GRAS Notice (GRN) No. 1063 https://www.fda.gov/food/generally-recognized-safe-gras/gras-notice-inventory



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  $1 \times 10^8$  CFU per serving throughout the shelf life of the product (with initial addition levels of  $2 \times 10^8$  CFU to  $8 \times 10^9$  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,



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

FOREW	ORD 4	
PART 1.	SIGNED STATEMENTS AND CERTIFICATION	4
A.	Claim of Exemption from the Requirement for Premarket Approval Pursuant to 21 CFR 170.30	4
PART 2	IDENTITY METHOD OF MANUFACTURE SPECIFICATIONS AND PHYSICAL OR TECHNICAL FEFECT	7
Α	Notified Substance Weissella cibaria CMU Identification	
7.	1 Common or Usual Name	7
	2 Historical Information on Weissella cibaria	7
	3 Characterization of <i>Weissella cibaria</i> CMU	7
	a Genomic Characterization	9
	b 16S rRNA Alignment	10
	c Average Nucleotide Identity (ANI)	11
	d Phenotypic Characterization	16
	e. Strain Specific Identification	
B.	Manufacturing Processes	20
2.	1. Raw Materials	23
C.	Product Specifications	
D.	Physical or Technical Effect	
E.	Stability Data	
		26
	DIETART EXPOSORE	<b>20</b> 26
A. R	Estimated Dietany Intake (EDI)	20 26
D. C	Estimated Dietary Exposure to Any Other Substance That is Expected to be Formed In or On Food	20 ۵۱
С. П	Diatary Exposure to Contaminants or Byproducts	
PART 4.	SELF-LIMITING LEVELS OF USE	
PART 5.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958	30
PART 5. PART 6.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958	30 30
PART 5. PART 6. A.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958 NARRATIVE	
PART 5. PART 6. A.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958     NARRATIVE     History of Safe Consumption and Other Information On Dietary Exposure     U.S. Regulatory History	
PART 5. PART 6. A.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1.       U.S. Regulatory History         a.       GRAS Status	
PART 5. PART 6. A.	<ul> <li>EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958</li> <li>NARRATIVE</li></ul>	
PART 5. PART 6. A.	<ul> <li>EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958</li> <li>NARRATIVE</li> <li>History of Safe Consumption and Other Information On Dietary Exposure</li> <li>1. U.S. Regulatory History</li> <li>a. GRAS Status</li> <li>2. European Regulatory</li> <li>3. Korean Regulatory History</li> </ul>	
PART 5. PART 6. A. B.	<ul> <li>EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958</li> <li>NARRATIVE</li></ul>	
PART 5. PART 6. A. B.	<ul> <li>EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958</li> <li>NARRATIVE</li> <li>History of Safe Consumption and Other Information On Dietary Exposure</li> <li>U.S. Regulatory History</li> <li>a. GRAS Status</li> <li>2. European Regulatory</li> <li>3. Korean Regulatory History</li> <li>W. cibaria Strain CMU Safety Evaluation</li> <li>1. Complete Genome Sequencing</li> </ul>	
PART 5. PART 6. A. B.	<ul> <li>EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958</li> <li>NARRATIVE</li> <li>History of Safe Consumption and Other Information On Dietary Exposure</li> <li>U.S. Regulatory History</li> <li>a. GRAS Status</li> <li>2. European Regulatory</li> <li>3. Korean Regulatory History</li> <li>W. cibaria Strain CMU Safety Evaluation</li> <li>1. Complete Genome Sequencing</li> <li>2. Assessment of Antibiotic Resistance</li> </ul>	
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1.       U.S. Regulatory History         a.       GRAS Status         2.       European Regulatory         3.       Korean Regulatory History         W. cibaria Strain CMU Safety Evaluation         1.       Complete Genome Sequencing         2.       Assessment of Antibiotic Resistance         a.       Antibiotic Susceptibility Testing (AST)	30 30 30 32 32 32 32 32 33 35 35 35 35 35 35
PART 5. PART 6. A. B.	<ul> <li>EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958</li> <li>NARRATIVE</li> <li>History of Safe Consumption and Other Information On Dietary Exposure</li> <li>U.S. Regulatory History</li> <li>a. GRAS Status</li> <li>2. European Regulatory</li> <li>3. Korean Regulatory History</li> <li><i>W. cibaria</i> Strain CMU Safety Evaluation</li> <li>1. Complete Genome Sequencing</li> <li>2. Assessment of Antibiotic Resistance</li> <li>a. Antibiotic Susceptibility Testing (AST)</li> <li>b. Genomic Assessment of Antibiotic Resistance Genes</li> </ul>	30 30 30 32 32 32 32 33 35 35 35 35 35 35 35 37
PART 5. PART 6. A. B.	<ul> <li>EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958</li> <li>NARRATIVE</li> <li>History of Safe Consumption and Other Information On Dietary Exposure</li> <li>U.S. Regulatory History</li> <li>a. GRAS Status</li> <li>2. European Regulatory</li> <li>3. Korean Regulatory History</li> <li><i>W. cibaria</i> Strain CMU Safety Evaluation</li> <li>1. Complete Genome Sequencing</li> <li>2. Assessment of Antibiotic Resistance</li> <li>a. Antibiotic Susceptibility Testing (AST)</li> <li>b. Genomic Assessment of Antibiotic Resistance Genes</li> <li>3. Assessment of Antimicrobial and Secondary Metabolites</li> </ul>	
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1.       U.S. Regulatory History         a.       GRAS Status         2.       European Regulatory         3.       Korean Regulatory History         W. cibaria Strain CMU Safety Evaluation         1.       Complete Genome Sequencing         2.       Assessment of Antibiotic Resistance         a.       Antibiotic Susceptibility Testing (AST)         b.       Genomic Assessment of Antibiotic Resistance Genes         3.       Assessment of Antimicrobial and Secondary Metabolites         4.       Assessment of Virulence	30 30 30 32 32 32 32 33 35 35 35 35 35 35 35 35 35 35 35 37 37 38 39
PART 5. PART 6. A. B.	<ul> <li>EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958</li> <li>NARRATIVE</li> <li>History of Safe Consumption and Other Information On Dietary Exposure</li> <li>1. U.S. Regulatory History.</li> <li>a. GRAS Status.</li> <li>2. European Regulatory.</li> <li>3. Korean Regulatory History</li> <li><i>W. cibaria</i> Strain CMU Safety Evaluation.</li> <li>1. Complete Genome Sequencing</li> <li>2. Assessment of Antibiotic Resistance.</li> <li>a. Antibiotic Susceptibility Testing (AST)</li> <li>b. Genomic Assessment of Antibiotic Resistance Genes</li> <li>3. Assessment of Antimicrobial and Secondary Metabolites</li> <li>4. Assessment of Virulence.</li> <li>a. In silico Assessment</li> </ul>	30 30 30 32 32 32 32 33 35 35 35 35 35 35 35 35 35 35 35 35
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1.       U.S. Regulatory History         a.       GRAS Status.         2.       European Regulatory.         3.       Korean Regulatory History         W. cibaria Strain CMU Safety Evaluation	30 30 32 32 32 32 32 33 35 35 35 35 35 35 35 35 35 35 35 35
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1.       U.S. Regulatory History         a.       GRAS Status.         2.       European Regulatory.         3.       Korean Regulatory History         w. cibaria Strain CMU Safety Evaluation.         1.       Complete Genome Sequencing         2.       Assessment of Antibiotic Resistance.         a.       Antibiotic Susceptibility Testing (AST)         b.       Genomic Assessment of Antibiotic Resistance Genes         3.       Assessment of Antibiotic Resistance Genes         3.       Assessment of Virulence         a.       In silico Assessment         b.       Cytotoxicity Assay.         5.       Biogenic Amine Production	
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1.       U.S. Regulatory History         a.       GRAS Status         2.       European Regulatory.         3.       Korean Regulatory History         W. cibaria Strain CMU Safety Evaluation       W. cibaria Strain CMU Safety Evaluation         1.       Complete Genome Sequencing         2.       Assessment of Antibiotic Resistance         a.       Antibiotic Susceptibility Testing (AST)         b.       Genomic Assessment of Antibiotic Resistance Genes         3.       Assessment of Antimicrobial and Secondary Metabolites         4.       Assessment of Virulence         a.       In silico Assessment         b.       Cytotxicity Assay         5.       Biogenic Amine Production         6.       Additional Safety Aspects Assessed	30 30 30 32 32 32 32 33 35 35 35 35 35 35 35 35 35 35 35 35
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1.       U.S. Regulatory History         a.       GRAS Status         2.       European Regulatory         3.       Korean Regulatory History         w. cibaria Strain CMU Safety Evaluation	30 30 30 32 32 32 32 33 35 35 35 35 35 35 35 35 35 35 35 35
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1. U.S. Regulatory History.         a. GRAS Status.         2. European Regulatory.         3. Korean Regulatory History.         w. cibaria Strain CMU Safety Evaluation.         1. Complete Genome Sequencing         2. Assessment of Antibiotic Resistance.         a. Antibiotic Susceptibility Testing (AST)         b. Genomic Assessment of Antibiotic Resistance Genes         3. Assessment of Antimicrobial and Secondary Metabolites.         4. Assessment of Virulence.         a. In silico Assessment         b. Cytotoxicity Assay.         5. Biogenic Amine Production         6. Additional Safety Aspects Assessed         7. Absorption, Distribution, Metabolism & Excretion (ADME) Studies         8. Genetic Toxicity Studies	30 30 30 32 32 32 32 33 35 35 35 35 35 35 35 35 35 35 35 35
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1. U.S. Regulatory History.         a. GRAS Status         2. European Regulatory         3. Korean Regulatory History         W. cibaria Strain CMU Safety Evaluation         1. Complete Genome Sequencing         2. Assessment of Antibiotic Resistance.         a. Antibiotic Susceptibility Testing (AST)         b. Genomic Assessment of Antibiotic Resistance Genes         3. Assessment of Antibiotic Resistance Genes         3. Assessment of Virulence         a. In silico Assessment         b. Cytotoxicity Assay         5. Biogenic Amine Production         6. Additional Safety Aspects Assessed         7. Absorption, Distribution, Metabolism & Excretion (ADME) Studies         8. Genetic Toxicity Studies         9. Toxicology Data	30 30 30 32 32 32 32 33 35 35 35 35 35 35 35 35 35 35 35 35
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1.       U.S. Regulatory History         a.       GRAS Status         2.       European Regulatory         3.       Korean Regulatory History <i>W. cibaria</i> Strain CMU Safety Evaluation	30         30         30         32         32         32         32         32         32         32         32         32         32         32         32         32         32         32         32         33         35         35         35         35         35         35         35         35         35         35         35         35         35         37         38         39         39         41         42         42         43         43         43         43          43
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1. U.S. Regulatory History         a. GRAS Status.         European Regulatory         3. Korean Regulatory History <i>W. cibaria</i> Strain CMU Safety Evaluation         1. Complete Genome Sequencing         2. Assessment of Antibiotic Resistance.         a. Antibiotic Susceptibility Testing (AST)         b. Genomic Assessment of Antibiotic Resistance Genes         3. Assessment of Antimicrobial and Secondary Metabolites         4. Assessment of Virulence.         a. In silico Assessment         b. Cytotoxicity Assay         5. Biogenic Amine Production         6. Additional Safety Aspects Assessed         7. Absorption, Distribution, Metabolism & Excretion (ADME) Studies         8. Genetic Toxicity Studies         9. Toxicology Data         a. In vivo Toxicity Studies         10. Clinical Safety Data	30         30         30         32         32         32         32         32         32         32         32         32         32         32         32         32         32         32         32         33         35         35         35         35         35         35         35         35         35         35         35         36         37         38         39         39         41         42         42         42         43         43         43         43         43         43         43         43          46
PART 5. PART 6. A. B.	EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958         NARRATIVE         History of Safe Consumption and Other Information On Dietary Exposure         1. U.S. Regulatory History         a. GRAS Status.         Consumption and Other Information On Dietary Exposure         1. U.S. Regulatory History         a. GRAS Status.         2. European Regulatory History <i>W. cibaria</i> Strain CMU Safety Evaluation         1. Complete Genome Sequencing         2. Assessment of Antibiotic Resistance.         a. Antibiotic Susceptibility Testing (AST)         b. Genomic Assessment of Antibiotic Resistance Genes         3. Assessment of Antimicrobial and Secondary Metabolites         4. Assessment of Virulence.         a. In silico Assessment         b. Cytotoxicity Assay         5. Biogenic Amine Production         6. Additional Safety Aspects Assessed         7. Absorption, Distribution, Metabolism & Excretion (ADME) Studies         8. Genetic Toxicity Studies         9. Toxicology Data         a. In vivo Toxicity Studies         10. Clinical Safety Data         Safety Decision Tree	30         30         30         32         32         32         32         32         32         32         32         32         32         32         32         32         32         32         33         35         35         35         35         35         35         35         35         35         35         35         35         36         37         38         39         39         41         42         42         42         43         43         43         43         43         43         43         46         48           48          48

E. Ex	pert Panel Findings on Safety of OraPharm's Weissella cibaria	
F. Co	mmon Knowledge Elements for GRAS Conclusions	
1. P	ublic Availability of Scientific Information	
2. S	cientific Consensus	52
G. Dis	scussion of Information Inconsistent with GRAS Conclusion	54
H. Co	nclusion	55
PART 7. LIST	OF SUPPORTING DATA AND INFORMATION IN THE GRAS NOTICE.	55
A. Re	ferences	55
B. Ap	pendices	60
APPENDIX 1	NCBI GENOMIC CHARACTERIZATION DATA	61
APPENDIX 2	MACROGEN 16S REPORTS AND CERTIFICATES OF ANALYSIS FOR MULTIPLE LOTS	64
APPENDIX 3	AVERAGE NUCLEOTIDE IDENTITY AND STRAIN SPECIFIC PCR RESULTS	103
APPENDIX 4	MANUFACTURING DOCUMENTATION	121
APPENDIX 5	REPRESENTATIVE ALLERGEN TESTING REPORTS	122
APPENDIX 6	REPRESENTATIVE PESTICIDE TESTING REPORTS	129
APPENDIX 7	INTAKE ANALYSIS – FOOD CODES	136
APPENDIX 8	EFFECTS OF W. CIBARIA CMU ON THE GROWTH OF LACTOBACILLI OVER TIME	139
APPENDIX 9	CENTER FOR GENOMIC EPIDEMIOLOGY – VIRULENCEFINDER 2.0 RESULTS	140
APPENDIX 10	BIOGENIC AMINE ANALYSIS	141
APPENDIX 11	GRAS ASSOCIATES EXPERT PANEL REPORT	148

# FIGURES

Figure 1. Cell Morphology of W. cibaria CMU <sup>a</sup>	8
Figure 2. Representative Image Showing Phylogenetic Homology of Strain CMU to <i>W. cibaria</i> Reference Strains JCM 12495	
(LC096236) and II-I-5 (NR_036924)	11
Figure 3. Manufacturing Process Flow Chart	22
Figure 4. Stability Data of W. cibaria CMU Lyophilized Commercial Product Stored in Various Conditions for 48 weeks	26

# TABLES

Table 1. Taxonomy of W. cibaria CMU	8
Table 2. Genome Comparison of W. cibaria strains	9
Table 3. 16S rRNA Alignment Data of Strain CMU to W. cibaria by Lot Number	10
Table 4. OrthoANIu Results by Genome	12
Table 5. ANIb Summary Results by Genome	14
Table 6. ANIm Summary Results by Genome	14
Table 7. Tetra-Nucleotide Signature Correlation Index Summary Results by Genome	15
Table 8. ANI Calculator Summary Results by Genome	15
Table 9. API ZYM Enzymatic Activity Profile of Weissella cibaria CMU <sup>1</sup>	17
Table 10. API 50 Carbohydrate Fermentation Profile of Weissella cibaria CMU	
Table 11. Ingredients Used in the Manufacturing Process	23
Table 12. Food Grade Specifications for W. cibaria CMU	24
Table 13. Analytical Results for <i>W. cibaria</i> CMU	24
Table 14. Daily Intake of Yogurt (2017-2018 NHANES)	
Table 15. Daily Intake of Frozen Desserts (2017-2018 NHANES)	
Table 16. Daily Intake of Hard Candy and Chewing Gum	

Table 17. Estimated Daily Intake of <i>W. cibaria</i> CMU	29
Table 18. Summary of FDA GRAS Inventory <sup>1</sup>	32
Table 19. Comparison of the Intended Daily Intake of W. cibaria CMU and the Daily Intake of the W. cibaria CMU in Korean	
Products	33
Table 20. Distribution and Sales Status of Products Containing W. cibaria CMU as Available in South Korea	34
Table 21. Minimum Inhibitory Concentrations of Antibiotics for <i>W. cibaria</i> CMU	36
Table 22. Virulence gene analysis of <i>W. cibaria</i> CMU	40
Table 23. Toxin Evaluation of Diarrheal and Emetic Type Food Poisoning	41
Table 24. Genetic Toxicity of <i>W. cibaria</i> CMU	43
Table 25. Results of W. cibaria CMU studies in humans	46
Table 26. Safety Decision Tree	49

# 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.

GRAS Notice – *Weissella cibaria* OraPharm

#### 3/11/2022

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.

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

# Table 1. Taxonomy of W. cibaria 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  $0.5-0.7 \mu m$  wide and  $1.3-2.5 \mu m$  long.



# Figure 1. Cell Morphology of W. cibaria CMU<sup>a</sup>

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

<sup>a</sup>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<sup>1</sup> 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).

	Assembly Level	Contigs	Total Length (Mb)	GC%	Protein Count	rRNA	tRNA	Other RNA	Gene	Pseudogene
<i>W. cibaria</i> median values (n=51 genome assemblies) <sup>a</sup>	N/A	N/A	2.45564	<mark>44.</mark> 9	2200	N/A	N/A	N/A	N/A	N/A
<i>W. cibaria</i> BC14 <sup>⊾</sup>	Contig	3	2.51323	44.9	2242	28	88	3	2386	25
W. cibaria 12495 °	Contig	25	2.32395	<mark>45.1</mark>	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 <sup>e</sup>	Complete	2	2.36349	45.239	2080	28	88	3	2221	22

# Table 2. Genome Comparison of W. cibaria strains

<sup>&</sup>lt;sup>1</sup> See <u>https://patents.google.com/patent/US7250162B2/en</u>. 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		A.	-	23	1
W. cibaria CMU <sup>f</sup>	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	8	255.5	<del>70</del> 8	22	1

<sup>a</sup> Available at: <u>https://www.ncbi.nlm.nih.gov/genome/3287</u>. Accessed Aug 26, 2021.

<sup>b</sup> W. cibaria BC14. NCBI species reference. Available at: https://www.ncbi.nlm.nih.gov/genome/3287?genome\_assembly\_id=648503. Accessed Aug 26, 2021.

<sup>c</sup> W. cibaria 12495. Species reference. Available at: https://www.ncbi.nlm.nih.gov/genome/3287?genome\_assembly\_id=524481. Accessed Aug 26, 2021.

https://www.ncbi.nlm.nih.gov/genome/3287?genome\_assembly\_id=301995. Accessed Aug 26, 2021.

<sup>f</sup> W. cibaria CMU. Values in this row include both the chromosome and plasmid. Available at: <u>https://www.ncbi.nlm.nih.gov/genome/3287?genome\_assembly\_id=418159</u>. 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*.

able 3. 16S rRNA Alig	gnment Data of Strain CM	MU to W. cibaria by	Lot Number
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		S	Score		Identities					
Sample <sup>a</sup>	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	<mark>151</mark> 6	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

<sup>&</sup>lt;sup>d</sup> 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: <a href="https://www.ncbi.nlm.nih.gov/genome/3287?genome\_assembly\_id=278405">https://www.ncbi.nlm.nih.gov/genome/3287?genome\_assembly\_id=278405</a>. 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:

		Score		Identities						
Sample <sup>a</sup>	Accession	Description	Length	Start	End	Coverage	Bit	E- Value	Match / Total	Pct (%)
Lot_Cl11- 0117N_contig_1	LC096236.1	Weissella cibaria	1516	6	1516	<mark>9</mark> 9	2787	0.0	1510/1511	99
Lot CI11- 0362N_contig_1	LC096236.1	Weissella cibaria	<mark>1516</mark>	4	1513	99	2780	0.0	<mark>1509/1511</mark>	99
Lot CI11- 0366N_contig_1	LC096236.1	Weissella cibaria	1516	6	1514	99	2776	0.0	1507/1509	99

<sup>a</sup> 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<sup>2</sup> (Yoon et al., 2017; Lee et al., 2016)
  - o Online calculator that uses the OrthoANIu algorithm, with USEARCH instead of BLAST

<sup>&</sup>lt;sup>2</sup> See: <u>https://www.ezbiocloud.net/tools/ani</u> (Accessed Nov. 24, 2021)

- JSpeciesWS<sup>3</sup> (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<sup>4</sup> (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.

#### OrthoANlu

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*.

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 (%)
<i>W. cibaria</i> CMU.fasta	W. cibaria CMS1.fasta	99.90	2,362,320	2,341,920	1,266,485	53.61	54.08
<i>W. cibaria</i> CMU.fasta	W. cibaria CMS2.fasta	99.93	2,362,320	2,341,920	1,531,922	64.85	65.41

#### Table 4. OrthoANIu Results by Genome

<sup>&</sup>lt;sup>3</sup> See: <u>http://ispecies.ribohost.com/ispeciesws/</u> (Accessed Nov. 24, 2021)

<sup>&</sup>lt;sup>4</sup> See: http://enve-omics.ce.gatech.edu/ani/ (Accessed Nov. 24, 2021)

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3/11/2022

Genome Sequence A	Genome Sequence B	OrthoANlu 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
<i>W. cibaria</i> CMU.fasta	W. cibaria JCM 12495.fasta	99.94	2,362,320	405,960	270,773	11.46	66.70
W. cibaria CMU.fasta	<i>W. cibaria</i> BC14.fasta	98.45	2,362,320	2,472,480	1,644,774	69.63	66.52
<mark>W. cibaria</mark> CMU.fasta	<i>W. cibaria</i> CH2.fasta	96.90	2,362,320	2, <mark>4</mark> 66, 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
<i>W. cibaria</i> 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	1,683,0 <mark>0</mark> 0	480,099	20.32	28.53
<i>W. cibaria</i> 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.

Genome Sequence A	Genome Sequence B	ANIb (%)	Aligned (%)	Aligned (bp)	Total (bp)
W. cibaria CMU.fasta	W. cibaria CMS1.fasta	99.99	99.9 <mark>1</mark>	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	9 <mark>1</mark> .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
<i>W. cibaria</i> CMU.fasta	W. paramesenteroides FDAARGOS 414.fasta	72.22	43.07	1,017,454	2,362,501

# Table 5. ANIb Summary Results by Genome

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
		(70)	(70)	(70)	(70)
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 hi	ts 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*.

