reference

Test Results

Test Items	Unit	Test Method	LOQ	Results
Histamine	mg/kg	Korea Food Code, HPLC/PDA	5	Not Detected

NOTE: (1) Not detected = ≤ LOQ, g/100g = %(w/w), - = No regulation, ** = Qualitative analysis (No Unit)
(2) LOQ = Limit Of Quantitation
(3) The test results are limited to the requested product(sample name, item no.), and the sample don`t have food Labeling information of Korea regulation.
(4) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025.
(5) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx.
(6) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

*** End of Report ***

Jungsub Shim

Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. 3F, 67, Malgeunnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 689 8600 f +82 (0)70 4332 1659 http://www.sgsgroup.kr

Member of the SGS Group (Société Générale de Surveillance)

Appendix 10.3 *W. cibaria* CMU Lot CI11-0366N

Certificate of Analysis

No. of Sample : Weissella cibaria CMU Lot No. CI11-0366N

Inspection Purpose : Reference only | Date of Application : 2021-11-17

Applicant
Name : OraPharm Inc, Eun-Sup Yoon
Company address : 04782, 905-ho, 9-16, Yeonmujang-5-gil, Seongdong-gu, Seoul, Republic of Korea

Analytical Result

Biogenic amines	Concentration (mg/kg)
Tryptamine	0.00
β-phenylethylamine	0.00
Putrescine	0.00
Cadaverine	0.00
Histamine	0.00
Tyramine	0.00
Spermidine	0.00
Spermine	0.00

Analysis of biogenic amines using chromatographic AOAC 1993, 76(3) method[1].

[1]Eerola S, Hinkkanen R, Lindfors E, Hirvi T, 1993. Liquid chromatographic determination of biogenic amines in dry sausages. Journal of AOAC International, 76(3), 575-577.

2021. 11. 17.

We hereby certify that the above are correct.

Korea University, College of Science and Technology, Department of Food and Biotechnology

Director : Jae-Hyung, Mah

Korea University Sejong Campus, 2511 Sejong-ro, Sejong City, 30019, Korea

KOREA UNIVERSITY SEJONG CAMPUS

SGS

Test Report (Reference) No. F690101/LF-CTSAYFN21-43148

Issued Date 2021. 10. 29 Page 1 of 1

ORAPHARM INC.
905-ho 9-16, Yeonmujang 5-gil
Seongdong-gu, Seoul
Republic of Korea

The following sample(s) was/were submitted and identified by/on behalf of the client as:-
This report is not related to the Ministry of Food and Drug Safety "ACT ON TESTING AND INSPECTION IN THE FOOD AND DRUG INDUSTRY"

SGS File No. : AYFN21-43148
Product Name : Weissella cibaria CMU
Item No./Lot No. : MFG:2021.05.20, EXP:2023.05.19 Lot NO: CI11-0366N
Test Period : 2021. 10. 21 to 2021. 10. 28
Purpose of Test Report : Reference
Test Results

Test Items	Unit	Test Method	LOQ	Results
Histamine	mg/kg	Korea Food Code, HPLC/PDA	5	Not Detected

NOTE: (1) Not detected = ≤ LOQ, g/100g = %(w/w), - = No regulation, ** = Qualitative analysis (No Unit)
(2) LOQ = Limit Of Quantitation
(3) The test results are limited to the requested product(sample name, item no.), and the sample don`t have food Labeling information of Korea regulation.
(4) This test report is not related to Korea Laboratory Accreditation and KS Q ISO/IEC 17025.
(5) Verify for authenticity and validity in web site : https://eecloud.sgs.com/index.aspx.
(6) This test report cannot be used for public relations, advertising or litigating purposes without the prior consent of our company and not be used for different purpose.

*** End of Report ***

Jungsub Shim
Technical Manager / SGS KOREA

SGS Korea Co.,Ltd. 3F, 67, Malgeunnae-gil, Uiwang-si, Gyeonggi-do, Korea #16071
t +82 (0)31 689 8600 f +82 (0)70 4332 1659 http://www.sgsgroup.kr

Appendix 11 GRAS Associates Expert Panel Report

The Generally Recognized as Safe (GRAS) Status of the Proposed Uses of *W. cibaria* CMU

Foreword

An independent panel of experts ("Expert Panel") was convened by GRAS Associates, LLC on behalf of their client, OraPharm, Inc., to evaluate the safety and Generally Recognized as Safe (GRAS) status of OraPharm's proposed food uses of *Weissella cibaria* strain CMU (*W. cibaria* CMU). The members of this Expert Panel[15] are qualified to serve in this capacity by virtue of their scientific training and experience in the safety of food and food ingredients.

GRAS Associates and OraPharm, Inc., ensured that all reasonable efforts were made to identify and select a balanced Expert Panel with expertise in food safety, toxicology, and nutrition. The Expert Panel was selected and convened in accordance with the Food and Drug Administration (FDA)'s guidance for industry on "Best Practices for Convening a GRAS Panel"[16]. Efforts were placed on identifying conflicts of interest or relevant "appearance issues" that could potentially bias the outcome of the deliberations of the Expert Panel and no such conflicts of interest or "appearance issues" were identified. The Expert Panel members received a reasonable honorarium as compensation for their time; the honoraria provided to the Expert Panel members were not contingent upon the outcome of their deliberations.