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	855	8	5	53	2	Ę.	157	58	9420	æ	859	5
Esterase (C4)	1941	×	3	-	ц.	ц	1.00	ं	+(3)	ē.	()#)(	+(3)
Esterase lipase (C8)	625	2	2	2	5		825	22	9 <u>4</u> 9	2	821	2
Lipase (C14)	( <b>.</b> =.)	×			r.	×			. <del></del> ?	9	( <b>.</b>	
Leucine arylamidase	124	2	14	2	2		+(3)	12	+(4)	4	122	12
Valine arylamidase	1572	5	-	-	-				-		1972	
Cystine arylamidase	1224	2	14	2	4	31		- 22	12	4	124	2
Trypsin	1275	2	12	5	-	ā	127	1.52	175	2	14 <b>7</b> 3	
α-chymotrypsin	(2 <b>2</b> )	2	2	-	2	2	(24)	- 2	120		(22)	
Acid phosphatase	+(3)	+(3)	+(3)	4	+(5)	R	15	+(3)	10 10	2	1	
Naphthol-AS-BI- phosphohydrolase	+(3)	+(3)	+(3)	3	+(3)	+(3)	+(4)	+(3)		+(3)	+(3)	+(4)
α-galactosidase	1243	2	4		2	2	122		+(3)	-	32	12
β-galactosidase	18 <b>7</b> 7	5	10	6	5		155	+(3)	+(5)	2	1070	
β-glucuronidase	() <del>-</del> (	×	-	e.	r.	Ţ	( <b>4</b> )		345	e.	(1 <b>4</b> )	×
α-glucosidase	8579	5	5	2	5	+(3)	857	100	+(5)		859	+(5)
β-glucosidase	5 <b>.</b>	×			-			+(5)				×
N-acetyl-β- glucosaminidase	124	2	14	2	2	а		- 25	101	-	ġ.	-
α-mannosidase	8359	8	2	18	5		:570	52	9 <b>4</b> 20	2	850	5
α-fucosidase	20 <b>4</b> 0	×	-	-	-	L.	( <b>-</b> )		1945	æ	(1 <b>4</b> )	-

# Table 9. API ZYM Enzymatic Activity Profile of Weissella cibaria CMU<sup>1</sup>

<sup>1</sup> 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,  $\beta$ -methyl-D-xyloside (Methyl- $\beta$ D-Xylopyranoside), D-galactose, L-sorbose, L-rhamnose, dulcitol, inositol, D-mannitol, D-sorbitol,  $\alpha$ -methyl-D-mannose mannoside (Methyl- $\alpha$ D-

Mannopyranoside), α-methyl-D-glucoside (Methyl-αD-Glucopyranoside), arbutin, D-lactose, Dmelibiose, D-trehalose, inulin, D-melezitose, D-raffinose, amidon, glycogen, xylitol, D-turanose, Dlyxose, D-tagatose, D-fucose, L-fucose, D-arabitol, L-arabitol, potassium gluconate, potassium 2ketogluconate 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 Dgalactose). 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*.

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	-	19 <b>1</b> 1	-	<u>e</u> i	-	NR	NR	NR	NR
Erythritol	. <del></del>	1071	1.2	<b>5</b> 1	2 <b>7</b> 2	NR	NR	NR	NR
D-arabinose		-	-	-1		+ (D,L not specified)	- (D,L not specified)	NR	NR
L-arabinose	+	+	+	+	*	+ (D,L not specified)	- (D,L not specified)	+	17
D-ribose	-	-	-	-1	+	- (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	20		12	÷	<u>12</u> 8	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)	+ (D,L not specified)
D-adonitol	125	1.00			: <del>.</del>	NR	NR	NR	NR
Methyl-βD- Xylopyranoside	-	-	-	-	-	NR	NR	NR	NR
D-galactose	-	-	-	5	÷	- (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		2. 2.	-	- 1		NR	NR	NR	NR

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

## GRAS Notice – *Weissella cibaria* OraPharm

3/11/2022

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		( <b>-</b> )	-	<u>-  </u>		NR	NR	NR	NR
Dulcitol	×.		Ð	1 1 1 1	9	NR	NR	NR	NR
Inositol	-	( <del>=</del> )	-	- 1		NR	NR	NR	NR
D-mannitol	20	-21	12	÷ I	-	NR	NR	- (D,L not specified)	ND
D-sorbitol	170 170	1.71		<del>,</del>	1 <b>7</b> 9	NR	NR	NR	NR
Methyl-αD- Mannopyranoside	-	7-1	-	41		NR	NR	NR	NR
Methyl-αD- Glucopyranoside		s <b>-</b> 0	-	- 1		NR	NR	NR	NR
N-Acetylglucosamine	+	+	+	+	+	NR	NR	NR	NR
Amygdalin	+	+	+	+	+	NR	NR	+	ND
Arbutin	-	-	-	<del>2</del>	<u>19</u> 0	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)	<u>1</u> 26	0 <b>2</b> 3	_	-	<u>1</u> 21	NR	NR	2	ND
D-melibiose	×.	181	÷	į.		- (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	-	2. 2. <b>.</b>	-	-1	.=:	- (D,L not specified)	- (D,L not specified)	- (D,L not specified)	- (D,L not specified)
Inulin	-	1. <del></del>		- 1		NR	NR	NR	NR
D-Melezitose	۶.		÷	2	9	NR	NR	NR	NR
D-Raffinose		् ध्र <del>त्र</del> ा	-	L.	. <del></del>	- (D,L not specified)	- (D,L not specified)	- (D,L not specified)	- (D,L not specified)
Amidon(starch)	-		-	- 1		NR	NR	NR	NR
Glycogen	×.		÷	ž.	۲	NR	NR	NR	NR
Xylitol		( <del></del> )	-	- 1		NR	NR	NR	NR

#### GRAS Notice – *Weissella cibaria* OraPharm

#### 3/11/2022

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	-	) <del></del>	÷	÷	•	NR	NR	NR	NR
D-Lyxose	-	0 <b>.</b> =0	-	- 1		NR	NR	NR	NR
D-Tagatose	١.	3 <del>3</del> 3	Ξ	× I	•	NR	NR	NR	NR
D-Fucose	-	0 <b>.</b> =0	-	L		NR	NR	NR	NR
L-Fucose	<u>.</u>	3 <del>3</del> 3	÷	1 1 1	•	NR	NR	NR	NR
D-Arabitol	350	2.50)	-		170	NR	NR	NR	NR
L-Arabitol	3 <u>≌</u> e	6 <u>4</u> 7	12	÷ I	245	NR	NR	NR	NR
Potassium Gluconate	353			E.	152	NR	NR	NR	NR
Potassium 2- Keto <mark>Gluconate</mark>		1 <b>-</b> 1	-	Ξì	r <b>a</b> e	NR	NR	NR	NR
Potassium 5- KetoGluconate	-	-	-	21	124	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°C 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.

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Figure 3. Manufacturing Process Flow Chart

\* Media : Raw materials for fermentation of probiotics

\* The used ingredients are suitable for food standard in Korea

#### 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.

Component	Purpose			
Dextrose monohydrate	Fermentation Media Ingredient			
K <sub>2</sub> HPO <sub>4</sub>	Fermentation Media Ingredient			
MnSO <sub>4</sub>	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 <sub>2</sub> PO <sub>4</sub>	Cryoprotectant Ingredient			
Skim milk	Cryoprotectant Ingredient			
Processed Starch	Excipient			
(88% potato starch + 12% maltodextrin)				

# Table 11. Ingredients Used in the Manufacturing Process

#### **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<sup>5</sup>; however, milk was detected in all three samples (Method Detection Limit = 1 ng/ $\mu$ L). 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 βhexachlorocyclohexane (BHC), Dichlorodiphenyltrichloroethane (DDT), aldrin, dieldrin, and endrin. As shown in Appendix 6, no pesticides were detected in the production samples. There is no reason

<sup>&</sup>lt;sup>5</sup> 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.

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 109	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 Limi	its		
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)		

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

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	<b>Results for</b>	W.	cibaria	CMU
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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	NLT 1.0 x 10 <sup>9</sup>	KHFSC 4/3/3-57	1.2 x 1011	1.5 x 10 <sup>11</sup>	1.5 x 10 <sup>11</sup>	1.5 x 10 <sup>11</sup>	1.1 x 10 <sup>11</sup>
(CFU/g)		(ISO 27205:2010)	CFU/g	CFU/g	CFU/g	CFU/g	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	0.6	1.30	1.16	1.29	1.29
201 0120		(AOAC 900.02)					
		Heavy	Metals		No.		N.:
Lead (mg/kg)	NMT 1.0	KHFSC 8/9/9.1	0.01	0.01	0.02	0.0107	0.0096
		(AOAC 2013.06)	22250		227 - 2		
Cadmium (mg/kg)	NMT 0.3	KHFSC 8/9/9.1	0.04	0.05	0.04	0.0398	00383
		(AOAC 2013.06)	<i></i>		<i></i>		
Arsenic (mg/kg)	NMT 1.0	KHFSC 8/9/9.1	0.00	0.00	0.01	0.0067	0.0048
		(AOAC 2013.06)					
Mercury (mg/kg)	NMT 0.5	KHFSC 8/9/9.1	ND	ND	ND	0.0016	0.0022
		(AOAC 2013.06)					
		Microbiolog	ical Limits				
Coliforms (CFU/g)	Negative	KHFSC 8/4/4.7	Negative	Negative	Negative	Negative	Negative
		(AOAC 991.14)					
Yeast and Mold	NMT 100	KFSC 7/4/4.10	Negative	Negative	Negative	Negative	Negative
(CFU/g)		(AOAC 2002.11)					
E. coli (per g)	Negative	KFSC 7/4/4.8	Negative	Negative	Negative	Negative	Negative
	2.27	(AOAC 991.14)					
Salmonella	Negative	KFSC 7/4/4.15	Negative	Negative	Negative	Negative	Negative
(CFU/g)	214.5	(AOAC 989.14)	2011 100 11		2010 100 17		
Listeria	Negative	KFSC 7/4/4.15	Negative	Negative	Negative	Negative	Negative
monocytogenes (CFU/g)		(AOAC 998.08)					
S. aureus (per g)	Negative	KFSC 7/4/4.21	Negative	Negative	Negative	Negative	Negative
John State		(AOAC 975.55)	9-2-4-4 		952.97		0.000

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.





# 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  $1.0 \times 10^8$  CFU. OraPharm considers that the initial addition level of *W. cibaria* CMU in the products may be as high as  $8.0 \times 10^9$  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  $5.0 \times 10^8$  CFU and  $2.0 \times 10^8$  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.

f		Grams per Day Intake			Grams/kg bw/Day	
Age Group	Gender	Mean	90 <sup>th</sup> Percentile	N	Mean	90 <sup>th</sup> Percentile
Infants	Male	53.90*	137.49*	20	5.96*	<mark>13.95</mark> *
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	<b>1.44</b> *	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

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

\*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 90<sup>th</sup> 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. Dail	y Intake of Frozen I	Desserts (201	7-2018 NHANES)
		요즘 것이야 한 문어야 할 때 이 집에 집에 가지 않는 것이 없다.	

		Grams pe	r Day Intake		Grams/kg bw	/Day
Age Group	Gender	Mean	90 <sup>th</sup> Percentile	N	Mean	90 <sup>th</sup> 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

		Grams pe	er Day Intake		Grams/kg bw	/Day
Age Group	Gender	Mean	90 <sup>th</sup> Percentile	N	Mean	90 <sup>th</sup> 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	<mark>159.9</mark> 6	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 90<sup>th</sup> percentile.

Table 16. Daily Intake of Hard Candy and Chewing Gum

		Grams pe	r Day Intake		Grams/kg bw	/Day
Age Group	Gender	Mean	90 <sup>th</sup> Percentile	N	Mean	90 <sup>th</sup> 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	0.9 <mark>9</mark> *
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 90<sup>th</sup> 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.

Population	Intake	(mg/day)	Intake (mg/kg bw/day)		
	Mean	90th Percentile	Mean	90 <sup>th</sup> 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	

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

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 90<sup>th</sup> 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/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 90<sup>th</sup> percentile intake is 397 mg/day. Using the specification of not less than  $1 \times 10^9$  CFU per gram, the EDI in terms of CFU per day is  $3.97 \times 10^8$ . On a body weight basis, intake is 6.24 mg/kg bw/day, or  $6.24 \times 10^6$  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  $2.65 \times 10^7$  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<sup>6</sup>. 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.

LAB Counts W. cibaria

CFU/g	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

<sup>&</sup>lt;sup>6</sup> Calculated as follows (authors also reported as log CFU/g which is not included in this table):

## 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<sup>7</sup> 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<sup>1</sup>

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 <sup>9</sup> CFU/g of bacon	Chr. Hansen, Inc. FDA GRN 936 (2021)

<sup>1</sup> 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<sup>8</sup> (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** 

<sup>&</sup>lt;sup>7</sup> GRAS inventory available online at: <u>https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices</u>. GRN database search performed Jan. 04, 2022.

<sup>&</sup>lt;sup>8</sup> See: <u>https://zenodo.org/record/4498901#.YLEm0KhKj3Q</u>. 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  $\Box$  006800<sup>9</sup> 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<sup>10</sup>.

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 <sup>8</sup>	1.0 x 10 <sup>9</sup>	1.2 x 10 <sup>10</sup> / 3 tablets	2.4 x 10 <sup>10</sup> / 3 tablets			

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<sup>&</sup>lt;sup>9</sup> See <u>http://www.foodsafetykorea.go.kr/foodcode/01\_03.jsp?idx=12135</u>. Accessed February 22,2022.

<sup>&</sup>lt;sup>10</sup> See <u>https://www.foodsafetykorea.go.kr/portal/safefoodlife/foodMeterial/foodMeterialDB.do</u>. 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	<i>W. cibaria</i> 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 x 101º CFU/ 3 tablets/day
Conventional Foods	Sugar processed products	Ergen Com	Ora Denti	120 mg	1~3 tablets per day (1000 mg~3000 mg per day)	1.2 x 10 <sup>16</sup> 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 x 10º CFU/ 1 sachet/day
Conventional Foods	Other processed products	V.	Dental Care Biotics	80 mg	1 sachet per day (2000 mg per day)	1.0 x 10 <sup>9</sup> CFU/ 1 sachet/day
Conventional Foods	Sugar processed products	中市	Gigeunuk Bifidus Denti Fresh	64 mg	1 tablet per day (800 mg per day)	6.4 x 10 <sup>6</sup> 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 x 10 <sup>8</sup> 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 x 10 <sup>s</sup> CFU/ 1 tablet/day
Conventional Foods	Other processed products	5	Lactic acid bacteria in the Mouth 365	64 mg	1 tablet per day (800 mg per day)	6.4 x 10 <sup>8</sup> CFU/ 1 tablet/day

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#### 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.

	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 <sup>1</sup>	0.5	>256	16	128	64	0.03	0.03	8	4	32	8	16	2	2
W. cibaria CMS1 <sup>1</sup>	0.5	>256	4	32	16	0.03	0.03	4	4	16	4	8	2	1
W. cibaria CMS2 <sup>2</sup>	0.5	>256	4	32	16	0.03	0.03	4	4	8	4	8	2	1
W. cibaria CMS3 <sup>2</sup>	0.5	>256	4	64	16	0.06	0.03	4	4	16	4	16	2	1
L. <mark>reuteri</mark> Lr <sup>3</sup>	0.5	256	8	128	32	0.25	0.03	4	4	8	4	8	4	2
L. salivarius Ls <sup>4</sup>	0.5	>256	8	128	32	0.03	0.03	1	2	2	0.5	0.5	1	0.5
L. rhamnosus GG <sup>5</sup>	1	>256	8	32	8	0.03	0.03	0.25	1	256	0.1	0.1	0.25	0.5
E. faecalis ATCC 292126	1	2	256	256	>256	2	16	32	4	4	8	2	1	2

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

#### GRAS Notice – *Weissella cibaria* OraPharm

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	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 µ	ıg/mL						2
	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.	Max.
W. cibaria CM1 <sup>7</sup>	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM6 <sup>7</sup>	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM10 <sup>7</sup>	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	<mark>S (≤8)</mark>	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM18 <sup>7</sup>	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM34 <sup>7</sup>	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM23 <sup>7</sup>	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM32 <sup>7</sup>	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	<mark>S (≤4</mark> )	ND	ND	ND	ND	ND
W. cibaria CM9 <sup>7</sup>	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM19 <sup>7</sup>	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
W. cibaria CM27 <sup>7</sup>	S (≤4)	ND	R (>16)	R (>64)	R (>64)	ND	ND	S (≤8)	S (≤4)	ND	ND	ND	ND	ND
<i>Lactobacillus</i> Obligate Heterofermentative <sup>8</sup>	2	NR	16	<mark>32 (64</mark> )	<mark>64</mark>	1	1 (4)	8	4	ND	ND	ND	(NR)	ND
Leuconostoc <sup>8</sup>	2	NR	16	16	64	1	1	8	4	ND	ND	ND	(NR)	ND
L. reuteri <sup>®</sup>	2	NR	8	64	64	1	1 (4)	16 (32)	4	ND	ND	ND	(NR)	ND
Lactobacillus facultative heterofermentative (L. salivarius) <sup>8</sup>	4	NR	16	64	64	1	<mark>1 (4)</mark>	8	4	ND	ND	ND	(NR)	ND
L. rhamnosus <sup>8</sup>	4	NR	16	64	32	1	1 (4)	8	4	ND	ND	ND	(NR)	ND
Enterococcus <sup>8</sup>	2	4	32	1024	128	4	4	4	16	ND	ND	ND	(NR)	ND

<sup>1</sup> As reported by Kang et al. (2019)

<sup>2</sup> As reported by OraPharm

<sup>3</sup> As reported by Kang et al. (2019): L. reuteri isolated from a commercial product (Sweden)

<sup>4</sup> As reported by Kang et al. (2019): L. salivarius isolated from a commercial product (Japan)

<sup>5</sup> As reported by Kang et al. (2019): L. rhamnosus GG (KCTC 5033)

<sup>6</sup> As reported by Kang et al. (2019): E. faecalis ATCC 29212

<sup>7</sup> 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)

<sup>8</sup> 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 (<u>http://ardb.cbcb.umd.edu/index.html</u>), and the analysis proceeded without arbitrary adjustment values. CARD BLAST and RGI (<u>https://card.mcmaster.ca/analyze/rgi</u>) were also used for genome-based analysis of ARGs

The ARDB evaluation analyzed 7828 ARGs and used an E value of 1 x 10<sup>-10</sup> 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<sub>2</sub>O<sub>2</sub>) and had an H<sub>2</sub>O<sub>2</sub>-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<sub>2</sub>O<sub>2</sub> 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 *E. coli*, Virulence genes for *S. aureus*, Hostimm genes for *S. aureus*, Virulence genes for *S. aureus*, Virulence genes for *S. aureus*, Toxin genes for *S. aureus*, Hostimm genes for *S. aureus*, Virulence genes

completed using the VirulenceFinder 2.0 Server, a component of the CGE<sup>11</sup> (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*.

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

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

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).

<sup>&</sup>lt;sup>11</sup> See <u>http://www.genomicepidemiology.org/</u>. 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  $\beta$ -hemolytic activity and was found to display no hemolysis in a 5% sheep blood agar assay, indicating that this strain lacks  $\beta$ -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.

Toxin gene	Gene/protein	Accession number	W. cibaria CMU
Hemolysin BL (HBL)	hblC/L2	Accession: AY822584.1	None found
	hblD/L1		None found
	hblA/B	1	None found
Nonhemolytic enterotoxin	nheA/A	Accession: DQ885236.1	None found
(NHE)	nheB/B	7	None found
	nheC/C	1	None found
Cytotoxin (CytK)	CytK/CytK	Accession: KP409163.1	None found
Emetic toxin (Cereulide)	ces/ces	Accession: AY691650.1	None found

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

## 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  $\geq$  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,  $\beta$ -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-5phosphate 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), p-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  $0.8 \times 10^8$  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).

Endpoint	System	Concentrations Tested	Result	Reference
Reverse mutation (OECD 471)	S. typhimurium TA98, TA100, TA1535, TA1537, E. coli WP2uvrA	0, 62, 185, 556, 1667 and 5000 µg/plate ± S9 metabolic activation	Negative	
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	Dolan et al. (2022)
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	

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

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  $4.5 \times 10^8$ ,  $9.0 \times 10^8$ , and  $1.8 \times 10^9$  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 x  $10^9$  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  $4.5 \times 10^8$ ,  $9.0 \times 10^8$ , and  $1.8 \times 10^9$  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 x 10<sup>9</sup> 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  $1 \times 10^9$  CFU/day was tested in mice for 14 days and  $2 \times 10^9$  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.<sup>12</sup> The procedure was repeated every  $1 \pm 0.1$  hr for 4 hr, for a total of 5 applications. At the time of every administration and  $(24 \pm 2)$  hr after administration, cheek pouches were graded for erythema. At  $(24 \pm 2)$  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<sup>8</sup> CFU/g suspended in sterile distilled water. The positive control substance ( $\alpha$ -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  $0.8 \times 10^8 - 1.0 \times 10^9$  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  $0.8 \times 10^8$  CFU/day ( $8 \times 10^7$  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.

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

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

<sup>&</sup>lt;sup>12</sup> 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	No adverse effects on measured	
		did not eat or drink	indices of oral health.	
		afterwards (presumably		
		until morning).		
		Evaluations were obtained		
		prior to eating breakfast		
0.8 x 10 <sup>8</sup>	n = 92 without	Randomized, DB, placebo	14 Dropouts in test article group and	Kang et al. (2021)
CFU/day	periodontitis;	controlled, 8-week	8 dropouts in placebo group.	
<i>W. cibaria</i> strain	34/group analyzed	duration.	Reasons given for dropouts in each	
CMU	Age = 23.6 (±3.4)		group were withdrawn consent,	
(OraPharm)	yrs in placebo	Subjects were instructed	antibiotic use or <80% compliance.	
	group and 23.4	to place powdered test		
	(±2.9) yrs in test	article or placebo in mouth	No adverse effect on caries incidence	
	group*	before bed and swallow	and no increase in acidogenic	
		after melting. Subjects did	potential of plaque in test group.	
		not eat or drink afterwards		
		(presumably until		
		morning).		
		Evaluations were obtained		
		prior to eating breakfast		
1 x 10 <sup>8</sup>	n = 60 with halitosis	Randomized, DB, placebo	1 dropout/group (reason not stated).	Kim et al. (2020a)
CFU/day	and high breath	controlled, 8-week		
<i>W. cibaria</i> strain	VSC	duration.	No adverse effects of test material on	
CMU	concentrations;		indices of halitosis measured.	
(Oradentics	29/group analyzed	Subjects sucked on tablet		
Inc.)	Age = 20-30 yrs	containing the test article		
		or placebo before bed and		
		did not eat or drink		
		alterwards (presumably		
		Unui morning).		
		Evaluations were obtained		
0.9 v 108	n 02 without	Prior to eating preaklast	14 Dropouts in test article group and	$1 \circ \circ \circ t \circ 1$ (2020)
0.0 X 10° CELI/day	noriodontitic:	controlled 9 wook	9 dropouts in test afficie group and	Lee et al. (2020)
W cibaria strain	24/group analyzod	duration	Poasons given for dropouts in each	
	$\Lambda q = 20.30 \text{ yrs}^*$	uuration.	aroun were withdrawn consent	
(OraPharm)	190 - 20-37 yis	Subjects sucked on tablet	antibiotic use or $< 80\%$ compliance	
		containing the test article		
		or placebo before hed and	No adverse effects of test material on	
		did not eat or drink	indices of halitosis measured. No	
		afterwards (presumably	SAF observed, 1 AF per aroup (mild	
			xerostomia in test group and mild	
		Evaluations were obtained	diarrhea in placebo group).	
		prior to eating breakfast	9.00P/	

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

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	Yes.
accepted methodology?	Designation as W. cibaria is supported with WGS, 16S
(If YES, go to 2. If NO, the strain must be characterized and	rRNA analysis, ANI, phenotypic, and RAPD analysis.
unambiguously identified before proceeding).	
2. Has the strain genome been sequenced?	
(If YES, go to 3. If NO, the genome must be sequenced before	Yes.
proceeding to 3.)	
	Yes, there was no evidence of concern identified.
3. Is the strain genome free of genetic elements encoding	No virulence factors identified from genomic evaluations of
virulence factors and/or toxins associated with pathogenicity?	strain CMU based on the CGE and Gapped and PSI
(If YES, go to 4. If NO, go to 15.)	BLASI, as well as <i>in vitro</i> cytotoxicity, biogenic amine,
	and β-hemolysis analyses.
	Yes, there was no evidence of concern identified.
4. Is the strain genome free of functional and transferable antibiotic	Overall MIC results, genomic evaluation of ARGs, and
(If VES, marks 5, If NO, marks 15.)	lack of kanamycin and vancomycin resistance
(II TES, go to 5. II NO, go to 15.)	rial HCT
	No. no ovidence of concern identified
5. Does the strain produce antimicrohial substances?	Strain CMU does not inhibit growth of L acidonhilus L
(If NO go to 6 If YES go to 15)	fermentum and L reuteri in vitro and no safety concerns
(1110, go to 0.11120, go to 10.)	were raised in the animal and human studies
6. Has the strain been genetically modified using rDNA	
techniques?	No. Strain CMU has not been genetically modified.
(If YES, go to 7. If NO, go to 8.)	
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	77×
be safe before proceeding to 8.)	
8 Was the strain isolated from a food that has a history of cafe	No.
consumption for which the species to which the strain belongs	Strain CMU was isolated from human saliva. Strain
is a substantial and characterizing component (not simply an	CMU is in a chewing gum product in Korea and this
'incidental isolate')?	strain has been commercially available in Korea in
(If YES, go to 9, If NO, go to 13.)	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 sate for food use by an authoritative group of qualified	<u> </u>
scientific experts?	
(IT YES, go to 10. If NO, go to 13.)	
10 De sejestifie fondieren sublished sizze soulation of the	
10. Do scientific findings published since completion of the	
10. Do scientific findings published since completion of the comprehensive peer-reviewed safety evaluation cited in question	
<ul> <li>5. Does the strain produce antimicrobial substances? (If NO, go to 6. If YES, go to 15.)</li> <li>6. Has the strain been genetically modified using rDNA techniques? (If YES, go to 7. If NO, go to 8.)</li> <li>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.)</li> <li>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.)</li> <li>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.)</li> </ul>	No, no evidence of concern identified. Strain CMU does not inhibit growth of <i>L. acidophilus, L. fermentum,</i> and <i>L. reuteri in vitro</i> , and no safety concerns were raised in the animal and human studies. No. Strain CMU has not been genetically modified. 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.

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. <b>If NO, go to 14</b> .)	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.
<ul> <li>14. The strain is deemed to be safe for use in the manufacture of food, probiotics, and dietary supplements for human consumption.</li> <li>15. The strain is NOT APPROPRIATE for human or animal consumption.</li> </ul>	Strain CMU meets standards as defined by the Pariza decision tree and is deemed safe for human 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."<sup>13</sup>

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<sup>14</sup>:

<sup>&</sup>lt;sup>13</sup> See 21 CFR 170.3 (e)(i) and 81 FR 54959 Available at: <u>https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe</u> (Accessed on Jan. 04, 2022).

<sup>&</sup>lt;sup>14</sup> Eligibility for classification as generally recognized as safe (GRAS) pursuant to 21 CFR 170.30. Available at: <u>https://www.ecfr.gov/current/title-</u>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,  $\beta$ -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 x 10<sup>7</sup> – 1.0 x 10<sup>9</sup> 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  $1 \times 10^8$  CFU per serving throughout the shelf life of the products. The 90<sup>th</sup> percentile intake for all ages is 397 mg/day. Using the specification of not less than  $1\times10^9$  CFU per gram, the EDI in terms of CFU per day is 3.97 x 10<sup>8</sup>. On a body weight basis, intake is 6.24 mg/kg bw/day, or 6.24 x 10<sup>6</sup> 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 x 10<sup>7</sup> 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<sup>9</sup> CFU to 2.4 x 10<sup>10</sup> 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<sup>7</sup> 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<sup>9</sup> 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 x 10<sup>9</sup> CFU/kg bw/day), the highest dose tested.
- Based on the NOAEL of 1.8 x 10<sup>9</sup> 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 x 10<sup>7</sup> CFU/kg bw/day. This is considerably higher than the EDI for all ages of 6.24 x 10<sup>6</sup> CFU/kg bw/day.
- The margins of safety calculated from comparisons of EDI for specific populations to the NOAEL of 1.8 x 10<sup>9</sup> CFU/kg bw/day in rats are as follows:
  - EDI for all ages: 6.24 x 10<sup>6</sup> CFU/kg bw/day; margin of safety = 288.4
  - EDI for highest user, male child (6-11 yr) =  $2.65 \times 10^7$  CFU/kg bw/day; margin of safety = 67.9
- Results of clinical studies suggest that up to 1.0 x 10<sup>9</sup> CFU per day W. cibaria CMU is tolerated.
- Available commercialized products in Korea provide a daily intake of *W. cibaria* CMU of 1 x 10<sup>9</sup> CFU to 2.4 x 10<sup>10</sup> 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  $1 \times 10^8$  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

Microgram
Absorption, Distribution, Metabolism and Excretion
Average nucleotide identity
Average nucleotide identity based on BLAST+
Average nucleotide identity based on MUMmer
Antibiotic resistance gene
Antibiotic susceptibility testing
EFSA Panel on Biological Hazards
Basic Local Alignment Search Tool
Cell-free supernatant
Center for Genomic Epidemiology
Current Good Manufacturing Practice
Estimated dietary intake
European Food Safety Authority
Exopolysaccharides
Food Allergen Labeling and Consumer Protection Act of 2004
The Food Allergen Labeling and Consumer Protection Act of 2004
Federal Food Drug and Cosmetics Act

g GA GC GRAS GRN H <sub>2</sub> O <sub>2</sub> HGT IDF KFDA LAB Mb MBP MIC ML N/A NCBI NR QPS RACC RAPD-PCR RGI RNA rRNA TCS tRNA	Gram GRAS Associates Guanine-cytosine Generally Recognized as Safe GRAS Notification Hydrogen peroxide Horizontal gene transfer International Dairy Federation Korea Food and Drug Administration Lactic acid bacteria Megabases Microbial break points Minimal inhibitory concentration Milliliter Not available National Center for Biotechnology Information Not reported Qualified Presumption of Safety Reference amount customarily consumed Random amplification of polymorphic DNA-polymerase chain reaction Resistance gene identifier Ribonucleic acid Tetra Correlation Search Transfer ribonucleic acid
tRNA U.S.	Transfer ribonucleic acid United States
WGS	Whole genome sequencing

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## **B.** Appendices

# Appendix 1 NCBI Genomic Characterization Data

Name	Strain	BioSample	BicProject	Assembly	Level	Size (Mb)	Scaffolds	Symmetric Identity(%)	Gapped Identity(%)	Alignment
Weisseta citiaria	CMS3	SAMN04328350	PRJNA305558	GCA_001951095.1		2,36349		99.5524	99.999	•
Weissella cibarta	CMS2	SAMN04328345	PRJNA305557	GCA_001932895.1		2.34291		99.1833	99.9994	٠
Weissella cibaria	CMS1	SAMN07414780	PRJNA395775	GCA_002243305.1	•	2.34285	14.5	99.1819	99.9965	٠
Weissella cibarla	JCM 12495	SAMD00164450	PRJDB7793	GCA_005405525.1		2 32395	25	98.2474	99.9646	٠
Weissella cibarla KACC 11862	KACC 11852	SAMN02470197	PRJNA59737	GCA_000193635.2	0	2.31786	72	98.1659	99.9978	•
Weissella obalta	YRK005	SAMN15630641	PRJNA648245	GCA_014061105.1		- 1 ×	1 11	1 1 1 1	1 1	•
Weissella cibaria	d-23	SAMN09531641	PRJNA478797	GCA_008691985.1	1				1	•
Weissella cibarta	CT-37	SAMN09531783	PRJNA478799	GCA_008691995.1	5 51					
Weissella ciharia	BC10	SAMN12316825	PRINA555367	GCA_0077855851					/	•
Weisselia cioana	SRCM103448	SAMN10754492	PRJNA515381	GCA_004103855.1					/	•
Weisselta obaria	GGI4	SAMN12318342	PRJNA555367	GCA_007785726.1					1	٠
Welsseta obaria	UGM1	SAMN12316348	PRJNA555307	GCA_007785635.1						
Weisselta cibaria	GGM13-2	SAMN12318349	PRJNA555367	GCA_007785755.1				- /		٠
Weissella cibaria	BM2	SAMN08628864	PRJNA436626	GCA_003010455.1				1		٠
Weissella obaria	BC14	SAMN12317594	PRJNA555367	GCA_007785645,1	Cta			1		•
Weissolta cibaita	A23	SAMN10822535	PRJNA517198	GCA_011609836.1	la B	000		/		•
Weissella cibarta	DmW_103	SAMN06759976	PRJNA383151	GCA_002115575.1	dba	001		1	-	٠
Weissella cibarla	SP19	SANN10783023	PRJNA516164	GCA_004521955.1	la	621		1		٠
Weissella cabana	OF08-4	SAMN09736723	PRJNA482748	GCA_003439565.1	elsse	TA A		/	-	+
Weissella cibaria	GK3	SAMN12318507	PRJNA555367	GCA_007785675.1	We		1			•
Weissella olbaria	C8A3636	SAMN15669522	PRJNA649124	GCA_014081885.1	(a)		/		5-6	•
Weissella cibarla	C8A3612	SAMN12084129	PRJNA549358	GCA_006517775.1			/			٠
Weisseta obaria	92	SAMN14511405	PRJNA623105	GCA_012277625 1	91 J.		/		( - )	•
Weisseta obaria	DK12	SAMN12316339	PRJNA565367	GCA_007785715.1		1				•
Weissella cibarla	ISPR	SAMN03223849	PRJNA268711	GCA_000878215.1	1	1				+
Weisrella obaria	10M	SAMN13000890	PRJNA516760	GCA_000864045.1	1	1				•
Weissella cibaria	MGYG-HGUT- 00248	SANEA5849750	PRJEB33885	GCA_902364765.1		V.,		OP013936.1	2 20(345)	*
Websola citaria	AM27-2218	SAMN09738351	PRJNA462748	OCA_003469985.1		0	YYY	(Click to close)	-2.30(MD)	•
Weissella cibaria	AM27-24	SAMN09736352	PRJNA482748	GCA 003469955.1		2.50565	16	86.7536	98,4903	•

## Figure 1.1 NCBI Hit Plot Alignment of Strains CMU and BC14<sup>1</sup>

<sup>1</sup>NCBI Genome Neighbor Report CMU (2021)

Figure 1.2 NCBI Hit Plot Alignment of Strains CMU and CMS3<sup>2</sup>

Organism Overview ; C Neissella cibar	Senome Assembl	y and Annotation 1951075.2) g	report : Genom Jenome ne	e Neighbor rep ighbors	ort	230(M				/	ownload t
Name	Strain	BioSample	BioProject	Assembly	Le	1			/		Alignment
Weisselia Obarla	CMSJ	SAMN04328350	PRJNA305556	GCA_001951095.		NS3			/	-	
Weissella cibaria	CMS2	SAMN04328345	PRJNA305557	GCA 001932695.1		N N			/		
Weissella cibarla	CMS1	SAMN07414780	PRJNA395775	GCA_002243305.1		139			/	-	
Weisseita cibaria	JCM 12495	SAMD00164450	PRJDB7793	GCA_005405525.		CPD			1		
Welssella cibarta KACC 11862	KACG 11862	SAMN02470197	PRJNA59757	GCA_000183635.		Weisse			/		*
Weissella cibaria	YRK005	SAMN15636641	PRJNA648245	GCA_014061105.1				1			٠
Vveisselta cibaria	cf-23	SAMN00531641	PRJNA478797	GCA_008691085.				1			٠
Weissella cibana	GT-37	SAMN09531783	PRJNA478799	GCA_008691995.			1				
Weissella cibaria	BC10	SAMN12316825	PRJNA555367	GCA_007785585.1			1				+
Vyessella cibaria	SRCM103448	SAMN10754492	PRJNA515381	GCA_004103855.			1				+
Weissella cibaria	GGI4	SAMN12318342	PRJNA555367	GCA_007785725.1			1				
Weissella cibaria	GGM1	SAMN12318348	PRJNA555367	GCA_007785635.1		1					٠
Weissella cibarla	GGM13-2	SAMN12318349	PRJNA555367	GCA_007785755.			1	1. 1	Weissella cibaria CMU	2 38(Mb)	
Weissella cibarla	BM2	SAMN05625504	PRJNA430020	GCA_003010455.					(Click te close)	e'solum)	
Welssella cibaria	BC14	SAMN12317594	PRJNA555367	GCA_007785645.1		1.9	2.51323	3	89.7517	98.4144	•
Walcoolla rikadia	423	CALMINOSSESE	DO INIAS 17102	004 011000000		1.0		20	000440	00 5 40	

<sup>2</sup>NCBI Genome Neighbor Report CMU (2021)





<sup>3</sup> NCBI Genome Tree Report CMU (2021)



## Figure 1.4 NCBI Genome Report – Rectangle Cladogram for Strain CMU<sup>4</sup>

<sup>4</sup> 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 Cl11-0366N

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

## Macrogen 16S Report – Lot CI11-0115N

imple name.	HC00253794 .ot_CI11-0115N_col	ntig_1							
			Inform	ation -					
ner Informatior									
Sequencing P	rimer Name Primer	Sequences	<u>.</u>		PCR Prin	ner Nar	ne Prime	r Sequences	
785F 5' (GG/	A TTA GAT ACC CT	G GTA) 3'		27	F 5' (AGA	GTT T	GA TCM	TGG CTC AG	3
907R 5' (CCG	TCA ATT CMT TTR	AGT TT) 3	_	1492	R 5' (TAC	GGY T	AC CTT (	GTT ACG ACT	T) 3'
	Subje	çt				s	core	Identiti	es
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	(		Ge	nus			Species	
Bacteria	Lactobacilla	ceae		Wei	ssella		W	eissella cibaria	3
			[	w w w w w w w	eissella co eissella co eissella cit eissella cit eissella cit eissella co eissella pa eissella pa eissella pa	nfusa(gi nfusa(gi paria(gi:) paria(gi:) LSN_con lil(gi:NR_ irramese imbl(gi:) illenica(gi:)	INR_11323 ILC063164 INR_04083 ILC0962363 INR_036924 Elg_1 0256423 INTEroides1 IR_136437 DILC09622 DINR_1187	4) 1.6) 4) (g):LC096224) ) (6) (71)	
				W					

Query				Subject	100					Score		10.00	Identities		The second	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/LC0962	3 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_036	9 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/LC0631	6 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_113	2 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_040	8 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/LC0962	2 LC096226.1	1512	7	1512	2449	1326	0	1448	1508	96	Plus/Plus
CMU Lot CI11-0115N contig 1	1541	29	1538	Weissella paramesenteroides gene for 16S ribosomal RNA, partial sequence, strain: JCM 9890	https://www.ncbi.nlm.nih.gov/nucleotide/LC0962	2 LC096224.1	1518	13	1518	2446	1324	0	1452	1513	96	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	29	153	Weissella hellenica strain NCFB 2973 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_118	7 NR_118771.1	1527	11	1519	2444	1323	0	1450	1512	96	Plus/Plus
CMU_Lot_CI11-0115N_contig_1	1541	29	153	Weissella bombi strain R-53094 16S ribosomal RNA, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_136	4 NR_136437.1	1528	1	1510	2436	1319	0	1448	1512	96	Plus/Plus
CMULL at CI11.011EN contin 1	1641	20	1521	Weinselle sell strain MO29 16C shoemed PNA sone, partial approace	https://www.pabi.plm.pib.gou/puplaotide/NIP_026	CINE DOCCAD 1	1550	42	4602	2422	1217	0	1450	1515	06	Diug/Diug

## Certificate of Analysis – Lot CI11-0115N

Date of Auo	lication = 2021-04-02	Date ni	Manufartues : 2021-02-15
No. of Same	ie = D2021040318	Expirat	ion Date : 2023-02-13
Loi No Cl	111-01/5N	Langer an	TOR PARTY & PARKE PARTY &
Inspection 1	Purpose - For official use		
Commodity =	Veissella cibaria CMU		
Appel i cant	Name : OraPharm Inc. Eun-sup You Company address : 900-ho, 9-16 Korea	n Yeonau jang	ä−gil, Seongdong-gu, Seoul, Republir o
	Analyti	cal Resu	lt
1	Test Iter		Beenle
Sangaru	Test Item		Kesut r
bensory at	(1) DULE		Tellowish while powder
Probiotics	G(CFU/g)		000, 109 000 000 000, 137 000 000
End.			000)
End.			000)
End.	Apr .	9 - 2021	000)
End.	Apr . We hereby certify that	9 _ 2021 at the abo	ve are correct.
End. Korea	Apr . We hereby certify tha Health Supplements Association	9 2021 at the abo Sub. Kore	000) ve are correct. sa Health Supplements Institute.
End. Korea	Apr . We hereby certify tha Health Supplements Association Director : Yang, Joo-Hong	9 2021 at the abo Sub. Kore	000) ve are correct. sa Health Supplements Institute.

	ea Advanced Food Re	search Institute	
50, B TEL : 82-2	otdeul-ro, Uiwang-si, Gyeongg 2-3470-8200 FAX : 82-2-523-20	i <sup>ll</sup> i <sup>ll</sup> do, Republic of Korea )72 http://www.kafri.or.l	kr KAFRI
No Production of the	Certificate of Labo	oratory Testing(Re	ference)
Receipt No. (Rei e)	<sup>SSU</sup> 2021-11-003980	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company N	ame 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	2021.03.08
* The above tes	t items and results complied	with the test method notif	ied by MFDS.
* The above tes	t items and results complied	with the test method notif	ied by MFDS.

50, Bot TEL : 82-2-	a Advanced Food Rese deul-ro, Uiwang-si, Gyeonggi-d 3470-8200 FAX : 82-2-523-2072	arch Institute o, Republic of Korea http://www.kafri.or.	Kr KAFRI
	Certificate of Labora	tory Testing(Ret	ference)
eceipt No. (Reis )	<sup>su</sup> 2021-11-003981	Date of Receipt	2021.02.24
roduct Name	Weissella cibaria CMU		
lient Company Nam	ne OraPharm Inc.		
lient Address	905-ho 9-16, Yeonmujang 5-gi	1, Seongdong-gu, Seoul,	Republic of Korea
lîent Name	Eun-sup Yoon	Client Tel / Fax	02-2138-2573
ot No.	CI11-0115N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
est Purpose	For submission (MFDS)	Date of Issue	2021.03.02
* The above test	items and results complied wit	h the test method notif	fied by MFDS.
* The above test	items and results complied wit	h the test method noti	fied by MFDS.

50, B TEL : 82-2	ea Advance etdeul-ro, Uiv 2-3470-8200 F	wang-si, Gyeongg AX: 82-2-523-20	search Institute i-do, Republic of Korea M72 http://www.kafri.or.	kr KAFRI
	Certific	cate of Labo	ratory Testing(Re	ference)
leceipt No. (Rei )	ssu 2021-11-0	03987	Date of Receipt	2021.02,24
roduct Name	Weissella	cibaria CMU		
lient Company N	ame OraPharm	Inc.		
lient Address	905-bo 9-	16, Yeonmujang 5	-gil, Seongdong-gu, Seoul	, Republic of Korea
lient Name	Eun-sup Y	oon	Client Tel / Fax	02-2138-2573
ot No.	CI11-0115	N	Date of Manufacture /Expiration Date	2021.02,15 / 2023.02.14
est Purpose	For submi	ssion (MFDS)	Date of Issue	2021.03.10

Nu D2021063336

Page ( 1 ) / Pages ( 1 )

# Certificate of Analysis

Date of App	41cat10n - 2021-05-28	Deserved and the	Manufacture - 2021-02715
No. of Samp	le : D2021063336	Expiral	ion Date = 2023-02-14
Lei Nu. = C	111-0115N		
Inspection	Purpose Export		
Commonti i y	Weissella cibaria CMU		
Anni Lincost	Name = OraPharm Inc. Eur-sup	Yoon	
appricant	Company address : Bosho, 9-10	6, Yeonmujang	i-gil, Seongdong-gu, Seoul. Republic a
	Ånaly	vtical Resu	t
-	Test Item		Result
Mold & Yes	ast plate count(/a)		Greened & Mald OV
End.			
End.			

No D2021063341

Page ( J ) / Pages ( J )

# Certificate of Analysis

aute of tibb	4164110H - 3051-00-20	Date of Manufacture 2021-02-15
lo of Samp	le : D2021063341	Expiration Date : 2023-02-14
or No. : C	111-0115N	
aspection	Purpose = Export	
ommodity :	Weissella gibaria CMU	
	Name : OraPharm Inc. Eun-s	ир Үссэн
pplicant	Company address = 905-ho, Korea	9-18, Yeonmujang Ə-gil, Seongdong-gu, Seoul, Republi
	An	alytical Result
1	Test Item	Result
Escherich	ia coli(/g)	0
Salmonell	a špp.	Negative
Listeria (	nonocy10genes	Negative
P		
End.	occus aureus(/g)	0
End.	becus aureus(/g)	0
End.	becus aureus(/g)	Jul . 6 . 2021
End.	We bereby certi:	Jul . B . 2021 Ty that the above are correct.
End. Korea	We bereby certi: Health Supplements Associ	Jul . 6 . 2021 Ty that the above are correct. ation Sub. Korea Health Supplements Institute
End: Korea	We hereby certin Health Supplements Associ Director Yang, Joo-He	Jul . 6. 2021 Jul . 6. 2021 Ty that the above are correct. ation Sub. Korea Health Supplements Institute
End. End. Korea B-701	We hereby certin Health Supplements Associ Director Yang, Joo-He Rores Big Park., 700 Dassanguareur	Jul 6. 2021 iv that the above are correct. ation Sub. Korea Health Supplements Institute mg Dr. J. M. gamag

-KHSI
150, B TEL : 82-3	ea Advanced Food Re otdeul-ro, Uiwang-si, Gyeongg 2-3470-8200 FAX : 82-2-523-2	search Institute gi-do, Republic of Korea 072 http://www.kafri.or.	kr KAFR0
	Certificate of Labo	oratory Testing(Ret	ference)
Receipt No. (Rei e)	ssu 2021-11-003979	Date of Receipt	2021,02.24
Product Name	Weissella cibaria CMU		
Client Company N	ame OraPharm Inc.		
Client Address	905-ho 9-16, Yeonmujang f	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

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

### Macrogen 16S Report – Lot CI11-0116N

ample name : l	_ot_CI11-0116N_cont	tig_1						
		1	nformatic	n				
ner Information	1						_	_
Sequencing P	rimer Name Primer S	Sequences		PCR Pri	ner Nan	ne Prime	r Sequences	ę
785F 5' (GG	A TTA GAT ACC CTO	G GTA) 3'		27F 5' (AGA	GTT TO	SA TCM	TGG CTC AG	5) 3
907R 5' (CCG	ICA ATT CMT TTR	AGT 11) 3'		492R 5' (TAC	GGY 14	CCTT	GIT ACG AC	[ 1] 3'
	Subjec	st			S	ore	Identi	ties
Accession	Description	Length	Start E	nd Coverage	Bit	E-Value	Match/Total	Pct.(%
LC096236.1	Weissella cibaria	1516	6 15	16 99	2787	0.0	1510/1511	99
Kingdom	Family			Genus			Species	
Bacteria	Lactobacillac	eae		Weissella		N	eissella cibar	ia
			<u>[</u>	Weissella co Weissella co Weissella co	nfusa(gi nfusa(gi nfusa(gi	LC06316 NR_0408 NR 1132	4) 16) 58)	
			1 <u>r</u>	<ul> <li>Weissella co</li> <li>Weissella co</li> <li>Weissella co</li> <li>Weissella ci</li> <li>Weissella ci</li> <li>Uot_C11-01</li> <li>Weissella so</li> <li>Weissella bo</li> <li>Weissella ho</li> <li>Weissella ho</li> </ul>	nfusa(gi nfusa(gi nfusa(gi nfusa(gi nfusa(gi baria(gi 16N_cont li(gi:NR_ srameser smbilgi: N illenica(g illenica(g	LC06316 NR_0408 NR_1132 IR_03692 C096236 Ig_1 0256421 nteroides R_136437 :LC09622 :NR_1167	4) 16) 58) 4) g( LC096224) ) (6) 71)	
				Weissella co Weissella co Weissella ci Weissella ci Weissella so Weissella bo Weissella bo Weissella bo	nfusalgi: nfusalgi: nfusalgi: barialgi:N barialgi:N barialgi:N ligi:NR_i mbilgi:N sillenicalg	LCD6316 NR_0408 NR_1132 IR_03692 C096236 ig_1 0256421 nteroides R_136437 :LC09622 :NR_1187	4) (6) (58) (4) (g) LCO96224) () (6) (71)	