Discussion

OraPharm's *W. cibaria* CMU is intended to provide a dietary source of *W. cibaria* CMU as a food ingredient in selected conventional foods including yogurt, frozen desserts (dairy, ices, sorbets and sherbets) and mixes, hard candy and chewing gum with an intended use level of 1×10^8 CFU per serving throughout the shelf life of the products. OraPharm suggests that the initial addition level of *W. cibaria* CMU in the products may be as high as 8.0×10^9 CFU per serving to allow for loss of viability over time and the intended use levels may vary by food category. Use in hard candy and chewing gum would require the highest overage while use in frozen desserts and yogurt would likely be 5.0×10^8 CFU and 2.0×10^8 CFU per serving, respectively.

OraPharm has calculated the estimated daily intake using the proposed intended use levels and food intake of those foods as reported by National Health and Nutrition Examination Survey (NHANES) 2017-2018 survey. From this calculation, the "all ages" 90th percentile estimated intake for *W. cibaria* CMU was determined to be 397 mg/day. Using the specification of not less than $1x10^9$ CFU per gram,

[15] All three panelists have extensive technical backgrounds in the evaluation of food ingredient safety and in participating in deliberations of GRAS Expert Panels. Dr. Dziwenka holds a Doctor of Veterinary Medicine degree from the University of Saskatchewan and is a Diplomate with the American Board of Toxicology. She has over 24 years' experience as a practicing veterinarian and 20 years of experience in research, preclinical regulatory toxicology, and safety evaluation of food and animal feed additives and GRAS dossier preparation. R. Martin holds a Ph.D. in Chemistry with over 38 years of experience evaluating safety of food ingredients within FDA. Dr. Falk holds a PhD in Biochemistry from Cornell University. He is an independent consultant with over 20 years of experience in reviewing food safety issues, GRAS reviews, and new dietary ingredient notifications at the Life Science Research Office (LSRO) and LSRO Solutions.

[16] Available at: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm583856.htm (Accessed February 28, 2022)

the EDI in terms of CFU per day is 3.97 x 10^8. On a body weight basis, intake is 6.24 mg/kg bw/day, or 6.24 x 10^6 CFU/kg bw/day. These high intake scenarios are unlikely in that they assume that all of the foods consumed contain *W. cibaria* CMU at the highest amount.

The complete genome for OraPharm's *W. cibaria* CMU has been sequenced and deposited in GenBank under accession number CP013936. The Expert Panel reviewed the detailed characterization information provided including information on the initial source, taxonomy and identify information. Identify information provided included information on genomic characterization, 16S rRNA alignment, average nucleotide identity, phenotypic characterization and strain specific identification analysis. The Expert Panel also reviewed the detailed manufacturing process section of the GRAS dossier including a review of the raw ingredients used and the specifications OraPharm has set for its *W. cibaria* CMU. OraPharm has set physical and chemical parameter specifications for its *W. cibaria* CMU and has shown that the manufacturing process can produce a consistent product by supplying the results from the analysis of five non-consecutive lots. OraPharm has also supplied documentation that the substances used in the manufacturing process are fit for the intended purpose.

The Expert Panel considered several issues regarding the safety of OraPharm's *W. cibaria* CMU. Bacteria in the *Weissella* genus are commonly found in fermented foods. OraPharm's *W. cibaria* CMU is registered as a safe raw material by the Korea Food and Drug Administration under code number A 다 006800[17] and is found in several products in Korea. According to OraPharm, the available commercialized products provide a daily intake of *W. cibaria* CMU of 1 x 10^9 CFU to 2.4 x 10^{10} CFU per day in tablet or sachet form, and to date, they state that no reports of adverse reactions from distribution and sales have been received. *W. cibaria* CMU has been assessed for antibiotic resistance using antibiotic susceptibility testing and genomic assessment for antibiotic resistance genes. *W. cibaria* CMU has also been evaluated for its ability to produce antimicrobial substances which are important in human or veterinary medicine and that it will not alter the normal microflora in the organism consuming the *W. cibaria* CMU. The result of the testing demonstrates that *W. cibaria* CMU will not have a negative impact on the normal flora. OraPharm assessed the virulence of its *W. cibaria* CMU, the results of which did not raise any concerns with the Expert Panel. OraPharm also performed analyses of three representative samples of *W. cibaria* CMU for the ability to produce biogenic amines, using three methods and no biogenic amines were identified. The Expert Panel reviewed additional safety assessments conducted for *W. cibaria* CMU as outlined in the dossier and the Panel had no concerns regarding the safety information in the dossier.