Length Start 1539 22 1639 28 Certificate of Analysis – Lot CI11-0116N

No. of Sample : D2021040319 Expiration Date : 2023-02-14 Lat Na. + C111-0116N Inspection Purpose : For official use Commodity Weissella cibaria CMU Applicant Company address : 905-ho, 9-16, Yeonnujang 5-gil, Seongdong-gu, Secul, Republic o Gorea Applicant Test Item Result Sensory attribute Yellowish white powder Probiotics(CFU/g) End.			Date of Manufacture = 2021-02-15
Lat Na. : C111-0118N Inspection Purpose : For official use Commodity = Welssella cibaria CMU Appl(cant = OraPharm Inc. Eur-sup Yuon Company address : 905-ho, 9-16, Yeonmyjang 5-gil, Seongdong-gu, Seoul, Republic o Gorea = Analytical Result  Test Item = Result Sensory attribute = Yellowish white powder I50 000 000 CFU/g (156 000 000 000, 138 000 000 000, 150 000 000 000) End.	No. of Samp	le : 02021040319	Expiration Date = 2023-02-14
Inspection Purpose : For official use Commodity Weissella cibaria CMU Applicant Name : OraPharm Inc. Eur-sup Yoon Company.address : 905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu. Seoul: Republic o Borea Analytical Result Test Item Result Sensory attribute Yellowish white powder I50 000 000 000 CFU/g (156 000 000 000, 138 000 000 000, 150 000 000 000) End.	Lot No C	111-0116N	
Commodity         Weisselfa cibaria CMU           Applicant         Name : OraPharm Inc. Eur-sup Yoon           Company address :         905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu Scoul: Republic of Bored           Analytical Result           Test Item           Sensory attribute         Yellowish white powder           150 000 000 OCFU/g (156 000 000 000, 150 000 000 000, 150 000 000 000, 150 000 000 000)         000)	Inspection	Purpose : For official use	
Name:         OraPharmy Inc. Eur-sup Yoon           Company_address:         B05-ho, 9-16, Yeonomyjang 5-gil, Seongdoog-gu, Seoul; Republic of Korea           Analytical Result         Analytical Result           Sensory attribute         Yellowish white powder           Probiotics(CFU/g)         150 000 000 000 CFU/g (156 000 000 000, 150 000 000 000, 150 000 000 000)           End.         End.	Commodity	Weissella cibaria CMU	
Applicant       Company address :       905-ho, 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea         Analytical Result       Imalytical Result         Test Item       Result         Sensory attribute       Yellowish white powder         150 000 000 000 CFU/g (156 000 000 000 000, 150 000 000 000, 000,		Name : OraPharm Inc. Eur-sup	Yuon
Imalytical Result         Test Item       Result         Sensory attribute       Yellowish white powder         Probiotics(CFU/g)       000, 138 000 000 000, 150 000 000         Brd.	Applicant	Company address = 905-ho, 9- Borea	16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic o
Test Item         Result           Sensory attribute         Yellowish white powder           Drobiotics(CFU/g)         150 000 000 000 CFU/g (156 000 000 000 000, 150 000 000 000)           Brnd.         End.	_	Ana	ytical Result
Sensory attribute         Yellowish white powder           Probiotics(CFU/g)         150 000 000 CFU/g (156 000 000 000, 000, 150 000 000 000, 000)           End.         End.		Test Item	Result
Probiotics(CFU/g)         150 000 000 CFU/g (156 000 000 000, 150 000 000 000, 000)         000 000 000, 150 000 000 000         000 000           End.	Sensory at	tribute	Yellowish white powder
End.	Probiotics	s(CFU/g)	150 000 000 000 CFU/g (156 000 000 000, 138 000 000 000, 150 000 000
	End.		000)
ME DELETER LEEPE LEEPE LEEPE CONTRACTOR AND LEEPE AND	End.	Al We berefy period	r : 9 . 2021
Korea Health Supplements Association Sub Korea Health Supplements Institute	End.	Ar We hereby certify Health Supplements Association	r : 9 . 2021 that the above are correct. ion Sub. Korea Health Supplements Institute
Korea Health Supplements Association Sub. Korea Health Supplements Institute	End. Korea	A We hereby certify Health Supplements Associa Director : Yes Lo W	r : 9 . 2021 that the above are correct. ion Sub. Korea Health Supplements Institute
Korea Health Supplements Association Sub. Korea Health Supplements Institute Director : Yang, Joo-Hong <b>Dr.j. k. yang</b>	End.	A We hereby certify Health Supplements Associa Director : Yang, Joo-Hor	r : 9 . 2021 that the above are correct. ion Sub. Korea Health Supplements Institute g Dr. j. K. yang

No. 102021063334

Page ( 1 ) / Pages ( 1 )

### Certificate of Analysis

Mare DI WED	a construction of the state of the	the st multiplicity and the
No. of Samp	e : D2021063334	Expiration Date = 2023-02-14
lint No. 2 Cl	11-0116N	
Inspection	urpose : Export	
Commodity :	Weissella cibaria CMU	
Toutient	Name = DraPharm Inc. Eun-si	ір Упол
Apporcant	Company address 905-ho, 5	-16, Yeanmajang 5-gil, Seongdong-gu, Seoul, Republic
	Anica Ani	alytical Result
	Test Item	Result
Ash(张)		1.30 %
Moisture(4	)	2.85 %
End.		
End.		ful - 7 , 2021.
End.	We hereby cortif	ful . 7 . 2021: y that the above are correct.
End.	We hereby certif Health Supplements Associa	Nul . 7 . 2021. y that the above are correct. ation Sub. Korea Health Supplements Institute
End. Korea	We hereby certif Health Supplements Associ Director : Yang, Joo-Ha	Mul . 7 . 2021. y that the above are correct. ation Sub. Korea Health Supplements Institute ng
End. Korea	We hereby certif Health Supplements Associa Director : Yang, Joo-He Marka Big Park, 700, Dasaangpanayo	ful . 7 . 2021: y that the above are correct. ation Sub. Korea Health Supplements Institute ng

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50, B TEL ; 82-2	ea Advanced Food R otdeul-ro, Uiwang-si, Gyeong 2-3470-8200 FAX : 82-2-523-	esearch Institute gi-do, Republic of Korea 2072 http://www.kafri.or.l	Gr KAFRI
	Certificate of Lab	oratory Testing(Re	ference)
Receipt No. (Rei e)	<sup>SSU</sup> 2021-11-003982	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company N	ame 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.	CI11-0116N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
Test Purpose	For submission (MFDS)	Date of Issue	2021.03.02

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. (Reissu 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. Cl11-0116N Date of Norae 2021.02.15 / 2023.02. Test Purpose For submission (MFDS) Date of Issue 2021.03.10 Test Items and Results ColiformsNegative * The above test items and results complied with the test method notified by MFDS.	Kor	ea Advanced Food Re	search Institute	
Certificate of Laboratory Testing(Reference)         Receipt No. (Reissu e)       2021-11-003988       Date of Receipt       2021.02.24         Product Name       Weissella cibaria CMU       Image: Colspan State St	50, Bo TEL : 82-2	otdeul-ro, Uiwang-si, Gyeongg -3470-8200 FAX : 82-2-523-20	i-do, Republic of Korea )72 http://www.kafri.or.	kr KAFRI
Receipt No. (Reissu 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. Cli11-0116N Date 02021.02.15 / 2023.02. Test Purpose For submission (MFDS) Date of Issue 2021.03.10 Test Items and Results ColiformsNegative * The above test items and results complied with the test method notified by MFDS.		Certificate of Labo	oratory Testing(Re	ference)
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.         Cli11-0116N         Date of Manufacture /Expiration Date         2021.02.15 / 2023.02.           Test Purpose         For submission (MFDS)         Date of Issue         2021.03.10           Test Items and Results         Coliforms	Receipt No. (Rei	<sup>SSU</sup> 2021-11-003988	Date of Receipt	2021.02.24
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.       Cli11-0116N       Date of Manufacture       2021.02.15 / 2023.02.         Test Purpose       For submission (MFDS)       Date of Issue       2021.03.10         Test Items and Results         ColiformsNegative         * The above test items and results complied with the test method notified by MFDS.	Product Name	Weissella cibaria CMU		
Client Address       905-ho 9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic of Korea         Client Name       Eur-sup Yoon       Client Tel / Fax       02-2138-2573         Lot No.       Cli11-0116N       Date of Manufacture 2021.02.15 / 2023.02.         Test Purpose       For submission (MFDS)       Date of Issue       2021.03.10         Test Items and Results       Coliforms	Client Company Na	ame OraPharm Inc.		
Client Name       Eun-sup Yoon       Client Tel / Fax       02-2138-2573         Lot No.       Clil-0116N       /Expiration Date       2021.02.15 / 2023.02.         Test Purpose       For submission (MFDS)       Date of Issue       2021.03.10         Test Items and Results         Coliforms	Client Address	905-ho 9-16, Yeonmujang 5	-gil, Seongdong-gu, Seoul	, Republic of Korea
Lot No.         Clil-OlieN         Date of Manufacture /Expiration Date         2021.02.15 / 2023.02.           Test Purpose         For submission (MFDS)         Date of Issue         2021.03.10   Test Items and Results ColliformsNegative * The above test items and results complied with the test method notified by MFDS.	Client Name	Eun-sup Yoon	Client Tel / Fax	02-2138-2573
Test Purpose         For submission (MFDS)         Date of Issue         2021,03.10           Test Items and Results           Coliforms	Lot No.	C111-0116N	Date of Manufacture /Expiration Date	2021.02.15 / 2023.02.14
Test Items and Results Coliforms	Test Purpose	For submission (MFDS)	Date of Issue	2021,03,10
	* The above tes	t items and results complied	with the test method noti	fied by MFDS.
	* The above tes Note: 1. The above me 2. The results 3. No one can u 4. This certific This certificate door	t items and results complied rchandise was submitted and identifi shown in this certificate refer only use this certificate for the purpose cate has no legal effect.	with the test method noti ded by the client. / to sample tested and it does no of test, advertisement and litig g and inspection of Food and Dru	of cover the quality of all p gation without KAFRI's consen
「四周空南」	* The above tes	t items and results complied rchandise was submitted and identifi shown in this certificate refer only se this certificate for the purpose cate has no legal effect. es not comply with the Act on Testing	with the test method noti ied by the client. / to sample tested and it does no of test, advertisement and liting g and inspection of Food and Dru	fied by MFDS. of cover the quality of all pr gation without KAFRI's consent gs of Himistry of all pr

No. : 02021063337

Page ( ) / Pagen ( 1 )

Vo. of Samp	and the second se		all metal accord and a set of the
	le : 02021063337	Expira	tion Date : 2023-02-14
Lot No. 7 C	111-01168		
Inspection	Purpose ( Export		
Commod î try	Weissella cibaria CMU		
Amillanat	Name : OraPharm Inc. Eun-s	up Yoon	
debi i cam.	Company address : 905-ho, 9	9-16, Yeonmujang	5-gil Scongdong-gu, Seoul, Republic o
	An	alytical Res	ilt
	Test Item		Result
Mold & Yes	ast mlate count(/g)		O(Yeast 0, Mold 0)
Eng.			
Eng.			
Eng.	We hereby certil	Jul 6 . 2021 fy that the ab	ove are correct.
Korea	We hereby certi Health Supplements Associ	Jul . 6 . 2021 fy that the ab ation Sub. Kor	ove are correct. ea Health Supplements Institute
Korea	We hereby certil Health Supplements Associ Director : Vang Loo-He	Jul . 6 . 2021 fy that the ab ation Sub. Kor	Ove are correct. ea Health Supplements Institute
Korea	We hereby certi Health Supplements Associ Director : Yang, Joo-He	Jul . 6 . 2021 fy that the ab ation Sub. Kor	Ove are correct. ea Health Supplements Institute

No. D2021063342

Page ( 1 ) / Pages ( 1 )

### Certificate of Analysis

die of upp	fication 2021-06-28	Date of Manufacture : 2021-02-15	
o. of Samp	le ÷ 02021063342	Expiration Date : 2023-02-14	
ol No. : C	111-0116N		
nspection	Purpose Export		
ommodity [	Weissella cibaria CMU		
and i much	Name : OraPharm Inc. Eun-s	ар Үсол	
ppurcant	Company address - 905-hd, Korea	-16, Yeonmujang 5-gil, Seongdong-gu, Seoul	. Wepublic a
	An	alytical Result	
	Test Item	Result	
Escherichi	a coli(/g)	0	
Salmonell;	spp.	Negative	
Listeria «	Ronocytogenes	Negative	
Staphyloco	and a second for the second	0	
End.	iccus aureus(/g)		
End.	iccus aureus(/g)		
End.	areas(/g)	lu] . 6 . 2021	
End.	We hereby certi	Nul , 6 . 2021 y that the above are correct.	
End.	We hereby certi Health Supplements Associ	Jul , 6 . 2021 y that the above are correct. ation Sub. Korea Health Supplements In	istitute
End. Korea	We hereby certi Health Supplements Associ Director : Yang, Joo-Fi	Ju] , 6 . 2021 y that the above are correct. ation Sub. Korea Health Supplements In	istitute
End. Korea	We hereby certi Health Supplements Associ Director : Yang, Joo-He Sorra Bio Park, 780, Daewangmangy	<pre>hu) . 6 . 2021 y that the above are correct. ation Sub. Korea Health Supplements In ng to, Mondaug-gu. Seongane-si. Evensegi-to. Komubil</pre>	istitute 6 ol Korna

KHSI

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

### Macrogen 16S Report – Lot CI11-0117N

Irder Number : H ample name : L	IC00253794 ot_CI11-0117N_con	tig_1							
			Inform	ation					
mer Information			morm	ation					
Sequencing P	rimer Name Primer	Sequences			PCR Pri	mer Nar	ne Prime	Sequences	
785F 5' (GGA	TTA GAT ACC CT	G GTA) 3'		27	'F 5' (AGA	GTT T	GA TCM	TGG CTC AG)	3
907R 5' (CCG	TCA ATT CMT TTR	AGT TT) 3'		1492	R 5' (TAC	GGY T	AC CTT C	GTT ACG ACT	T) 3'
	Subje	ct				S	core	Identiti	es
Accession	Description	Length	Start	End	Coverage	Bit	E-Value	Match/Total	Pci.
LC096236.1	Weissella cibaria	1516	6	1516	99	2787	0.0	1510/1511	99
Kingdom	Family			Ge	enus			Species	
Bacteria	Lactobacillac	eae		Wei	ssella		W	eissella cibaria	9
			1	W	/eissella co /eissella co /eissella co /eissella cil	nfusa(gi nfusa(gi nfusa(gi baria(gi:1	LC063164 NR_04081 NR_11329 NR_036924	() .6) (8) ()	
		<u> </u>	-1	W	/eissella cil ot_Cl11-01 /eissella so /eissella pa /eissella bo /eissella ho	baria(gi:1 17N_cont bl(gi:NR_ aramese ombilgi:N ellenica(g ellenica(g	LC096236) tig_1 025642) nteroides( IR_136437 pi:LC09622 pi:NR_1187	gi LC096224) ) 6) 71)	

Query	42			Subject					Score	a stand and a stand		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/nucleotide/LC09621LC096236.1	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/nucleotide/NR_036(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/nucleotide/LC06316LC063164-1	1538	17	1532	2748	1468	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/nucleotide/NR_113[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/nucleotide/NR_040INR_040816.1	1477	1	1477	2654	1453	0	1469	1477	99	Plus/Plus
CMU Lot CITT-0117N contig 1	1542	23	1533	Weissella hellenica gene for 16S ribosomal RNA, partial sequence, strain: JCM 10103	https://www.ncbi.nlm.nih.gov/nucleotide/LC09622LC096226.1	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/nucleotide/LC09622LC096224.1	1518	9	1518	2460	1332	0	1457	1517	96	Plus/Plus
CMU Lot CI11-0117N config 1	1542	23	1537	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	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/hucleotide/NR_025(NR_025642.1	1558	9	1524	2447	1325	0	1456	1520	96	PlusPlus
ATTACK AND A STATE OF A DATE OF A DA	16.40	1912	16.77	Waisset/a brenchi steren D.F.2004 EES scheroscol DNA, matrixi sciences	Detroit Research who who are desired which 1201005 1202422.1	16.26		16.1.1	214.442	2224		2460		00	Olive Olive

### Certificate of Analysis – Lot CI11-0117N

RE

No. : D2021040320

Page ( 1 ) / Pages ( 1 )

ate of Appl	ication : 2021-04-02	Date of Manufacture - 2021 02 10
o. of Sampl	e : D2021040320	Expiration Date : 2023-02-14
ot No. : CI	11-0117N	
nspection P	Purpose : For official use	
ommodîty :	Weissella cibaria CMU	
CONTRACTOR IN	Name : OraPharm Inc. Eun-sup	Yoon
pplicant	Company address : 905-ho, 9-1 Korea	6, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic
	Anal	ytical Result
	Test Item	Result
Sensory at	tribute	Yellowish white powder
Probiotics	(CFU/g)	150 000 000 000 CFU/g (112 000 000 000, 160 000 000 000, 167 000 000
End.		000)
End.		000)
End.	Ap	000) r . 9 . 2021
End.	Ap We hereby certify	r . 9 . 2021 that the above are correct.
End.	Ap We hereby certify Health Supplements Associat	r . 9 . 2021 that the above are correct. ion <u>Sub. Korea Health Supplements Institute</u>
End. Korea	Ap We hereby certify Health Supplements Associat Director : Yang, Joo-Hon	r . 9 . 2021 that the above are correct. ion Sub. Korea Health Supplements Institute
End. Korea B-101. J	Ap We hereby certify Health Supplements Associat Director : Yang, Joo-Hon Korea Bio Park. 700. Daewangpangyo-r	r . 9 . 2021 that the above are correct. ion Sub. Korea Health Supplements Institute g o, Bundang-gu, Seongnam-s1, Gyeongg1-do, Kepublic of Korea

Ro. D2021063335

Page ( 1 ) / Pages ( 1 )

Vo. of Samp	le : D2021063335	Expiration Date = 2023-02-14
of No. : C	111-0117N	
Inspection	Purpose : Export	
Commodity =	Weissella cibaria CMO	
and I don't	Name 1 OraPharm Inc. Eun-si	ир Үссл
ibiri i cant	Company address = 905+ho, 9	9-16, Yeonmujang 5-gil, Scongdong-gu, Seoul, Republic of
	Ana	alytical Result
	Test Item	Result
Ash(%)		1.16 集
Moisture(9	()	3.05 %
		Jul 4 7 × 2021
	We hereby certif	Jul : 7 : 2021 Ty that the above are correct.
ãorea	We hereby certif Health Supplements Associa	Jul , 7 , 2021 Ty that the above are correct. ation Sub. Korea Health Supplements Institute
Korea	We hereby certif Health Supplements Associa Director : Yang, Joo-Ho	Jul 7 2021 by that the above are correct. ation Sub. Korea Health Supplements Institute

50, B	ea Advanced Food R otdeul-ro, Uiwang-si, Gyeon	esearch Institute ggi-do, Republic of Korea	- 0
TEL : 82-2	-3470-8200 FAX : 82-2-523-	2072 http://www.kafri.or.l	kr KAFRI
Receipt No. (Rei	Certificate of Lab	oratory Testing(Re	terence)
e)	2021-11-003983	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU		
Client Company N	ame OraPharm Inc.		D. 1.1.1 2 17
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	/Expiration Date	2021.02.15 / 2023.02.14
Test Purpose	For submission (MFDS)	Date of Issue	2021.03.02
* The above tes	t items and results complie	d with the test method notif	fied by MFDS.
* The above tes	t items and results complie	d with the test method notif	fied by MFDS.

THE ATTACK REALITY, THE STREET

	Advanced Food Res	earch Institute	
50, Botd TEL : 82-2-34	eul-ro, Uiwang-si, Gyeonggi- 170-8200 FAX : 82-2-523-207	-do, Republic of Korea 2 http://www.kafri.or.	kr KAFRI
1	Certificate of Labor	atory Testing(Re	ference)
Receipt No. (Reissu	2021-11-003989	Date of Receipt	2021.02.24
Product Name	Weissella cibaria CMU	and the second	
Client Company Name	OraPharm Inc.		
Client Address	905-ho 9-16, Yeonmujang 5-g	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

3/11/2022

No. : D2021063338

Page ( 1 ) / Pages ( 1 )

No. of Samp Lot No. 4 C Inspection	le = D2021063338		
ot No. : C Inspection		Expirat	ion Dare : 2023-02-14
Inspection	111-0117N		
The second state of the second	Purpose = Export		
.ommodily .	Weissella cibaria CMU		
and insert	Rame : OraPharm Inc. Eun-su	p Yoon	
duttent	Company address : 905-ho, 9-	-16, Yennmujang S	rgil, Seongdong-gu, Seoul, Republic
	Апа	lytical Resul	£
1	Test Item		Result
Mold & Yes	ast plate count(/g)		O(Yeast 0, Mold 0)
	I	ul <u>6 2021</u>	
	J We hereby certify	ul 6 2021 y that the abov	/e are correct.
Korea	J We hereby certify Health Supplements Associa	ul 6 2021 y that the abov tion Sub, Kore	ve are correct. a Health Supplements Institute
Korea	J We hereby certify Health Supplements Associa Director : Yang, Joo-Hon	ul 6 2021 y that the abov tion Sub. Kore	ve are correct. a Health Supplements Institute

No. ; D2021063343

Page ( 1 ) / Pages ( ( )

	Remark Lawrence Inc.	pare or summarente byst op to
io. of Samp.	le   02021083343	Expiration Date : 2023-02-14
at No. * Cl	111-0117N	
uspection	urpose Export	
ommodity	Weissella cibaria (MU	11
polecant	Name - OraPharm Inc. Eun-s	up Yoon
	Company address = Korea	s-in, leonmalang p-gil, Seongdong-gu, Seoul, Republic (
	An	alytical Result
	Test Item	Result
Escherichi	a coli(/g)	0
Salmonella	spp,	Negative
Listeria m	onocytogenes	Negative
Staphyloco	ccus aureus(/g)	0
End.		
End.		
End.		Jul 6 2021
End.	We hereby certi	Jul . 6 . 2021
End.	We hereby certi Health Supplements Associ	Jul . 6 . 2021 fy that the above are correct.
End. Korea	We hereby certi Health Supplements Associ	Jul . 6 . 2021 fy that the above are correct. ation Sub. Korea Health Supplements Institute
End. Korea	We hereby certi Health Supplements Associ Director / Yang, Joo-H	Jul . 6 . 2021 fy that the above are correct. ation Sub. Korea Health Supplements Institute ong Dr. J. L. gama

### Appendix 2.4 *W. cibaria* CMU Lot Cl11-0362N

### Macrogen 16S Report – Lot Cl11-0362N

mer Informatior									
mer Information			Inform	ation –	_		_		-
Sequencing P	rimer Name Primer S	Sequences			PCR Prin	ner Nam	e Prime	Sequences	
785F 5' (GG	A TTA GAT ACC CTO	G GTA) 3'		27	F 5' (AGA	GTT TO	ATCM	TGG CTC AG	3
907R 5' (CCG	TCA ATT CMT TTR	AGT TT) 3'		1492	R 5' (TAC	GGY TA	CCTT	GTT ACG ACT	T) 3'
	Subjer	et				S	ore	Identiti	20
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			Ge	nus			Species	
Bacteria	Lactobacillac	eae		Wei	ssella		W	eissella cibaria	1
			<u> </u>	Weis Weis Weis Weis	sella confi sella confi sella confi sella cibar sella cibar	usalgi:L( usa(gi:Ni usa(gi:Ni ria(gi:LC( ria(gi:NR	C063164 R_04081 R_11325 D96236) _036924	5) 3)	

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  $(1\rightarrow 6)$  linkages.

Query	1			Subject						Score			identities	100000		Strand
Name	Length	Start	End	Description	Link	AC	Length	Start	End	Bit	Ran	E-value	Match	Total	Pct(%)	
CMU_CI11-0362N_config_1	1512	2	1512	Weissella cibana gene for 16S ribosomal RNA, partial sequence, strain: JCM 12495	https://www.ncbi.nlm.nih.gov/nucleotida/LC0952	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/nucleotide/NR_036	NR 036924.1	1529	1.	1504	2761	1495	0	1501	1505	99	Plus/Plus
CMU CI11-0362N conlig 1	1512	2	1512	Weissella confusa gene for 16S ribosomal RNA, partial sequence, stram JCM 1093	https://www.ncbi.nlm.nih.gov/nucleotide/LC0631	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/nucleotide/NR_113	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.nim.nih.gov/nucleotide/NR_040	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 nbosomal RNA, partial sequence, strain. JCM 10103	https://www.ncbi.nlm.nih.gov/nucleotide/LO0962	LC096226.1	1512	1	1509	2457	1330	0	1452	1512	96	Plus/Plus
CMU_CIT1-0362N_config_1	1512	2	1512	Weissella paramesenteroides gene for 16S ribosomal RNA, partial sequence, strain: JCM 9890	https://www.ncbi.nim.nih.gov/nucleotide/LC0962	LC096224-1	1518	1	1514	2451	1327	B	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/nucleotide/NR_118	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 M268 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_025	NR_025642.1	1558	7	1516	2438	1320	0	1451	1515	.96	Plus/Plus
CMU CITT-0362N config 1	1512	2	1512	Weissella soli cene for 165 ribosomal RNA, partial sequence, strain, JCM 12536	https://www.ncbi.nlm.nib.gov/nucleotide/LC2581	LC258131.1	1518	7	1516	2435	1318	0	1450	1515	96	Plus/Plus

### Certificate of Analysis – Lot Cl11-0362N

No. : D2021060278

Page ( 1 ) / Pages ( 1 )

o, of Sample : D2021060278 of No. : Cl11-0362N nspection Purpose : Export ommodity : Weissella cibaria CMU Same : OraPharm Inc. Eun-sup Yoon Company address : 905-ho. 9-16. Yeor Korea Analytica Ensory attribute Probletics(CFU/g) End.	Expiration Date : 2023-05-17 onmujang 5-gil, Seongdong-gu, Seoul, Republic o al Result yellowish white powder 150 000 000 000 CPU/g (134 000 000 000, 173 000 000 000, 141 000 000 000)
at No. : Clil-0362N nspection Purpose : Export commodity : Weissella cibaria CMU pplicant Company address : 905-ho. 9-16. Year Korea Analytica Sensory attribute Probiotics(CFU/g) End.	anmujang 5-gil, Seongdong-gu, Seoul, Republic o al Result yellowish white powder 150 000 000 000 CFU/g (134 000 000 000, 173 000 000 000, 141 000 000 000)
nspection Purpose : Export commodity : Weissella cibafia CMU pplicant Rame : OraPharm Inc. Eun-sup Yoon Company address : 905-ho. 9-16. Yeor Korea Analytica Sensory attribute Probiotics(CFU/g) End.	annuijang 5-gil, Seongdong-gu, Seoul, Republic o al Result yellowish white powder 150 000 000 000 CFU/g (134 000 000 000, 173 000 000 000, 141 000 000 000)
Commodity : Weissella cibaria CMU Name : OraPharm Inc. Eun-sup Yoon Company address : 905-hu. 9-16. Yeor Korea Analytica Sensory attribute Probiotics(CFU/g) End.	enmujang 5-gil, Seongdong-gu, Seoul, Republic o al Result yellowish white powder 150 000 000 000 CFU/g (134 000 000 000, 173 000 000 000, 141 000 000 000)
Applicant Name : OraPharm Inc. Eun-sup Yoon Company address : 905-ho. 9-16. Yeor Korea Analytica Sensory attribute Probiotics(CFU/g) End.	anmujang 5-gil, Seongdong-gu, Seoul, Republic o al Result yellowish white powder 150 000 000 000 CPU/g (134 000 000 000, 173 000 000 000, 141 000 000 000)
Implicant       Company address : 905-hú. 9-16. Yeor         Analytica         Analytica         Sensory attribute         Probiotics(CFU/g)         End.	Result           Result           150 000 000 000 CFU/g (134 000 000 000 000 000 000 000 000 000 0
Analytica Test Item Sensory attribute Probiotics(CFU/g) End.	Result           yellowish white powder           150 000 000 000 CFU/g (134 000 000 000 000, 141 000 000 000 000, 141 000 000 000)           000)
Test Item Sensory attribute Probiotics(CFU/g) End.	Result           yellowish white powder           150 000 000 000 CFU/g (134 000 000           000, 173 000 000 000, 141 000 000           000)
Sensory attribute Probiotics(CFU/g) End.	yellowish white powder 150 000 000 000 CFU/g (134 000 000 000, 173 000 000 000, 141 000 000 000)
Probiotics(CFU/g) End.	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 Su	ub. Korea Health Supplements Institute
Director : Yang, Joo-Hong	A 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
H-101, Koron D(6 Park, 700, Darwangpangyo-ro, Hunda	Dar to a gang
Korea Health Supplements Association Su Director : Yang, Joo-Hong	ub. Korea Health Supplements Institute

No. : D2021060280

Page (1) / Pages (I)

	itedetion again to be	Dare of wallotacin(6 - 2021-00-r0
o, of Samp	le : D2021060280	Expiration Date : 2023-05-17
ot No. : C	111-0362N	
nspection	Purpose : Export	
ommodity -	Weissella cibaria CMU	
anlicant	Name - OraPharm Inc. Eun-si	up Yoon 1.10 Vacuutians E-sil Sagadapa-wa Sagal, Papublic s
der en ander	Company address : Korea	-10, Teommulang 5-Bil, Scongdong-Ru, Scoul, Republic o
	Ana	alytical Result
	Test Item	Result
Sensory a	ttribute	yellowish white powder
Calorie(K	cal/100g) -	382.82 Kcal/100g
Carbohydr	ate(%)	89.49 %
Crude pro	tein(%)	6.17 %
Crude fat	(%)	0.02 %
	g()	3:03 %
Moisture(	- /	0.00 *
Moisture( Ash(%)		1.29 %
Moisture( Ash(%) Sodium(mg End.	/100g)	1.29 % 27.00 mg/100g
Moisture( Ash(%) Sodium(mg End.	/100g)	1.29 % 27.00 mg/100g
Moisture( Ash(%) Sodium(mg End.	/100g)	1.29 % 27.00 mg/100g
Moisture( Ash(%) Sodium(mg End.	/100g) We hereby certi	I.29 % 27.00 mg/100g Jun : 14 : 2021 fy that the above are correct.
Moisture( Ash(%) Sodium(mg End. Korea	/100g) We hereby certi a Health Supplements Associ	1.29 %       27.00 mg/100g   Jun : 14 : 2021 fy that the above are correct. ation Sub. Korea Health Supplements Institute
Moisture( Ash(%) Sodium(mg End. Korea	/100g) We hereby certi a Health Supplements Associ Director : Yang, Joo-He	1.29 %         27.00 mg/100g         Jun : 14 : 2021         fy that the above are correct.         ation Sub. Korea Health Supplements Institute         ong       Dr. J. K. gang
Moisture( Ash(%) Sodium(mg End. End. Korea 8-)01	/100g) We hereby certi a Health Supplements Associ Director : Yang, Joo-He Korea Biu Pars., 700, Daewangpangyo	1.29 %       27.00 mg/100g   Jun : 14 : 2021 fy that the above are correct. ation Sub. Korea Health Supplements Institute ong Dr. J. M. gamg one, Bundang-gu, Scongnammai, Gyeonggi-do, Republic of Korea

No. D2021060286

Page ( 1 ) / Pages ( L )

and our other	rication soor of de	bare of Manufacture - 2021-02-19
o. of Samp	le = 02021060286	Expiration Date : 2023-05-17
0) No E	111-03628	
nspection	Purpose = Export	
ommodity :	Weissells cibaria CMU	
ant insert	Name : OraPharm Inc. Eun-si	ip Yoon
PER COMPANY	Company address Rorea	-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Republic o
	An	alytical Result
1	Test Item	Result
Lead(mg/kg	g)	0.0107 mg/kg
Arsenic(mg	g/kg)	0.0067 mg/kg
Cadmium(mg	g/kg)	0.0398 mg/kg
Mercury(mg	g/kg)	0.0016 mg/kg
End		
End		
End		Jun . 7 . 2021
End	We hereby certif	Jun . 7 . 2021 Yy that the above are correct.
End	We hereby certi Health Supplements Associ	Jun 7 . 2021 by that the above are correct. ation Sub. Korea Health Supplements Institute
End	We hereby certii Health Supplements Associ Director : Yang, Joo-He	Jun 7 . 2021 Sy that the above are correct. ation Sub. Korea Health Supplements Institute mg

No. : D2021060282

Page ( 1 ) / Pages ( 1 )

The A. C. Distant		and the second se	addition of a the star work
vo_ 01 Samp	le : D2021060282	Expirat	ion Date = 2023-05-17
ot No C	111=0362N		
Inspection	Purposé : Export		
Commodity -	Weissella ribaria CMU	_	
well i mank	Name : OraPharm Inc. Eun-su	ip Yoon	
abter return	Company address 805-bo, 9	-16, Yeonmujang	5-gil. Seongdong-gu. Seoul, Republic o
	Ana	alytical Resu	It
-	Test Item		Result
Coliform (	iroup		Negative
	1	fun : 9 : 2021	
	J We hereby certif	fun : 9 : 2021 y that the abov	ve are correct.
Korea	J We hereby certif Health Supplements Associa	fun : 9 : 2021 y that the abo stion Sub. Kore	ve are correct. a Health Supplements Institute
Korea	J We hereby certif Health Supplements Associa Director : Yang, Joo-Ho	fun : 9 : 2021 y that the abo ation Sub. Kore	ve are correct. a Health Supplements Institute

No. : 02021063339

Page ( 1 ) / Pages ( ) )

### Certificate of Analysis

No, of Samp Lot No. : Cl		mare of annuraceure i about ne to
Lot No. : C)	le D2021063339	Expiration Date = 2023-05-17
	111-0362N	
Inspection H	Purpose : Export	
: gribomnoù	Weissella cibaria CMU	
	Name : OraPharm Inc. Elin-s	μρ Τοοπ
Ipp1 (cant	Company address : 905-hd. S Korea	1-16, Yeonmujang 5-gil, Senngdong-gu, Seoul, Republic o
	An	alytical Result
	Test Item	Result
Mold & Yea	ist plate count(/g)	O(Yeast 0, Mold 0)
		Jul - 6 - 2021
	We hereby certif	Jul . 6 . 2021 Y that the above are correct.
Korea	We hereby certif Health Supplements Associa	Jul . 6 . 2021 Y that the above are correct, ation Sub, Korea Health Supplements Institute
Korea	We hereby certif Health Supplements Associa Director : Yang Loo-He	Jul . 6 . 2021 Y that the above are correct, ation Sub, Korea Health Supplements Institute

KHSI

No. : D2021063344

Page ( 1 ) / Pages ( 1 )

o of Samp		Date of me	mardesmic i source ao ro
	1e : D2021063344	Expiration	Date = 2023-05-17
or No. 3 C	111-0362N		
uspection	Purpose 7 Export		
ommodity :	Weissella cibaria CMU		
mlicant	Name : OraPharm Inc. Eun-sup	Yoon	
ppircuit	Company address : 905-h6, 9-	6. Yeenmujang 5-g	1. Seongdong-gu, Seoul, Republic ul
	Anal	ytical Result	
	Test Item		Result
Escherich	ia coli(/g)	0	
Salmonel1:	a spp.	N	egative
Listeria	nonocytogenes	N	gative
Staphyloco	occus aureus(/g)	0	
	Ju	1 6 2021	
	Ju We hereby certify	1 6 2021 that the above	are correct.
Korea	Ju We hereby certify Health Supplements Associat	1 6 2021 that the above ion Sub. Korea 1	are correct. Mealth Supplements Institute
Korea	Ju We bereby certify Health Supplements Associat Director : Yang, Joo-Hong	1 6 2021 that the above ion Sub. Korea 1	are correct. Health Supplements Institute

No. D2021060284

Page ( 1 ) / Pages ( ) )

ate of App	11641108 - 2021-08-02	Date of Manufacture 2021-05-18
o. of Samp	le 02021060284	Expiration Date = 2023+05-17
ot No, $= C$	111-0362N	
aspection	Purpose = Export	
ommodily :	Weissella cibaria CMU	
and the	Name : OraPharm Inc. Eun-si	υρ Υροή
ppricant	Company address	-16, Yeonmujang 5-g)l, Seongdong-gu, Seoul, Republic
	Ana	alytical Result
	Test Item	Result
BHC(mg/kg)	)	Not detected
DDT(mg/kg	)	Not detected
Aldrin(mg)	/kg)	Not detected
		Not detected
Dieldrin(	ng/kg)	And the second s
Dieldrin(m Endrin(mg/ End	ng/kg) /kg)	Not detected
Dieldrin(mg/ Endrin(mg/	ng/kg) /kg)	Not detected
Dieldrin(mg/ Endrin(mg/ End	ng/kg) /kg) /kg) /kg) /kg) /kg) /kg) /kg)	Not detected un . 10 2021 y that the above are correct : ation Sub. Korea Health Supplements Institute
Dieldrin(mg) Endrin(mg) End. Korea	/kg) /kg) J We hereby certif Health Supplements Associa Director - Vang Legati	UN detected un . 10 2021 y that the above are correct; ation Sub. Korea Health Supplements Institute
Dieldrin(m Endrin(mg) End Korea	/kg) /kg) J We hereby certif Health Supplements Associa Director : Yang, Joo-Ho	Not detected un . 10 2021 y that the above are correct. ation Sub. Korea Health Supplements Institute



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

### Macrogen 16S Report – Lot CI11-0366N

nple name : 0	CI11-0366N_contig_1								
			Inform	ation	_				
ner Information	1								
Sequencing P	rimer Name Primer S	Sequences			PCR Pri	mer Nan	ne Prime	r Sequences	
785F 5' (GG/	A FIA GAT ACC CTO	GIA) 3'	6	1405	7F 5' (AGA	GITIC	SA ICM	IGG CIC AG	) 3 - T\ 2'
30111 3 (CCO	TCA ATT CMT TTK	AGTTI)3		1432	and (TAC	00117	CONT	STI ACO ACI	1)3
	Subje	at				S	core	Identiti	ies
Accession	Description	Length	Start	End	Coverage	Bit	E-Value	Match/Total	Pct.(%
.C096236.1	cibaria	1516	6	1514	99	2776	0.0	1507/1509	99
Kingdom	Family		1	c	onus			Spacias	
Bacteria	Lactobacillac	020	1	Me	enus		10	opecies	•
					Weissella co	onfusa(gi	LC063164	4)	
			[		Weissella co Weissella co Weissella co Weissella ci Weissella ci Meissella so Weissella bo Weissella bo Weissella bo	onfusa(gi onfusa(gi onfusa(gi: baria(gi: N baria(gi: N contig_1 bli(gi: NR_i arameser ombi(gi: N allenica(g ellenica(g	LC053164 NR_0408: NR_1132: C096236) IR_036924 025642) nteroides( R_136437 i: LC09622 i: NR_1187	4) 16) 58) 4) gi LCO96224) ) ; 6) 71)	

Qu	Jery			1-0-1	Subject		1947	6 27 18 27 14		Score	-	97 - 18 - 19	Identities	1	Strand	5
Na	ime	Length	Start	End	Description	Link	AC	Length Start	End	Bit	Raw	E-value	Match	Total Pct	\$6)	
CN	MU CI11-0366N contig 1	154	4	28 1	535 Weissella cibana gene for 16S ribosomal RNA, partial sequence, strain: JCM 12495	https://www.ncbi.nlm.nih.gov/nucleotide/I,C0962	LC096236.1	1516 6	1514	2776	1503	0	1507	1509	99 Plus/P	lus
CM	MU CI11-0366N contig 1	154	4	31 1	541 Weissella cibaria strain II-1-59 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_03/	NR 036924.1	1529	1513	2771	1500	0	1508	1513	99 Plus/P	lus
CN	WU CH11-0366N conbg 1	154	4	22 19	541 Weissella confusa gene for 16S ribosomal RNA, partial seguence, strain: JCM 1093	https://www.ncbi.nlm.nih.gov/nucleotide/LC0631	LC063164.1	1538 10	1533	2739	1483	0	1511	1524	99 Plus/P	lus
CM	MU CI11-0366N contig 1	154	4	31 15	529 Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_111	NR 113258.1	1499 1	1499	2724	1475	0	1491	1499	99 Plus/P	hus
CN	MU CITT-0366N contig 1	154	4	41 1	517 Weissella confusa strain JCM 1093 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleobde/NR_04	NR 0408161	1477	1477	2684	1453	0	1459	1477	99 Plus/P	lus
CN	MU CI11-0366N contig 1	154	4	28 1	535 Weissella hellenica gene for 16S ribosomal RNA, partial sequence, strain: JCM 10103	https://www.ncbi.nlm.nih.gov/nucleotide/LC0962	LC096226.1	1512 3	1510	2453	1328	0	1450	1510	96 Plus/P	lus
CN	MU CI11-0366N contig 1	154	4	22 19	535 Weissella paramesenteroides gene for 16S ribosomal RNA, partial sequence, strain: JCM 9890	https://www.ncbi.nlm.nih.gov/nucleotide/LC0962	LC096224.1	1518 2	1515	2449	1326	0	1458	1521	96 Plus/P	lus
CN	MU CI11-0366N contig 1	154	4	28 18	535 Weissella hellerica strain NCFB 2973 16S ribosomal RNA gene, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_11	NR 118771.1	1527 7	1513	2446	1324	0	1449	1510	96 Plus/P	lus
CN	MU_CI11-0366N_contig_1	154	4	31 1	541 Weissella bombi strain R-53094 16S ribosomal RNA, partial sequence	https://www.ncbi.nlm.nih.gov/nucleotide/NR_13/	NR_136437.1	1528 1	1512	2440	1321	0	1450	1514	96 Plus/P	lus
12.64	ALL CITE COLON AND A	18.	4	221 11	511 Weissells and state MORE 122 shineseed DNA more partial and write	https://auto.nebi.eles.ph.gou/puplaotida/MD_020	LCL33CD CHAR	164.0	12:36	2320	13:30	0	1460	1639	OF Durits	Marin

### Certificate of Analysis – Lot Cl11-0366N

No. : D2021060279

Page ( 1 / / Pages ( f )

o. of Sampl	PLAYER IN A REPORT OF PLANT		
40. of Sample = D2021060279 .or No. = U111-0366N		Expiration Date : 2023-05-19	
or No UI	11-0366N		
nspection P	urpose : Export		
Commodity :	Weissella cibaria CMU		
onlicant	Name : OraPharm Inc. Eun-s	sup Yoon	
but (éaui	Company address : 805-hg	9-16, Yeonmujang 5-gil, Seongdong-gu, Seoul, Repub	ic
	An	alytical Result	
	Test Item	Result	
Sensory at	tribute	yellowish white powder	
Probiotics	(CFU/g)	110 000 000 000 CFU/g (104 000 ( 000, 108 000 000 000, 123 000 00 000)	00 0
End.			
End.			
End.		Jun , 10 , 2021	
End.	We hereby certi	Jun 10 2021 fy that the above are correct.	
End. Korea	We hereby certi Nealth Supplements Associ	Jun , 10 , 2021 fy that the above are correct. iation Sub. Korea Mealth Supplements Institut	45
End. Korea	We hereby certi Health Supplements Associ Director - Yang. Joo-H	Jun , 10 , 2021 fy that the above are correct. iation Sub. Korea Health Supplements Institut	86

No. : D2021060281

Page ( 1 ) / Pages ( 1 )

## Certificate of Analysis

nt No. : Clll-0366 ispection Purpose ommodity : Weisse pulicant Compa Sensory attribute Calorie(Kcal/100g Carbohydrate(%) Crude protein(%) Crude fat(%) Moisture(%) Ash(%) Sodium(mg/100g) End.	N = Export Ha cibaria CMU = OraPharm Inc. Eun-sup ny address = 905-ho, 9-1 Korca Anal Test Item )	Yoon 16, Yeonmujang D-gil. Seongdong-gu, Seoul. Republic ytical Result yellowish white powder 381.53 Kcal/100g 89.35 % 6.01 % 0.01 % 3.34 % 1.29 % 44.76 mg/100g
inspection Purpose Commodity : Weisse Name Compa Sensory attribute Calorie(Kcal/100g Carbohydrate(%) Crude protein(%) Crude fat(%) Moisture(%) Ash(%) Sodium(mg/100g) End.	Export IIa cibaria CMU OraPharm Inc. Eun-sup ny address 905-ho, 9-1 Korca <u>Anal</u> Test Item	Yoon         Beill Seongdong-gu, Seoul, Republic         ytical Result         ytical Result         yellowish white powder         381.53 Kcal/100g         89.35 %         6.01 %         0.01 %         3.34 %         1.29 %         44.76 mg/100g
Commodity : Weisse Applicant Compa Sensory attribute Calorie(Kcal/100g Carbohydrate(%) Crude protein(%) Crude fat(%) Moisture(%) Ash(%) Sodium(mg/100g) End.	Ila cibaria CMU : OraPharw Inc. Eun-sup ny address : 905-ho, 9-1 Korca Anal Test Item )	Yoon 16, Yeonsmijang D-gil. Seongdong-gu, Seoul, Republic ytical Result Result yellowish white powder 381.53 Kcal/100g 89.35 % 6.01 % 0.01 % 3.34 % 1.29 % 44.76 mg/100g
Applicant Compa Sensory attribute Calorie(Kcal/100g Carbohydrate(%) Crude protein(%) Crude fat(%) Moïsture(%) Ash(%) Sodium(mg/100g) End.	OraPharm Inc. Eun-sup ny address : 905-ho, 9-1 Korea <u>Anal</u> Test Item	Yoon         (6, Yeonmujang D-gil, Seongdong-gu, Seoul, Republic         ytical Result         Result         yellowish white powder         381.53 Kcal/100g         89.35 %         6.01 %         0.01 %         3.34 %         1.29 %         44.76 mg/100g
Compa Sensory attribute Calorie(Kcal/100g Carbohydrate(%) Crude protein(%) Crude fat(%) Moïsture(%) Ash(%) Sodium(mg/100g) End.	ny address : 905-ho, 9-1 Korca Anal Test Item	If Result       Result         ytical Result       Result         yellowish white powder       381.53 Kcal/100g         89.35 %       6.01 %         0.01 %       3.34 %         1.29 %       44.76 mg/100g
Sensory attribute Calorie(Kcal/100g Carbohydrate(%) Crude protein(%) Crude fat(%) Moisture(%) Ash(%) Sodium(mg/100g) End.	<u>Anal</u> Test Item	Result           Result           yellowish white powder           381.53 Kcal/100g           89.35 %           6.01 %           0.01 %           3.34 %           1.29 %           44.76 mg/100g
Sensory attribute Calorie(Kcal/100g Carbohydrate(%) Crude protein(%) Crude fat(%) Moisture(%) Ash(%) Sodium(mg/100g) End.	Test Item	Result.           yellowish white powder           381.53 Kcal/100g           89.35 %           6.01 %           0.01 %           3.34 %           1.29 %           44.76 mg/100g
Sensory attribute Calorie(Kcal/100g Carbohydrate(%) Crude protein(%) Crude fat(%) Moisture(%) Ash(%) Sodium(mg/100g) End.	>	yellowish white powder 381.53 Kcal/100g 89.35 % 6.01 % 0.01 % 3.34 % 1.29 % 44.76 mg/100g
Calorie(Kcal/100g Carbohydrate(%) Crude protein(%) Crude fat(%) Noisture(%) Ash(%) Sodium(mg/100g) End.	)	381.53 Kcal/100g 89.35 % 6.01 % 0.01 % 3.34 % 1.29 % 44.76 mg/100g
Carbohydrate(%) Crude protein(%) Crude fat(%) Moisture(%) Ash(%) Sodium(mg/100g) End		89.35 % 6.01 % 0.01 % 3.34 % 1.29 % 44.76 mg/100g
Crude protein(%) Crude fat(%) Moisture(%) Ash(%) Sodium(mg/100g) End.		6.01 % 0.01 % 3.34 % 1.29 % 44.76 mg/100g
Crude fat(%) Moisture(%) Ash(%) Sodium(mg/100g) End		0.01 % 3.34 % 1.29 % 44.76 mg/100g
Moisture(%) Ash(%) Sodium(mg/100g) End		3.34 % 1.29 % 44.76 mg/100g
Ash(%) Sodium(mg/100g) End		1.29 % 44.76 mg/100g
Sodium(mg/100g) End		44.76 mg/100g
End		
	Ju	n . 14 . 2021
Real Processo	We hereby certify	inat the above are correct.
Dire	ctor : Yang, Joo-Hon	g
B-101, Koren Hi	i Park. 700, baewangpangya-r	o, Hundang-gu. Seongnam-si. Gyeongg(-do, Republic of Korea