The Expert Panel also reviewed the results of GLP compliant studies conducted with *W. cibaria* CMU including multiple GLP compliant studies for genotoxicity (OECD Guideline studies 471, 473 and 474) and an OECD Guideline 408 90-day repeat dose study in rats. The Panel concurs with OraPharm's

[17] See http://www.foodsafetykorea.go.kr/foodcode/01_03.jsp?idx=12135. Accessed February 28,2022.

conclusions that the NOAEL from the repeat dose study was the highest dose tested (5000 mg/kg bw/day) and that there was no evidence of mutagenicity or clastogenicity.

The Expert Panel considered the published animal studies and clinical trials as key evidence. The Expert Panel considers NOAELs derived from animal studies are not limiting and that human data from clinical studies and commercially available products should be taken into consideration when setting safe intake limits. The Expert Panel reviewed the results of six randomized, double-blinded, placebo-controlled clinical trials administering 8×10^7 to 1×10^9 CFU *W. cibaria* CMU daily for 4 to 8 weeks for a total of 322 patient-days exposure without the report of adverse events. It is also aware that various products containing *W. cibaria* CMU have been sold since 2017 and that no adverse events were reported after sale of over 189,000 units of products providing a daily intake of 1×10^9 CFU to 2.4×10^{10} CFU.

Conclusion

A compelling case can be made that scientific consensus exists regarding the safety of OraPharm's *W. cibaria* CMU which is intended to provide a dietary source of *W. cibaria* CMU as a food ingredient in selected conventional foods. The Expert Panel concludes that there is sufficient evidence to support the safety of OraPharm's *W. cibaria* CMU given the following conditions:

- *W. cibaria* CMU continues to meet the designated specifications;
- The proposed intended use and use levels do not change; and
- *W. cibaria* CMU continues to be produced in accordance with Current Good Manufacturing Practices

The Expert Panel has critically reviewed the information provided by OraPharm, Inc., as well as publicly available published information obtained from peer-reviewed journals as well as other assessments by well-respected international regulatory bodies.

The Expert Panel unanimously concludes that the proposed uses of OraPharm's *W. cibaria* CMU, manufactured under CGMP standards, meets the FDA definition of safety in that there is "reasonable certainty of no harm under the intended conditions of use" as described herein, and that OraPharm's *W. cibaria* CMU is generally recognized as safe (GRAS).

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that OraPharm's *W. cibaria* CMU, when used as described in this dossier, is GRAS based on scientific procedures.

[Signatures on the following page]

[redacted]

Margitta Dziwenka, DVM, DABT
Chair

[redacted]

Robert Martin, PhD

[redacted]

Michael Falk, PhD

END

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

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

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
001063	May 24, 2022
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration,5001 Campus Drive, College Park, MD 20740-3835.

SECTION A – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3 Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd)*: _____

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

SECTION B – INFORMATION ABOUT THE NOTIFIER

1a. Notifier

Name of Contact Person	Position or Title
Yoon Eun-Sup	CEO

Organization *(if applicable)*: OraPharm, Inc.

Mailing Address *(number and street)*: 905 ho, Bluestone Tower, 9-16, Yeonmujang 5-gil

City	State or Province	Zip Code/Postal Code	Country
Seoul	Seongdong-gu		Republic of Korea

Telephone Number	Fax Number	E-Mail Address
+82-2-2138-2572	+82-2-2054-0154	ora2014@orapharm.com

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

Name of Contact Person	Position or Title
William Rowe	President

Organization *(if applicable)*: GRAS Associates, LLC

Mailing Address *(number and street)*: 11810 Grand Park Avenue Suite 500

City	State or Province	Zip Code/Postal Code	Country
North Bethesda	Maryland	20852	United States of America

Telephone Number	Fax Number	E-Mail Address
519-341-3660	1-888-531-3466	wrowe@nutrasource.ca

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

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

Weisella cibaria Strain CMU

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

_____

3. For paper submissions only:

Number of volumes _____

Total number of pages _____

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) and 170.250(d) and (e))

☐ 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.

OraPharm, Inc. intends to use *W. cibaria* CMU as a food ingredient in selected conventional foods including yogurt, frozen desserts (dairy, ices, sorbets and sherbets) and mixes, hard candy and chewing gum at use levels to provide 1×10^8 CFU per serving throughout the shelf life of the product (with initial addition levels of 2×10^8 CFU to 8×10^9 CFU per serving depending on the specific product).

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 Yoon Eun-Sup
(name of notifier)

has concluded that the intended use*(s)* of Weisella cibaria Strain CMU
(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. Yoon Eun-Sup *(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.

905 ho, Bluestone Tower, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea
(address of notifier or other location)

The notifying party certifies that this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, pertinent to the evaluation of the safety and GRAS status of the use of the substance.The notifying party certifies that the information provided herein is accurate and complete to the best or his/her knowledge. Any knowing and willful misinterpretation is subject to criminal penalty pursuant to 18 U.S.C. 1001.

3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
Amy Mozingo Digitally signed by Amy Mozingo Date: 2022.03.15 09:53:20 -04'00'	Amy Mozingo on behalf of William J. Rowe, President	03/14/2022

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)
	Appendices 1-11 in the body of the dossier.	

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. (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.