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No. D2021060287

Page ( 1 ) / Pages ( 1 )

1		
n. of Samp	le ; D2021060287	Expiration Date = 2023-05-19
at No. ; C	T11-0366N	
aspection	Purpose : Export	
ommodity -	Weissella cibaria CMU	
policant	Name - Oral'harm Inc. Eun-s	up Yoan 9-16 Yaanniisha A-mil Saxandong-mi Sowil Panublic a
	Company address : Korea	s to reconcional o give according by secure repairie o
	An	alytical Result
	Test Item	Result
Lead(mg/kg	g)	0.0096 mg/kg
Arsenic(m	g/kg)	0.0048 mg/kg
Cadmium(m	g/kg)	0.0383 mg/kg
Mercury(m	g/kg)	0.0022 mg/kg
		Jun - 7 - 2021
	We hereby certi	Jun - 7 - 2021 fy that the above are correct.
Korea	Wc hereby certi a Health Supplements Assoc	Jun - 7 . 2021 fy (hat the above are correct. iation Sub. Korea Health Supplements Institute
Korea	We hereby certi a Health Supplements Assoc Director : Yang, Joo-H	Jun . 7 . 2021 fy (hat the above are correct. mation Sub. Korea Health Supplements Institute long

No. : 02021060283

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to, of Samp	le = D2021060283	Espirat	ion Date / 2023-05-19		
ot Na 3 C	11-0366N				
inspection 1	Purpose : Export				
commodity =	Weissella cibaria CMU				
the fit have b	(ican) Name : OraPharm Inc. Eun-sup Yoon				
uppi i cani	Company address : 905-to 5	)-16, Yeonmujang	5-gil. Seengdong-gu. Seoul, Republic of		
	An	alytical Resu	11		
	Test Item		Result		
Coliform (	froup		Negative		
		Jun 9 _ 202)			
	We hereby certin	Jun 9 2021 fy that the abo	ve are correct.		
Korea	We hereby certin Health Supplements Associ	Jun 9 2021 fy that the abo ation Sub. Kor	ve are correct. ea Health Supplements Institute		
Korea	We hereby certin Mealth Supplements Associ Director : Yang, Joo-He	Jun 9 202) fy that the abo ation Sub. Kor-	ve are correct. ea Health Supplements Institute		
Korea	We hereby certin Mealth Supplements Associ Director : Yang, Joo-He Korea Bio Park. 1000 Decemanyanyo	Jun 9 2021 fy that the abo ation Sub. Kor ong	ve are correct. sa Health Supplements Institute		

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Page ( 1 ) / Pages ( 1 )

### Certificate of Analysis

No. of Samp	le 1 D2021063340	Expiration	Date : 2023-05-19
Lot No. : Cl	11-0366N		
Inspection I	Purpose : Export		
Commodity :	Weissella cibaria CMU		
Inntionne	Name : OraPharm Inc. Eun-su	p Yoon	
when evolue	Company address : 905-ho. 9- Korea	-16, Yennmujang 5-g	il, Seongdong-gu, Seoul, Republic of
	Ana	lytical Result	
1	Test Item		Result
Mold & Yea	st plate count(/g)	0	Yeast 0, Mold 0)
	J	ul., 6., 2021	
	J We hereby certify	al , 6 . 2021 That the above	are correct.
Korea	J We hereby certify Health Supplements Associa	ul. 6 . 2021 T that the above tion Sub. Korea 1	are correct. Mealth Supplements Institute
Korea	J We hereby certify Health Supplements Associa Director : Yang, Joo-Hor	ul , 6 , 2021 that the above tion Sub. Korea 1	are correct. Mealth Supplements Institute

No. : D2021063345

Page ( I ) / Pages ( I )

e. of Samp	The second s	
e. of Sample   D2021063345 et No. ; Cl11-0366N		Expiration Date = 2023-05-19
01.740 CI	11-0366N	
nspection (	Parpose : Export	
ommodity :	Weissella cibaria CMU	
p)icant Communications 905-ho.		9-16 Versenings T-gil Separatora-mi Secul Republic :
PP 1 Count	Company address : Korea	a-in, reonaulang a-gir, seonggoing-gu, seonit, kepuarit t
	An	alytical Result
	Test Item	Result
Escherich	ia coli(/g)	0
Salmonel1;	a spp.	Negative
Listeria	nonocytogenes	Negative
Staphyloco	occus aureus(/g)	0
		Jul , 6 . 2021
	We hereby certi	Jul , 6 . 2021 fy that the above are correct.
Korea	We hereby certi a Health Supplements Assoc	Jul . 6 . 2021 fy that the above are correct. fation Sub. Korea Health Supplements Institute
Korea	We hereby certi a Health Supplements Assoc Director : Yang, Joo-I	Jul , 6 . 2021 fy that the above are correct. fation Sub. Korea Health Supplements Institute long

No. 02021060285

Page ( 1 ) / Pages ( ) /

lo, of Sampl		Date of administration
ko, of Sample : D2021060285		Expiration Date > 2023-05-19
01 00: 1 01	11-0366N	
nspection F	Purpose : Export	
commodity =	Weissella cibaria CMU	
mlicant	Name OraPharm Inc. Eun-sup	y Yoon
ppresents	Company address : 508-no, 9-	To, reonnulang 5-gil, seongdong-gu, seoul, kepublic o
	Апа	lytical Result
	Test Item	Result
BHC(mg/kg)		Not detected
DUT(mg/kg)		Not detected
Aldrin(mg/	kg)	Not detected
Dieldrin(m	g/kg)	Not detected
Endrin(mg/	kg)	Not detected
	11	m . 10 . 2021
	Ji We hereby certify	m . 10 . 2021 y that the above are correct.
Korea	Ji We hereby certify Health Supplements Associa	m . 10 . 2021 y that the above are correct. tion Sub. Korea Health Supplements Institute
Korea	Ji We hereby certify Health Supplements Associa Director : Yang, Joo-Hou	m . 10 . 2021 y that the above are correct. tion Sub. Korea Health Supplements Institute

### 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

		ANI of Weiss	ella ciba	ria CMU	by EZ Bio	Cloud		
			0114 0100		.,	orouu		
	1 Upload FASTA							
F	asta QC W. clbarta CM	NJ. Fasta						
A	-	Test lesses and						
	1	2,362,501	646,493	534,795	535,929	645,284	0	45.32
P. 1	1 Upload FASTA							
F	asta QC W. cibaria GM	IS1.fasta						
В								
	1	2,342,849	639,737	532,143	529,573	641,396	0	45.32
	a							
	Calculate ANI							
. 0	rthoANIu Results							
						-		
		OrthoANIu value (%)				99,9	0	
		Genome A length (bp)				2,362,	320	
		Genome B length (bp)				2,341,	920	
		Average aligned length (bp)				1,266,	485	
		Genome A coverage (%)				53.6	a	
		Genome B coverage (%)				.54.0	6	
VI use	earch algorit	thm						Ora
VI use	earch algorit	hm ANI of Weiss	ella ciba	aria CMU	by EZ Bio	oCloud		Ora
VI use	earch algorit	hm ANI of <i>Weiss</i>	ella ciba	aria CMU	by EZ Bio	oCloud		Ora
VI use	earch algorit	hm ANI of <i>Weiss</i>	ella ciba	nria CMU	by EZ Bio	oCloud		Ora
	earch algorit Deloed FAST	thm ANI of <i>Weiss</i>	ella ciba	aria CMU	by EZ Bi	oCloud		Ora
NI use	earch algorit ♪ Upload FAST Fasta QC W. coberto	ANI of Weiss	ella ciba	nria CMU	by EZ Bid	oCloud		Ora
1 enorthe uence A	earch algorit	ANI of Weiss	ella ciba	nria CMU 534,795	by EZ Bid	0 <b>Cloud</b> 645,284	0	<b>Ora</b>
1 enorme uence A	earch algorit ⊥ Upload FAST Fasta QC W. oberin 1	ANI of Weiss	ella ciba 646,493	nria CMU 534,795	by EZ Bio 535,929	645284	0-	<b>Ora</b>
1 enorme uence A	Luploed FAST	ANI of Weiss	ella ciba 646,493	594,795	by EZ Bid	645,284	0	<b>Ora</b>
1 enorme uence A	Luploed FAST	ANI of Weiss	ella ciba 646,492	ssa,705	by EZ Bid	645,284	ð	<b>Ora</b>
	Luploed FAST Fasta QC W. closed 1 Fasta QC W. closed Fasta QC W. closed	ANI of Weiss	ella ciba 646,492	534,795	by EZ Bid	645284	0	<b>Ora</b>
1 enorme uence A enorme uence B	Carch algorit ↓ Upload FAST Fasta QC (W. oberia 1 ↓ Upload FAST Fasta QC (W. oberia	ANI of Weiss	ella ciba 646,492	534,795	by EZ Bid	645284	8	<b>Ora</b>
1 enorme uence A snorme uence B	Earch algorit	ANI of Weiss ANI of Weiss CMUfasts 2,362,501	ella ciba 646,493 641,402	534,795 529,602	by EZ Bid 535,929 532,163	639,746	0	Ora 45.32 45.32
1 enorme uence A snorme uence B	Lupload FAST Fasta QC W. oberro 1 Lupload FAST Fasta QC W. oberro 1	ANI of Weiss	ella ciba 646,493 641,402	554,795 529,602	by EZ Bid	645,284 639,746	0.	<b>Ora</b> 45.32 45.32
anorre unnee A 2 snorre unnee B 4 3	Luploed FAST Fasta QC W. oberro 1 Luploed FAST Fasta QC W. oberro 1 Luploed FAST Fasta QC W. oberro 1 Luploed FAST	thm ANI of Weiss	ella ciba 646,492 641,402	534,705 529,602	by EZ Bid 535,929 532,163	645,284 639,746	0	<b>Ora</b> 45.32 45.32
	Luploed FAST Fasta QC W closers 1 Luploed FAST Fasta QC W closers 1 Calculate Al OrthoANiu Results	thm ANI of Weiss ANI of Weiss 2.362.501 A CM62 fasta 2.342.914	ella ciba 646,493 641,403	534,795 529,602	by EZ Bid	645,284 639,746	8	Ora 45.32 45.32
1 endrtw uence A snorme uence B dealate ANI	Earch algorit ↓ Uploed FAST Fasta QC W observe 1 Fasta QC W observe 1	ANI of Weiss ANI of Weiss 2.362.501	ella ciba 646,492 641,402	534,795 529,602	by EZ Bid	639,746	0	<b>Ora</b> 45.32 45.32
1 enorme uence A enorme uence B deduate ANI	Lalculate Al OrthoANiu Results	thm ANI of Weiss ANI of Weiss 2,362,501 A 2,362,501 A 2,342,914.	ella ciba	534.795 529,602	by EZ Bid 535,929 532,163	609,746	0	Ora 45.32 45.32
1 enorme uence A enorme uence B deulate ANI	Calculate Af OrthoANiu Results	ANI of Weiss ANI of Weiss CAL fasts 2,362,501 CALSS fasts 2,342,914. COMSS fasts 2,342,914.	ella ciba	534,795 529,602	by EZ Bid 535,929 532,163	645,284 639,746 99,93 2,362,920	0.	Ora 45.32 45.32
1 enorme uence A anorme uence B deculate ANI	Calculate Al	ANI of Weiss ANI of Weiss CALL 2,362,501 CALS 2,362,501 CALS 2,362,914 CONS2 fasts 2,342,914 CONS2 fasts CONS2 fas	ella ciba 646,493 641,402	534,795 529,602	by EZ Bid 535,929 532,169	639,746	0	Ora 45.32 45.32
1 enorme uence A anorme uence B dealate ANI	Calculate Al OrthoANiu Results	ANI of Weiss ANI of Weiss CAU feats 2.362.501 CAUS2 feats 2.342.914 OrthoANIu value (%) Genome A length (bp) Genome B length (bp) Average aligned length (bp)	ella ciba 646,492 641,402	554,795 529,602	by EZ Bid 535,929 532,163	645,284 645,284 639,746 99,93 2,362,920 2,341,920 1,531,922	0	Ora 45.32 45.32
1 enorme uence A anome uence B declarte ANi	earch algorit	ANI of Weiss ANI of Weiss CAUfests 2,362,501 A CAUS2 fasts 2,342,914 OrthoeMiu value (%) Genome A length (bp) Genome B length (bp) Average aligned length (bp) Genome A coverage (%)	ella ciba 646,492 641,402	554,795 529,602	by EZ Bid 535.929 532,163	645,284 645,284 639,746 99,93 2,362,920 2,341,920 1,531,922 64,85	0	Ora 45.32 45.32

21	11	1/2	ഹാദ	)
3/		1/Z	UZZ	<u>_</u>

(1) OrthoANI	usearch algor	ithm						OraPharm ·:·
		ANI of Weis	ssella ciba	ria CMU b	oy EZ Bio	Cloud		
Genome sequence A	⊥ Upload FAST	A CMU.fasta						
	1	2,362,501	646,493	534,795	535,929	645,284	0	45,32
2 Génome sequence B	⊥ Upload FAST	A CMS3.fasta						
	Ţ	2,342,907	641,401	529,601	532,163	639,742	D	45.32
3 Calculate ANI	Calculate AM OrthoANIu Results	41						
		OrthoANIu value (%	.)			99,9	2	
		Genome A length (b	p)			2,362,3	320	
		Genome B length (b	p)			2,341,9	20	
		Average aligned length	(bp)			1,679,1	93	
		Genome A coverage	(%)			71.0	В	
		Genome B coverage	(%)			71,7	0	

### (1) OrthoANI usearch algorithm

### OraPharm ·:·

		ANI of We	issella ciba	ria CMU b	y EZ Bio	Cloud		
Genome	⊥ Upload FAST	rA a CMU.fasta						
quence A		The large be						
	1	2,362,501	646,493	534,795	535,929	645,284	0	45.32
	-							
2	. ⊥ Upload FAS	TA						
Genome equence B	Fasta QC W. cibaria	a JCM 12495 fasta						
	1	406,515	107,274	105,100	80,931	113,210	0	45.76
1	Calculate Al	NI						
alculate ANI	Colculate Al OrthoANIu Results	NI						
a calculate ANI	🗑 Calculate Al OrthoANIu Results	NI OrthoANiu value (	5)			99.5	14	
a Salculate ANI	Calculate Al OrthoANIu Results	NI OrthoANIu value ( Genome A length (	%) bp)			99.5 2.362	14	
a Calculate ANI	Colculate A	NI OrthoANIu value ( Genome A length ( Genome B length (	%) bp)			99.5 2,362 405,5	14 320 160	
a Salculate ANI	Colculate A	NI OrthoANIu value ( Genome A length ( Genome B length ( Average aligned lengt	%) bp) bp) h (bp)			99.5 2,362, 405,5 270,7	04 320 773	

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OrthoAN	Il usearch algo	orithm					OraPharm
		ANI of We	eissella ciba	aria CMU I	by EZ Bio	Cloud	
Genome		A CMU fasta					
sequence A		The state of the second state of the					
	4	2,362,501	646,493	534,795	535,929	645,284	0 45.32
2		A					
Genome sequence B	Fasta QC W. cibaria	BC14.fasta					
	1	2,473,048	677,691	559,095	555,425	680,837	0 45.07
(3)	🗑 Calculate AN	11					
Calculate	OrthoANIu Results						
ANI							
		OrthoANIu value (1	e)			98,45	
		Genome A length (b	pp)			2,362,320	
		Genome B length (b	(qe			2,472,480	
		Average aligned lengt	h (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. Upload FASTA Fasta QC W. cibaria CMU.fasta Genome sequence A 2,362,501 646,493 534,795 535,929 645,284 45.32 1 Ô. 1 Upload FASTA Fasta QC W. cibana CH2.fasta Genome sequence 8 2,466,961 680,613 553,286 558,949 674,113 45.09 0 OrthoANlu Results Calculate ANI OrthoANIu value (%) 96.90 2,362,320 Genome A length (bp) Genome 8 length (bp) 2,466,360 Average aligned length (bp) 1,526,677 64.63 Genome A coverage (%) 61.90 Genome B coverage (%)

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OrthoANI u	usearch algo	rithm						<b>OraPharm</b>
		ANI of We	issella ciba	aria CMU I	by EZ Bio	Cloud		
1 Genome sequence A	① Upload FAST     Fasta QC     W. cibaria	TA a CMU fasta						
	1	2,362,501	646,493	534,795	535,929	645,284	0	45.32
2 Genome		TA se VTT E-133279,fasta						
sequence b	1	2,212,145	604,915	495,769	501,367	610,094	D	45.DB
3 Calculate	Celculate Al OrthoANIu Results	NI						
ANI								
		OrthoANiu value (%	)			79.0	n.	
		Genome A length (b	p)			2,362,	320	
		Genome B length (b	p)			2,211,	360	
		Average aligned length	(bp)			957,2	12	
		Genome A coverage	(%)			40.5	2	
		Genome B coverage	(%)			43.2	9	
OrthoANI	usearch algo	orithm						OraPharm
		ANI of We	issella ciba	aria CMU	by EZ Bio	Cloud		

	0	土 Upload FASTA							
Genome	Genome	Fasta QC W. cibaria CM	MU fasta						
	sequence A		The second second						
		1	2,362,501	646,493	534,795	535,929	645,284	0	45.32
	2								
	Genome sequence B	Fasta QC W. hellenica	CCUG 33494.fasta						
		1	380,413	118,663	81,507	60,801	119,442	0	37.41
	3	Galculate ANI							
	Calculate ANI	OrthoANIu Results							
			Ortho Ability value (V)				247	15	
			Genome A length (bp)				2.362	320	
			Genome B length (bp)				379,4	140	
			Average aligned length (bp)	1			127,0	025	
			Genome A coverage (%)				5.3	8	
			Genome B coverage (%)				39.4	18	


	A \$11 - 6 14/-1-					Urar
	ANI of Weis	sella ciba	aria CMU	by EZ E	BioCloud	
1 Deload	FASTA					
Genome Fasta QC W.c	ibaria CMU.fasta					
sequence A						
1	2,362,501	646,493	534,795	535,929	645,284 0	45.32
2 I Upload	FASTA					
Genome Fasta QC W k	andleri DSM 20593.fasta					
sequence B						
1	327,196	102,592	51,600	74,523	97,709 772	38.64
A						
3 E Caloula	te ANI					
Calculate OrthoANlu Res	ults					
ANI						
	OrthoANiu value (%	)			68.16	
	Genome A length (bp	)			2,362,320	
	Genome B length (b)	s) (h=)			326,400	
	Average aligned length	(bp)			00,720	
	Genome A coverage (	*)			2.02	
	Genome E couproso /	10.1			2.1.1.100	

		ANI of Weis	sella ciba	ria CMU I	by EZ Bio	oCloud		ora
	⊥ Upload FA	STA						
Genome	Fasta QC W, ciba	ria CMU,fasta						
sequence A	-	1						
	1	2,362,501	646,493	534,795	535,929	645,284	0	45.32
2	🛧 Upload FA	STA						
Genome sequence 8	asta QC W. soli	KACC 11848.fasta						
acquerice b	1	1683184	472.087	369.764	366.339	474.994	0	43.73
			1. 414 - 1			- to are t		1999
3	Calculate	ANI						
Calculate	OrthoANIU Result	5						
		OrthoANIu value (	\$)			71.	75	
		Genome A length (	bp)			2,362	320	
		Genome B length (	bp)			1,683	000	
		Genome B length ( Average aligned lengt	bp) h (bp)			1,683 480,0	000 199	

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UANI U	search aigona		alla aiba			Claud		OraPh
		ANI OT Weiss	ella ciba	ria CMU I	by EZ BIC	ocioua		
-	1. Upload FASTA							
	Fasta OC W charle Ch	All facto						
sequence A	The Colorid Co	NO.7054						
1	1	2,362,501	646,493	534,795	535,929	645,284	0	45.32
-	-							
2	1 Upload FASTA							
Genome sequence B	Fasta QC W. thailander	nsis JCM 10695 fasta						
		1000 million (1000						100 million (100 million)
	4	198,590	03,115	35,858	39,652	29,800	99	38.04
3	Galculate ANI							
Calculate	OrthoANIu Results							
ANI							-	
		OrthoANIu value (%)				65	9,79	
		Genome A length (bp)				2,36	2,320	
		Genome B length (bp)	6			19	7,880	
		Genome A coverane (%)	,			30	.28	
		A coverage (1)						

## Appendix 3.2 JSpeciesWS Algorithm

## (2) JSpeciesWS algorithm

## OraPharm 🕂

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

Show ANIb and [a	ligned nucleotide	ts][%] + ▲ Dov	vnload as .csv				Legent Abovese	nall (= 1074) Delaw cuts	6 (* 99%) Surgeonium Alig	Executed .			
	W. cibaria CMU.fasta	W. cibaria CMS1.fasta	W. cibaria CMS2.fasta	W. cibaria CM\$3.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	*	99.95 (99.91)	99.95 (99.94)	88.89 (99.95)	<b>93.29</b> (93.94)	96.72 (91.75)	38.01 (17.84)	78.23 (65.61)	71.75 (8.50)	67 33 (4 42)	77.22 (43.07)	71.28 (35.65)	\$8.45 (2.24)
W. elbaria CMS1.fasta	100.00 (99.85)	*		*								•	-
W. cibaria CMS2.fasta	100.00 (90.84)	<b>T</b>	4		7		. *	-	£	÷	a -	*	~
W. cibaria CMS3.fasta	100.00 (99.69)				-	8				7	*		
W. cibaria BC14.fasta	98.20 (89.17)		9	X	*	1	1	1		1	1	1	3
W. cibaria CH2.fasta	96.58 (87.76)		2	2	2			•	÷	1		*	÷
W. cibaria JCM 12495.fasta	100.00 (99.84)	10	3	4	1			*	5		4		
W. confusa VTT E-133279.fasta	77,89 (67,43)	7	3	à.			1	1	0	*	-		*
W. helienica CCUG 33494.fasta	73.52 (#6.30)	1	2	-	7	1	1	1	5		-		2
W. kandleri DSM 20593.fasta	67.64 (30.07)	141	1	1	7	1	1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 -	•	1	1		-	Y
W. paramesenteroider FDAARGOS 414.fasta	7232) \$(4026)											*	
W. soli KACC 11848.fasta	70.85 (47.52)	-				-	1	÷	6	*		•	2
W. thailandensis JCM 10695.fasta	59.02 (26.30)	2	4	14-2	a :	2	-	÷	6	÷	ž.	÷	3

## (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	Laganit: Abu	we calloff (> 66%)   Below cutoff (< 95%)   Son	spicious 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
Wcibaria_CMS3.fasta	99.99	99.95	2361358	2362501
W_cibaria_BC14 fasta	98.29	93.94	2219251	2362501
Wcibaria_JCM_12495 fasta	10.86	17.84	421460	2362501
Wcibaria_CH2 fasta	96.72	91.75	2167678	2362501
Wconfusa_VTT_E-133279.fasta	78.23	63.61	1502901	2362501
Wparamesenteroides_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

#### 3/11/2022

## OraPharm ·:·

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

Show ANIm and [	aligned nucleotid	es][%]+ (± <u>Do</u>	enload as csv				Legend Almoore	laff (* 86%) Delew cale	if (+ 35%) Despitions	alignenenti .			
	W. cibaria CMU.fasta	W. cibaria CM\$1.fasta	W. cibaria CM\$2.fasta	W. cibaria CM\$3.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. paramesenteroide: FDAARGOS 414.fasta	sW. 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)	<b>58.48</b> (94.79)	96.53 (93.14)	99.99 (17.54)	87.36 (28.14)	87.39 (1.39)	84.85 (0.12)	88.26 (6.11)	86 41 (5 56)	85.65 (0.02)
W. cibaria CMS1.fasta	99.98 (100.00)	*	1	1			1	+		7	*	*	
W. cibaria CMS2.fasta	99,99 (100.00)		- 21	4	95		1	*	5	1	÷	ŧ	2
W. olbaria CMS3.fasta	99.99 (100.00)		2	4				1	1	-	*		
W. cibaria BC14.fasta	58.50 (89.69)			1	1		-						*
W. cibaria CH2.fasta	96.93 (88.81)		4	-1	1			-	*				1
W. cibaria JCM 12495.fasta	99.99 (100.00)						1		-		1		*
W. confusa VTT E-133279.fasta	87.35 (29.45)	,		1	'	1		1		1	-	1	1
W. hellenica CCUG 33494.fasta	87.39 (8.64)		2				1	7	1	1	1	7	1
W. kandleri DSM 20593.fasta	84 86 (0,81)				- 18-1		*	*		-	×	*	*
W. paramesenteroide FDAARGOS 414.fasta	88.58 (6.48)					*		1		<u>.</u>		*	
W. soli KACC 11848.fasta	86,39 (6,29)				*	14		-		+	*	*	1
W. thailandensis JCM 10695.fasta	85.65 (0.24)			1	1	1	1	1	7	1	1		1

## (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	Legena Abu	re catolif (> 16%) Below cutoff (< 95%) Sure	picious alignment	
Genome	ANIm [%]	Aligned [%]	Aligned [bp]	Total [bp]
W_cibana_CMS2.fasta	99.99	100.00	2362501	2362501
Wcibaria_CMS3.fasta	99,99	100.00	2362500	2362501
W_cibaria_JCM_12495 fasta	99.99	17.54	414378	2362501
Wcibaria_CMS1.fasta	99.98	100,00	2362501	2362501
W_cibaria_BC14.fasta	98.48	94.79	2239482	2362501
Wcibaria_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
Wconflusa_VTT_E-133279.tasta	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
Wkandleri_DSM_20593.fasta	84.86	0.12	2797	2362501

## (2) JSpeciesWS algorithm

## OraPharm ·:·

3/11/2022

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

The second se			second a second s	Bacteria ( Premiuma / Becali ) Lacossectores / Lacossectores and	07952	<b>A 10</b> 0
W_prhatis_Ch5.) fants · Allowenses as bev · Ant associat (II)	Legarer (Managamer Chinese) Internet (Chinese)	tion in a state of the local diversity of the	[1] - construction and a set of the set of the set	Garcera / Fumicizes / Barcel - Lacobarcears / Lacobarcears	10 /9872	
			(P) some processing in press filter shall	Enclayer's Forminger's Enclair's personal dates ( Landona date enclase and	070540	a 🖬 🖻
13 Sigunan	Doetaen ( Phytom / Class / Order / Family	2-Score	[1] Backbachmathak antingpank 1112	Machenia / Pornanchen / Machini ( Santabacilitates ) ( Lantabacilitate and	in Tadica 🚺	100
(9) Winnersky Winkey (2014) (2019).	Bactoria ( Perroquins / Bacelli Ladolitacibales / Lactoriacibacibat	53004 U D	C A A A A A A A A A A A A A A A A A A A	Bartera / Formune / Built / Caralianilates / Lactina illa con	079480	
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Particular as (CCC)	Decknie / Pinistann / Decili I Lactore Rans / Lactore Ranne	D C	C	Beckere (Permarks (Beck)) secondaria (Secondaria)	073420	
Amongal Jama 1201	Decema / Persoants / Decair Lacobachaetti Lacobachaetter	ante B D	C Destination of the Contract	Electrica i Furminian / Bacill / Lacindacibilitis i Lacindacibilitarian	579256	
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Farewayer Here Westerry	Bacteria (Pinterutes / Bacilii) Lachisacitales / Lactobacitacene	EM6746 🚺 🚺	LI IN approximate presenting per	Michelle / Emissibles / Bieller / Lacobacilities / Lacobacilities	078442	
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Records of Villa.	Bacteria / Ferricutes / Bacdl / Lactobacillates / Lactobacillacese	0.65045 🚺 🎑	U	Bacone / Provides / Belit / Ladolaschers / Ladolaschere	0.77400	
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T) Vimarkit primerovno AUTO 5203	Badena / Princutes / Bacili / Lactobaciliates / Lactobaciliaceae	0.84206 🚺 🛄		Baltera / Persulan / Baltit / Labobackara / Caliblacidarae	077417	
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## (2) JSpeciesWS algorithm

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

Tetra Results Mat	trix Tétra Re	sult by Genome											
A Download as	392						Legend Above:	aloff (> 0.428) In range (	> 0.389) Below outo	a (< 0.583)			
	W. cibaria CMU.fasta	W. cibaria CMS1 fasta	W. elbaria 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. paramésenteroi- FDAARGOS 414.fasta	desW. soli KACC 11848.fasta	W. thailandensis JCM 10695.fasta
W. cibaria CMU.fasta	1	0.99998	0.99998	86666.0	0.9991	0,99651	0,97501	0.97469	0.81143	0.67592	0.83494	0,9047	0.76344
W. cibaria CMS1.fasta	0.99998	*		-	-	-		-	2	-	-	-	-
W. cibaria CMS2.fasta	0.99998												
W. cibaria CMS3.fasta	0.99998	-	-	•	-	-	-	-	-	-	-	-	-
W. cibaria BC14.fasta	0.9991	-	1	-	•	-	0	9	1	-	-	-	-
W. cibaria CH2.fasta	0.99891	-	-	1	-		-	-	-	-	-	-	-
W. cibaria JCM 12495.fasta	0,97501		-	-	-	-		-	-	-	-	-	
W. confusa VTT E-133279.fasta	0,97489		-			-	-	à i	-	-		-	
W. hellenica CCUG 33494.fasta	0.01143	~	-	-	-	-	-	-	*	-	8	-	7
W. kandleri DSM 20593.fasta	0.67592	-	-	-	-		-	-	-	•	1	-	-
W. paramesenteroide FDAARGOS 414.fasta	0.83494 S	-	*	-	7	-		-	-	-	*	-	
W. soli KACC 11848.fasta	0.9047	-	-	-	-	-	1		-		-	1.00	
W. thailandensis	0.76344												1

# OraPharm ·:

## (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 (> 6,809) In range (> 0.589) Below cutoff (< 0.589)	
Genome			PCC
Wcibaria_CMS1 fasta			0.99998
Wcibaria_CMS2.fasta			0.99998
Wcibaria_CMS3.fasta			0.99998
Wcibaria_BC14.fasta			0.9991
W_cibaria_CH2.fasta			0.99891
W_cibaria_JCM_12495 fasta			0 97501
Wconfusa_VTT_E-133279.fasta			0.97489
Wsoli_KACC_11848 fasta			0.9047
Wparamesenteroides_FDAARGOS_414.fasta			0.83494
W_hellenica_CCUG_33494 fasta			0.81143
W_thailandensis_JCM_10695.fasta			0.76344
W_kandlerl_DSM_20593 fasta			0.67592



## Appendix 3.3 ANI Calculator Algorithm





Score (b/b)





#### (3) ANI calculator algorithm

#### ANI of Weissella cibaria CMU by ANI calculator





1000

Score (pits)

1500

2000

3/11/2022











#### (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. 77.15 Identity distribution 2 77.30 mean = 77.02 80 median = 77.02 27.05 Nequency 0.4 0.5 0.4 77.00 20 78.95 0.0 10 15 N.80 101 x (%) 699.0 **Bit-Score distribution** 2 658.5 mean = 698 30 median = 698 Frequency 0.4 0.6 698.0 02 697.5 9 200 400 000 800 \$97.0 Score (bits)

## 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. Cl11-0115N;
 13 = W. cibaria CMU Production Lot No. Cl11-0116N; 14 = W. cibaria CMU Production Lot No. Cl11-0117N; 15 = W. cibaria CMU Production Lot No. Cl11-0366N; 16 = W. cibaria CMU Production Lot No. Cl11-0362N

## Appendix 4 Manufacturing Documentation

발급번호: 11H9-QJO7-8B47-XNZR-DXBZ





#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, Munsanreup, Jinjursi, Gyeongsangnam-do, Republic of Korea
- Name of Representative : Minn Solm
- Name of registered Production Manager | Jonghie Yoor
- Name of registered Quality Control Manager Chunho Park
- Notice : This certificate is valid only for Health Functional Food manufactured by Good Manufacturing Practices Applied Manufacturers.

Safety

- Approval Date = 20171109
- Remarks : Purpose of be

Signature :

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



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 Cl11-0366N

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

#### Milk and Soy – Lot CI11-0116N



#### 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

Product Name

: AYFN21-31115 : 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.

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FQP-32-F2 (3)

SGS Korea Co. Ltd.

Memory of the DGS Group (Sociale Générale de Surveillande)

#301, 67, Malgeumnae-gli, Ukerang-sl, Gyeonggi-da, Korsa #16071 1+82 (0)31 689 3800 1+82 (0)70 4332 1655 http://www.sgsgroup.kr

Page 1 of 1

Issued Date 2021. 08. 12

## Gluten - Lot CI11-0116N

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1	.8	100		
	98			38

#### Test Report (Reference) No. F690101/LF-CTSAYFN21-31116

ORAPHARM INC.

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

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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 Rep	ort:	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.

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#301, 67, Malgeunnae-gi, Ulwang-s, Gyeonggi-do, Korea #16071 1 +52 /0/31 659 5500 #+52 /0/70 4332 1559 http://www.agegroun.kr

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

#### Milk and Soy – Lot CI11-0117N



#### Test Report (Reference)No. F690101/LF-CTSAYFN21-31118

: AYFN21-31118

Issued Date 2021. 08. 12 Page 1 of 1

ORAPHARM INC.

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

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SGS File No

Product Name

: Weissella cibaria CMU

Item No./Lot No.

: MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0117N

: 2021.08.04 to 2021.08.12

**Testing Period** : Reference **Purpose of Test Report** 

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

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		Lineaton of the 2010 Press (Coulds) Condenie for Council	-

## Gluten – Lot CI11-0117N

SG	S		
Test Report	(Reference) No. F690101/LF-CTSAYFN21-31119	Issued Date 2021. 08. 12	Page 1 of 1
ORAPHARM INC. 905-ho 9-16, yeor seongdong-gu, se korea	nmujang 5-gil eoul		
The following samp	ole(s) was/were submitted and identified by/on behalf of the clien	t as:-	
This report is not n AND DRUG INDUS	elated to the Ministry of Food and Drug Safety "ACT ON TESTIM STRY"	NG AND INSPECTION IN THE FOOD	
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	1	2021.08.04 to 2021.08.12
Purpose of Test Rep	ort :	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.

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Issued Date 2021. 08. 12 Page 1 of 1

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

#### Milk and Soy – Lot CI11-0366N



#### Test Report (Reference)No. F690101/LF-CTSAYFN21-31121

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 Product Name : AYFN21-31121 : Weissella cibaria CMU : MFG 2021.02.15, EXP 2023.02.14, Lot No. CI11-0366N

 Item No./Lot No.
 : MFG 2021.02.15, EXP 2023.02.14, Lot No. 0

 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.

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## Gluten – Lot CI11-0366N

SG:		Issued Date 2021, 08, 12	Page 1 of 1
ORAPHARM INC. 905-ho 9-16, yeon seongdong-gu, se korea	mujang 5-gil eoul		
The following samp	le(s) was/were submitted and identified by/on behalf of the clie	ent as:-	
This report is not re AND DRUG INDUS	elated to the Ministry of Food and Drug Safety "ACT ON TEST TRY"	TING AND INSPECTION IN THE FOOD	
SGS File No.	: AYFN21-31122		
Product Name	; Weissella cibaria CMU		
Item No./Lot No.	: MFG 2021.02.15, EXP 2023.02.14, Lot No. C111-03	366N	
Test Period	: 2021.08.04 to 2021.08.12		

Reference Purpose of Test Report :

#### **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.),

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Member of the SGS Group (Societé Génerale de Sorveillande)

#201, 67, Maigeunnaeigi, Liwangis, Gyeongg-do, Kotea #16075 1 -52 (0)31 685 5800 Y +82 (0)70 4332 1659 http://www.sosorouo.kr.

# 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 Cl11-0366N

Page 1 of 2

Issued Date : 2021. 08. 12

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



#### Test Report (Reference)No. F690101/LF-CTSAYFN21-31117

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 detecte 2) The test resu	d = ≤LOQ (0.01mg/kg), LOQ= Limit of quantitation Ilts are limited to the requested product(sample name, item no.),

and the sample don't have food Labeling information of Korea regulation ...

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SGS File No	: AYEN21-31117		
Product Name	: Weissella cibaria CMU		
Pesticide 245 items			
Acetamiprid, Acrinathrir Benthiavalicarb-isoprop Butachlor, Cadusafos, G Chlorantraniliprole, Chk Chlorpyrifos, Chlorpyrif Cyhalofop-butyl, Cyhale Dichlofluanid, Dichlorvo Dimethenamid, Dimetho Dithiopyr, Diuron, Edifer Ethiofencarb, Ethion, Eth Fenazaquin, Fenbuconz MPP, Fenvalerate, Feri Fluopicolide, Fluquincor Heptachlor, Heptachlor Indoxacarb, Iprobenfos/ Malathion, Mandipropar Methabenzthiazuron, M Metolcarb, Metribuzin, I Oxaziclomefon, Oxyflud Pentoxazone, Permethr Pirimiphos-methyl, Prot Pyraclofos, Pyraclostrol Pyrimidifen, Pyriminoba pentachlorophenyl sulfin Tebufenozide, Tebufeng Tetradifon, Thiabendaz Tiadinil, Tolclofos-methy Triflumizole, Triflumuror	Alachlor, Aldicarb, Aldrin, Amisulbrom, Anilofos, Azinphos-methyl, yl, Benzoximate, BHC, Bifenox, Bifenthrin, Biteranol, Boscalid, Bron Zaptan, Carbaryl(NAC), Carbendazim, Carbofuran, Carbophenothio ordane, Chlorfenapyr, Chlorfenvinphos, Chlorfluazuron, Chlorobenzi os-methyl, Chromafenozide, Clofentezine, Clothianidin, Cyazofamid, thrin-lambda, Cymoxanil, Cypermethrin, Cyproconazole, Cyprodinil, s/DDVP, Diclofop-methyl, Dicloran, Dicofol, Diethofencarb, Difenoco bate, Dimethomorph(E,Z), Dimethylvinphos(Z), Diniconazole, Dipher phos, Endosulfan (alpha, bata,sulfate), Endrin(dieldrin), EFN, Espr hoprophos, Etoxazole, Etofenprox, Etridiazole, Etrimfos, Fenamidor azole, Fenitrothion : MEP, Fenobucarb, Fenothiocarb, Fenoxanil, Fe mzone, Fipronil, Fluacrypyrim, Flubendiamide, Flucythrinate, Fludiou hazole, Hexaconazole, Hexaflumuron, Hexythiazox, Imazalil, Imibe IBP, Iprodione, Iprovalicarb, Isofenphos, Isoprocarb : MIPC, Isoprot mid, Mecarbam, Mefenacet, Mepanipyrim, Mepronil, Methaxyt, Meta ethidathion, Methiocarb, Methomyl, Methoxychlor, Methoxyfenozide Aevinphos, Molinate, Myclobutanil, Napropamide, Novaluron, Nuarir rfen, Paclobutrazole, Parathion, Parathion-methyl, Penconazole, Pe in, Phenthoate:PAP, Phorate, Phosalone, Phosphamidone, Piperopa bin, Pyrazophos, Pyribenzoxim, Pyributicarb, Pyridaben, Pyridalyl, Pc c-methyl(E,Z), Pyriproxyfen, Pyroquilon, Quinoclamine, Quintozene de), Silafluofen, Simazine, Simeconazole, Simetryn, Spiordiclofen, S yrad, Tebupirimfos, Teflubenzuron, Tefluthrin, Terbufos, Terbuthylaz ole, Thiacloprid, Thiamethroxam, Thiazopyr, Thifluzamide, Thiobencc 4, Tolylfluanid, Tralomethrin, Triadimefon, Triadimenol, Triazophos, T n, Trifluralin, Uniconazole, Vinclozolin, Zoxamide	Azoxystrobin, Bendiocarb, nobutide, Bromopropylate, Buprofezin, n, Chinomethionat(Oxythioquinox), late, Chlorothalonil, Chlorpropham, , Cyflufenamid, Cyfluthrin (beta), , DDT, Deltamethrin, Diazinon, onazole, Diflubenzuron, Dimepiperate, namid, Diphenylamine, Disulfoton, ocarb, Ethaboxam, Ethalfluralin, ne, Fenamiphos, Fenarimol, npropathrin, Fenpyroximate, Fenthion : konil, Flufenoxuron, Flumioxazine, Fthalide, Furathiocarb, Halfenprox, anconazole, Imidacloprid, Indanofan, hiolane, Kresoxim-methyl, Lufenuron, amifop, Metconazole, s, Metobromuron, Metolachlor, mol, Ofurace, Oxadiazon, Oxamyl, ancycuron, Pendimethalin, hos, Pirimicarb, Pirimiphos-ethyl, il, Propiconazole, Propoxur, Prothiofos, Yyridaphenthion, Pyrimethanil, (pentachloroaniline, Methyl Spiromesifen, Tebuconazole, arb, Thiodicarb, Thiophanate-methyl, Tricyclazole, Trifloxystrobin,	

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



#### 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

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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 detecte 2) The test resu and the same	d = ≤LOQ (0.01mg/kg), LOQ= Limit of quantitation Its are limited to the requested product(sample name, item no.), ole 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...
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lest Report (F	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	The second s		
Acetamiprid, Acrinathrii Benthiavalicarb-isoprop Butachlor, Cadusafos, ( Chlorantraniliprole, Chl Chlorpyrifos, Chlorpyrif Cyhalofop-butyl, Cyhak Dichlofluanid, Dichlorvo Dimethenamid, Dimeth Dithiopyr, Diuron, Edife Ethiofencarb, Ethion, g Fenazaquin, Fenbucon MPP, Fenvalerate, Feri Fluopicolide, Fluquinco Heptachlor, Heptachlor Indoxacarb, Iprobenfos Malathion, Mandipropa Metolcarb, Metribuzin, 1 Oxaziclomefon, Oxyflud Pentoxazone, Permeth Pirmiphos-methyl, Prol Pyraclofos, Pyraclostro Pyrimidifen, Pyriminoba pentachlorophenyl sulfi Tebufenozide, Tebufeny Tetradifon, Thiabendazi Tiadinil, Tolclofos-methy, Triflumizole, Triflumurou	h, Alachlor, Aldicarb, Aldrin, Amisulbrom, Anilofos, Azinphos-methyl, yyl, Benzoximate, BHC, Bifenox, Bifenthrin, Biteranol, Boscalid, Bron Captan, Carbaryl(NAC), Carbendazim, Carbofuran, Carbophenothio ordane, Chlorfenapyr, Chlorfenvinphos, Chlorfiuazuron, Chlorobenzi os-methyl, Chromafenozide, Clofentezine, Clothianidin, Cyazofamid, sthrin-lambda, Cymoxanil, Cypermethrin, Cyproconazole, Cyprodinil os/DDVP, Diclofop-methyl, Dicloran, Dicofol, Diethofencarb, Difenoco bate, Dimethomorph(E,Z), Dimethylvinphos(Z), Diniconazole, Dipher nphos, Endosulfan (alpha, bata,sulfate), Endrin(dieldrin), EPN, Espr thoprophos, Etoxazole, Etofenprox, Etridiazole, Etrimfos, Fenamidor azole, Fenitrothion : MEP, Fenobucarb, Fenothiocarb, Fenoxanil, Fe mizone, Fipronil, Fluacrypyrim, Flubendiamide, Flucythrinate, Fludioz nazole, Hexaconazole, Hexaflumuron, Hexythiazox, Imazalil, Imibu (IBP, Iprodione, Iprovalicarb, Isofenphos, Isoprocarb : MIPC, Isoprot Mevinphos, Molinate, Myclobutanil, Napropamide, Novaluron, Nuarii orfen, Paclobutrazole, Parathion, Parathion-methyl, Penconazole, Pero rin, Phenthoate:PAP, Phorate, Phosalone, Phosphamidone, Piperop penazole, Prochloraz, Procymidone, Profenofos, Prometryn, Propan bin, Pyrazophos, Pyribenzoxim, Pyributicarb, Pyridaben, Pyridalyl, F ic-methyl(E,Z), Pyriproxyfen, Pyroquilon, Quinoclamine, Quintozene de), Silafluofen, Simazine, Simeconazole, Simetryn, Spirodiciofen, S byrad, Tebupirimfos, Teflubenzuron, Tefluthrin, Terbufos, Terbuthylaz ole, Thiacloprid, Thiamethoxam, Thiazopyr, Thifluzamide, Thiobencz /, Tolylfluanid, Traiomethrin, Triadimefon, Triadimenol, Triazophos, n, Trifluralin, Uniconazole, Vinclozolin, Zoxamide	Azoxystrobin, Bendiocarb, nobutide, Bromopropylate, Buprofezin, n, Chinomethionat(Oxythioquinox), ilate, Chlorothalonil, Chlorpropham, , Cyflufenamid, Cyfluthrin (beta), , DDT, Deltamethrin, Diazinon, onazole, Diflubenzuron, Dimepiperate, namid, Diphenylamine, Disulfoton, ocarb, Ethaboxam, Ethalfluralin, ne, Fenamiphos, Fenarimol, enpropathrin, Fenpyroximate, Fenthion : xonil, Flufenoxuron, Flumioxazine, Fthalide, Furathiocarb, Halfenprox, enconazole, Imidacloprid, Indanofan, hiolane, Kresoxim-methyl, Lufenuron, amifop, Metconazole, a, Metobromuron, Metolachlor, mol, Ofurace, Oxadiazon, Oxamyl, encycuron, Pendimethalin, hos, Pirimicarb, Pirimiphos-ethyl, il, Propiconazole, Propoxur, Prothiofos, Pyridaphenthion, Pyrimethanil, (pentachloroaniline, Methyl spiromesifen, Tebuconazole, arb, Thiodicarb, Thiophanate-methyl, Tricyclazole, Trifloxystrobin,	

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

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#### 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

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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 detecte 2) The test resu	d = ≤LOQ (0.01mg/kg), LOQ= Limit of quantitation ults 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...

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Kwangsoo Jeon

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Fest Report (F	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			
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\*\*\* End of Report \*\*\*

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SGS Korea Co.,Ltd.

#301, 57, Malgelumse-gll, Ulwang-el, Gyeonggi-do, Korea #16071 1 +62 (0)31 689 8600 1 +62 (0)70 4332 1659 <u>http://www.sgsgroup.kr.</u> Member of the SGS Group (Société Générale de Survellianne)

# Appendix 7 Intake Analysis – Food Codes

Food code	Main food description	WWEIA Category description	
	Yogurts	<b>~ ~ ·</b>	
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	
	Yogurt, whole milk, baby food, with fruit and multigrain		
11480020	cereal puree, NFS	Baby food: yogurt	
	Yogurt, whole milk, baby food, with fruit and multigrain		
11480030	cereal puree, plus iron	Baby food: yogurt	
	Yogurt, whole milk, baby food, with fruit and multigrain		
11480040	cereal puree, plus DHA	Baby food: yogurt	

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

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         67404500       Bianan 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         67430500       Yogurt, and fruit snack, baby food       Baby food: yogurt         67430500       Yogurt, coconut milk       Yogurt, regular         1420380       Yogurt, coconut milk       Yogurt, regular         11459990       Frozen yogurt, NFS       Ice cream and frozen dairy desserts         11460000       Frozen yogurt, soft serve, vanilla       Ice cream and frozen dairy desserts         11460500       Frozen yogurt, soft serve, vanilla       Ice cream and frozen dairy desserts         11460500       Frozen yogurt soft serve, vanilla       Ice cream and frozen dairy desserts         11460500       Frozen yogurt	
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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         67403700       Peach 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, strained       Baby food: yogurt         674030500       Yogurt, and fruit snack, baby food, strained       Baby food: yogurt         67404200       Yogurt, and fruit snack, baby food, strained       Baby food: yogurt         674030500       Yogurt, and fruit snack, baby food, strained       Baby food: yogurt         674042000       Fozen yogurt, sop       Processed soy products         42401100       Yogurt, coconut milk       Yogurt, regular         Frozen yogurt, sop         11459990       Frozen yogurt, soft serve, vanilla       Ice cream and frozen dairy desserts         11460000       Frozen yogurt, soft serve, vanilla       Ice cream and frozen dairy desserts         11460510       Frozen yogurt sandwich       Ice cream and frozen	
67404500     Mixed fruit yogurt dessert, baby food, strained     Baby food: yogurt       67404070     Apple yogurt dessert, baby food, strained     Baby food: yogurt       67408500     Banan 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       67430500     Yogurt and fruit snack, baby food     Baby food: yogurt       67430500     Yogurt, and fruit snack, baby food     Baby food: yogurt       67430500     Yogurt, soy     Processed soy products       42401100     Yogurt, coconut milk     Yogurt, regular       Frozen yogurt, vanilla       11459990       Frozen yogurt, soft serve, vanilla       11460100       Frozen yogurt, soft serve, vanilla       11460100       Frozen yogurt, soft serve, chocolate       11460100       Frozen yogurt, soft serve, chocolate       11460100       Frozen yogurt, soft serve, chocolate       11461200       Frozen yogurt sandwich       11461200       Frozen yogurt cone, chocolate       11461200       Frozen	
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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	
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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	WcC
	Mixed La	5.62	7.60	8.30	La
-	Lf only	6.30	8.29	9.67	Lf
	Mixed Lf	6.28	8.26	9.20	Lr
2	Lr only	5.26	8.14	8.92	
	Mixed Lr	5.48	7.85	8.20	

h	0	8	24
Wc GMU 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

Center for Genomic Epidemiology				Center for Genomic Epidemiology				
Home	Services	Instructions	Output	Home	Services	Instructions Output		
Virulence Finder-2.0 Server - Results  Arganism(s): Escherichia coli  Ehig-toxin penes  Virulence factor Insector Insector Insector Cullery / Template length Config Protein function Accession number  Virulence factor Identity Query / Template length Config Pasition in config Protein function Accession number  Virulence factor Identity Query / Template length Config Pasition in config Protein function Accession number				Norme         Services         Instructions         Output           VirulenceFinder-2.0 Server - Results         Organism(s): Enterococcus         Virulence genes for Enterococcus         Virulence genes for Enterococcus           Virulence factor         Ideetry         Guery / Template length         Contig         Protein function         Accession number				
	extended	cutput		Results as text Results tov	Hits in genome segs Virulence factor seqs			
Results as text    Results tay	extended           Hits in genome segs         Virulence factor segs	output		Results as text Results tev	Hits in genome segs Vinsence factor seqs			
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Results as read Results tay nput Files: CMU.1 TRATIONS	extended :    Hits in genume segs    Virulence factor segs    //asta	adpd		Results as text Results tev Input Files: CMU.: CITATIONS For publication of results, please	Hite in genome eep:    Vinuense fastor segs    asta			
Results as text   Results as nput Files: CMU.I CHATIONS at publication of results, please • face irres and agronen- Jocens RG Schutz F. I. J. Cim. Micobiol. 2014. 92 Wee the abstract	extended: 1993 in genome sear. Vinience factor sear fasta sea. we working for routine ryping curvetteres, and outstate und U. Helenen H. Kalan RS. Noblee EM. Annuting PM (p) 1097-1070	dutection of versioning one Exercise the coll		Results as text Results for Input Files: CMU. CITATIONS For publication of results, please • Read/one addressment accesses KG, Schuert F. • One Module 2014, 50 View The abstract	Hite in genome week as I a other recovering for routine fixing, surveillance, and collion with D. Hannan H. Kase Rid. Nielsen Fill, Aansanpi 59, 4501–1510	edi delastion of verotoogens: Eacherschia coli. FM		

Center for Genomic Epidemiology			Center fo	or Genomic Epide	emiology		
Home	Services	Instructions	Output	Home	Services	Instructions	Output
Home Services Instructions Output //irulenceFinder-2.0 Server - Results //ganism(s): Listeria //inulence lactor / sentby Guery / Templote length   Gonig   Position in sentig   Protein function   Accession number //initence lactor / sentby Guery / Templote length   Gonig   Position in sentig   Protein function   Accession number			VirulenceFinder-2.0 Server - Results Organism(s): S. Rureus Reconstruction Record Identity Durry / Template length: Conto, Position in contog Protein function Accession number To at a word Virulence Sector I identity Ouery / Template length: Conto, Position in contog Protein function Accession number Virulence Sector I identity Ouery / Template length: Conto, Position in contog Protein function Accession number			n Accession Number	
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Support	Scientific problems	Technic	cal problems	Support	Scientific problems	Technic	al problems

# 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

No. of Sample :	Weissella <mark>cib</mark> aria CMU Lot No	. CI11-0116N
nspection Purpose	e : Reference only	Date of Application : 2021-11-17
0.05	Name : OraPharm Inc, Eu	in-Sup Yoon
Applicant	Company address : 0478 Republic of Korea	2, 905-ho, 9-16, Yeonmujang-5-gil, Seongdong-gu, Seoul,
		Analytical Result
	Biogenic amines	Concentration (mg/kg)
Tryptamine		0.00
β-phenyleth	ylamine	0.00
Putrescine	1	0.00
Cadaverine		0.00
Histamine		0.00
Tyramine		
Tyramine		0.00
Tyramine Spermidine		0.00
Tyramine Spermidine Spermine Analysis of I	biogenic amines using chrom	0.00 0.00 0.00 atographic AOAC 1993, 76(3) method <sup>1</sup> .
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Tyramine Spermidine Spermine Analysis of I <sup>1</sup> Eerola S, Hinkka AOAC Internatio	biogenic amines using chrom anen R, Lindfors E, Hirvi T, 1993. Liquid o nal, 76(3), 575-577. We hereby c niversity, College of Science a Director	0.00         0.00         0.00         atographic AOAC 1993, 76(3) method <sup>1</sup> .         atographic determination of biogenic amines in dry sausages. Journal of         2021. 11. 17.         ertify that the above are correct.         and Technology, Department of Food and Biotechnology         :
Tyramine Spermidine Spermine Analysis of I <sup>1</sup> Eerola S, Hinkka AOAC Internatio	anen R, Lindfors E, Hirvi T, 1993. Liquid o nal, 76(3), 575-577. We hereby c Iniversity, College of Science a Director Korea University Sejong Can	0.00         0.00         0.00         atographic AOAC 1993, 76(3) method <sup>1</sup> .         atographic determination of biogenic amines in dry sausages. Journal of         2021, 11, 17.         ertify that the above are correct.         and Technology, Department of Food and Biotechnology         :Jae-Hyung, Mah

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est Report	(Reference)	No. F690101/LF-CTSAYFN21-43146	
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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 Rep	ort :	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 \*\*\*

![](_page_143_Picture_20.jpeg)

Jungsub Shim

Technical Manager / SGS KOREA

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FQP-32-F2 (3)

35, 67, Malgeumaeigi, Ulwang-ei, Gyeongg-ea, Korea≢(607) I +82 (0)31 699 8600 ++82 (0)70 4332 1669 http://www.sgligtoup.kr.

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

of Sample : \	Weissella cibaria CMU Lot No	o. CI11-0117N
ction Purpose	e : Reference only	Date of Application : 2021-11-17
	Name : OraPharm Inc, Eu	un-Sup Yoon
Applicant	Company address : 0478 Republic of Korea	32, 905-ho, 9-16, Yeonmujang-5-gil, Seongdong-gu, Seoul,
		Analytical Result
	Biogenic amines	Concentration (mg/kg)
Tryptamine		0.00
β-phenyleth	ylamine	0.00
Putrescine		0.00
Cadaverine		0.00
Histamine		0.00
+ markers		0.00
lyramine		0.00
Tyramine Spermidine		0.00
Spermidine Spermine Analysis of b	piogenic amines using chrom	0.00 0.00 0.00 natographic AOAC 1993, 76(3) method <sup>1</sup> .
Spermidine Spermine Analysis of b <sup>1</sup> Eerola S, Hinkka AOAC Internation	piogenic amines using chrom nen R, Lindfors E, Hirvi T, 1993. Liquid ( nal, 76(3), 575-577.	0.00 0.00 0.00 hatographic AOAC 1993, 76(3) method <sup>1</sup> .
Spermidine Spermine Analysis of b <sup>1</sup> Eerola S, Hinkka AOAC Internation	piogenic amines using chrom nen R, Lindfors E, Hirvi T, 1993. Liquid d nal, 76(3), 575-577.	0.00 0.00 0.00 hatographic AOAC 1993, 76(3) method <sup>1</sup> .
Spermidine Spermine Analysis of k <sup>1</sup> Eerola S, Hinkka AOAC Internation	piogenic amines using chrom nen R, Lindfors E, Hirvi T, 1993. Liquid ( nal, 76(3), 575-577.	chromatographic determination of biogenic amines in dry sausages. Journal of 2021. 11. 17.
Spermidine Spermine Analysis of b <sup>1</sup> Eerola S, Hinkka AOAC Internation	piogenic amines using chrom nen R, Lindfors E, Hirvi T, 1993. Liquid nal, 76(3), 575-577. We hereby c	chromatographic determination of biogenic amines in dry sausages. Journal of 2021. 11. 17. certify that the above are correct.
Spermidine Spermine Analysis of b <sup>1</sup> Eerola S, Hinkka AOAC Internation	nen R, Lindfors E, Hirvi T, 1993. Liquid ( nal, 76(3), 575-577. We hereby c niversity, College of Science (	chromatographic determination of biogenic amines in dry sausages. Journal of 2021. 11. 17. certify that the above are correct. and Technology, Department of Food and Biotechnology
Spermidine Spermine Analysis of b <sup>1</sup> Eerola S, Hinkka AOAC Internation	nen R, Lindfors E, Hinvi T, 1993. Liquid d nal, 76(3), 575-577. We hereby c niversity, College of Science d Director	chromatographic AOAC 1993, 76(3) method <sup>1</sup> .

3/11/2022

Page 1 of 1

Issued Date 2021. 10. 29



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

**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 Rep	ort :	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.

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Jungsub Shim

Technical Manager / SGS KOREA

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SGS Korea Co.,Ltd.

3F, 67, Malgeunnae-gil, Ulwang-si, Gyeonggi-tio, Korea #16071 1+62 (0)31 699 8600 +1-62 (0)70 4332 1669 <u>http://www.sgegroup.kr</u>

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

o. of Sample : W	/eissella cibaria CMU Lot No	o. CI11-0366N
pection Purpose	: Reference only	Date of Application : 2021-11-17
1	Name : OraPharm Inc, Eu	un-Sup Yoon
Applicant	Company address : 0478 Republic of Korea	2, 905-ho, 9-16, Yeonmujang-5-gil, Seongdong-gu, Seoul,
		Analytical Result
	Biogenic amines	Concentration (mg/kg)
Tryptamine		0.00
β-phenylethy	lamine	0.00
Putrescine		0.00
Cadaverine		0.00
Histamine		0.00
Tyramine		
Tyramine		0.00
Tyramine Spermidine		0.00
Tyramine Spermidine Spermine Analysis of bi	iogenic amines using chrom	0.00 0.00 0.00 atographic AOAC 1993, 76(3) method <sup>1</sup> .
Tyramine Spermidine Spermine Analysis of bi <sup>1</sup> Eerola S, Hinkkan AOAC Internationa	iogenic amines using chrom en R, Lindfors E, Hirvi T, 1993. Liquid o al, 76(3), 575-577.	0.00 0.00 atographic AOAC 1993, 76(3) method <sup>1</sup> .
Tyramine Spermidine Spermine Analysis of bi	iogenic amines using chrom en R, Lindfors E, Hirvi T, 1993. Liquid d al, 76(3), 575-577.	0.00 0.00 0.00 atographic AOAC 1993, 76(3) method <sup>1</sup> .
Tyramine Spermidine Spermine Analysis of bi	iogenic amines using chrom en R, Lindfors E, Hirvi T, 1993. Liquid d al, 76(3), 575-577.	chromatographic determination of biogenic amines in dry sausages. Journal of
Tyramine Spermidine Spermine Analysis of bi	en R, Lindfors E, Hirvi T, 1993. Liquid d al, 76(3), 575-577. We hereby c	chromatographic determination of biogenic amines in dry sausages. Journal of 2021. 11. 17. ertify that the above are correct.
Tyramine Spermidine Spermine Analysis of bi <sup>1</sup> Eerola S, Hinkkan AOAC Internation	en R, Lindfors E, Hirvi T, 1993. Liquid o al, 76(3), 575-577. We hereby c iversity, College of Science a	chromatographic determination of biogenic amines in dry sausages. Journal of 2021. 11. 17. ertify that the above are correct. and Technology, Department of Food and Biotechnology
Tyramine Spermidine Spermine Analysis of bi <sup>1</sup> Eerola S, Hinkkan AOAC Internationa	en R, Lindfors E, Hirvi T, 1993. Liquid o al, 76(3), 575-577. We hereby c iversity, College of Science a Director	chromatographic determination of biogenic amines in dry sausages. Journal of 2021. 11. 17. ertify that the above are correct. and Technology, Department of Food and Biotechnology :
Tyramine Spermidine Spermine Analysis of bi <sup>1</sup> Eerola S, Hinkkan AOAC Internationa	en R, Lindfors E, Hirvi T, 1993. Liquid d al, 76(3), 575-577. We hereby c iversity, College of Science a Director Korea University Sejong Car	0.00         0.00         0.00         atographic AOAC 1993, 76(3) method <sup>1</sup> .         atographic determination of biogenic amines in dry sausages. Journal of         2021. 11. 17.         ertify that the above are correct.         and Technology, Department of Food and Biotechnology         :Jae-Hyung, Mah

3/11/2022

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Issued Date 2021. 10. 29



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

#### **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.

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# 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<sup>15</sup> 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"<sup>16</sup>. 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  $1 \times 10^8$  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  $8.0 \times 10^9$  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  $5.0 \times 10^8$  CFU and  $2.0 \times 10^8$  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" 90<sup>th</sup> percentile estimated intake for *W. cibaria* CMU was determined to be 397 mg/day. Using the specification of not less than 1x10<sup>9</sup> CFU per gram,

<sup>&</sup>lt;sup>15</sup> 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.

<sup>&</sup>lt;sup>16</sup> Available at: <u>https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm583856.htm</u> (Accessed February 28, 2022)

the EDI in terms of CFU per day is  $3.97 \times 10^8$ . 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<sup>17</sup> 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 109 CFU to 2.4 x 10<sup>10</sup> 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

<sup>&</sup>lt;sup>17</sup> See <u>http://www.foodsafetykorea.go.kr/foodcode/01\_03.jsp?idx=12135</u>. Accessed February 28,2022.

### 3/11/2022

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 x 10<sup>7</sup> to 1 x 10<sup>9</sup> 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 x 10<sup>9</sup> CFU to 2.4 x 10<sup>10</sup> 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]





Robert Martin, PhD

Michael Falk, PhD

END

			Form Approved: OMB No. 0910-0342; Expiration Date: 07/31/2022 (See last page for OMB Statement,			
				FDA US	EONLY	
DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration GENERALLY RECOGNIZED AS SAFE (GRAS) NOTICE (Subpart E of Part 170)			GRN NUMBER 001063		DATE OF RECEIPT May 24, 2022	
			ESTIMATED DA	ILY INTAKE	INTENDED USE FOR INTERNET	
			NAME FOR INTE	ERNET		
			KEYWORDS			
Transmit comple completed form Food Safety and	eted form and attachm and attachments in p d Applied Nutrition, Fo	nents electronically via the E aper format or on physical n bod and Drug Administration	Electronic Subm media to: Office n,5001 Campus	ission Gateway (se of Food Additive S Drive, College Pa	ee <i>Instructions)</i> ; OR Transmit Safety <i>(HFS-200)</i> , Center for rk, MD 20740-3835.	
	SECTION	A – INTRODUCTORY INF	ORMATION A	BOUT THE SUB	MISSION	
1. Type of Submi	ssion (Check one)					
New	Amendment	to GRN No.	Supple	ement to GRN No.		
2. All electr	onic files included in th	is submission have been che	ecked and found	to be virus free. (Cl	neck box to verify)	
3 Most recent p FDA on the st	resubmission meeting ubject substance (уууу	(if any) with //mm/dd):		401	1287	
4 For Amendme	ents or Supplements: I	s your (Check one)	optor the date o	f		
response to a	communication from I	FDA? No comm	unication (yyyy/	/mm/dd):		
		43 - 32				
		SECTION B – INFORMA	TION ABOUT	THE NOTIFIER		
	Name of Contact Per	son		Position or Title		
	Yoon Eun-Sup			CEO		
to Notifiar	Organization (if applied	cable)			5	
ia. Noullel	OraPharm, Inc.					
	Mailing Address (nun	nber and street)	<u>8</u>			
	905 ho, Bluestone To	ower, 9-16, Yeonmujang 5-g	il			
City		State or Province	Zip Code/P	ostal Code	Country	
Seou		Seongdong-gu			Republic of Korea	
Telephone Number Fax Number		Fax Number	E-Mail Address			
+82-2-2138-2572		+82-2-2054-0154	ora2014@c	prapharm.com		
	Name of Contact Per	son		Position or Title		
	William Rowe			President		
1b. Agent	Organization (if appli	cable)		d		
(if applicable)	GRAS Associates, LLC					
	Mailing Address (num	nber and street)			τ.	
	11810 Grand Park A	venue Suite 500				
City	1	State or Province	Zip Code/P	ostal Code	Country	
North Bethesda		Maryland	20852		United States of America	
Telephone Numbe	er	Fax Number	E-Mail Add	ress	1	
519-341-3660 1-888-531-3466			wrowe@nutrasource.ca			

SECTION C – GENERAL ADMINISTRATIVE INFO	ORMATION
1. Name of notified substance, using an appropriately descriptive term Weisella cibaria Strain CMU	
2. Submission Format: (Check appropriate box(es))     Electronic Submission Gateway     Paper     Fampliashing size number and time 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 commo	n use in food (21 CFR 170.30(a) and (c))
<ul> <li>7. Does the submission (including information that you are incorporating) contain information or as confidential commercial or financial information? (see 21 CFR 170.225(c)(8) and 170</li> <li>Yes (Proceed to Item 8</li> <li>No. (Proceed to Section D)</li> </ul>	ι that you view as trade secret J.250(d) and (e))
8. Have you designated information in your submission that you view as trade secret or as of	onfidential commercial or financial information
(Check all that apply)	
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	
SECTION D – INTENDED USE	
<ol> <li>Describe the intended conditions of use of the notified substance, including the foods in which such foods, and the purposes for which the substance will be used, including, when approximately a substance will be used.</li> </ol>	nich the substance will be used, the levels of use opriate, a description of a subpopulation expected
to consume the notified substance.	
OraPharm, Inc. intends to use <i>W. cibaria</i> CMU as a food ingredient in selected co desserts (dairy, ices, sorbets and sherbets) and mixes, hard candy and chewing g serving throughout the shelf life of the product (with initial addition levels of 2 x depending on the specific product).	nventional foods including yogurt, frozen um at use levels to provide 1 x 10 <sup>8</sup> CFU per 10 <sup>8</sup> CFU to 8 x 10 <sup>9</sup> CFU per serving
mana en el longo apportante de la mana social de la constante de la const	
2. Does the intended use of the notified substance include any use in product(s) subject to reg	julation by the Food Safety and Inspection
Service (FSIS) of the U.S. Department of Agriculture?	
(Check one)	
Yes 🛛 No	
<ol> <li>If your submission contains trade secrets, do you authorize FDA to provide this information U.S. Department of Agriculture? (Check one)</li> </ol>	n to the Food Safety and Inspection Service of the
Yes No , you ask us to exclude trade secrets from the information FDA will	send to FSIS.

SECTION (check list to help ensure your subn	E – PARTS 2 -7 OF YOUR GRAS NOTICE nission is complete – PART 1 is addressed in other sections	s 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 (1	170.235).	
PART 4 of a GRAS notice: Self-limiting levels of	of use (170.240).	
PART 5 of a GRAS notice: Experience based of	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 d	ata and information in your GRAS notice (170.255)	
Other Information         Did you include any other information that you want         Yes       No         Did you include this other information in the list of an Xes         Yes       No	t FDA to consider in evaluating your GRAS notice? ttachments?	
SECTION F - S	IGNATURE AND CERTIFICATION STATEMENTS	
1. The undersigned is informing FDA that Yoon E	un-Sup	
Weisell	(name of notifier)	
has concluded that the intended use(s) of	(name of notified substance)	
described on this form, as discussed in the attached	d notice, is (are) not subject to the premarket approval requirement	nts 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 allow FDA to review and copy the asks to do so; agrees to send these data a	agrees to make the data and information that are the conclusion of GRAS status available to FDA if FDA ese data and information during customary business hours at the ind information to FDA if FDA asks to do so.	e basis for the asks to see them; following location if FDA
905 ho, Bluestone Tower, 9-16, Yeonm	ujang 5-gil, Seongdong-gu, Seoul, Republic of Korea (address of notifier or other location)	1
The notifying party certifies that this GRAS as well as favorable information, pertinent party certifies that the information provided misinterpretation is subject to criminal pen	S notice is a complete, representative, and balanced submission th to the evaluation of the safety and GRAS status of the use of the d herein is accurate and complete to the best or his/her knowledge alty pursuant to 18 U.S.C. 1001.	nat includes unfavorable, substance.The notifying e. Any knowing and willful
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.			
<b>OMB Statement:</b> 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, <u>PRAStaff@fda.hhs.gov</u> . (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.				