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July 19, 2023

Via Fed Ex

Dr. Susan Carlson
Director, Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740-3835

Re: GRAS Notice for Scott Laboratories Inc. ML Prime™

Dear Dr. Carlson:

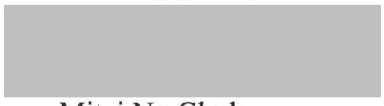
We respectfully submit the attached GRAS Notice on behalf of our client, Scott Laboratories, Inc. (Scott Labs), for its ML Prime™ product. ML Prime™ is intended for use in wine production to induce malolactic fermentation (turning malic acid into lactic acid) and to prevent the growth of microorganisms that could cause off flavors in the finished product. More detailed information regarding product identification, intended use levels, the manufacturing process, and safety of the ingredient is set forth in the attached GRAS Notice. In keeping with the Agency's preference, we also are submitting a complete copy of the Notice on CD-ROM.

Scott Labs has determined that ML Prime™ is GRAS for the intended uses based on scientific procedures in accordance with 21 C.F.R. § 170.30 (b) and in conformance with the guidance issued by the Food and Drug Administration (FDA) under 21 C.F.R. § 170.36, 81 Fed. Reg. 54960 (Aug. 17, 2016). Therefore, the use of ML Prime™, as described in this GRAS Notice, is exempt from the requirement of premarket approval as set forth in the Federal Food, Drug, and Cosmetic Act.

The analytical data, published studies, and information that form the basis for this GRAS Notice are available for FDA review and copying at reasonable times at Keller and Heckman LLP, 1001 G Street, NW, Suite 500W, Washington, DC 20001, or will be sent to the FDA upon request.

We look forward to the agency's review of this submission and would be happy to provide agency officials with any information they may need to complete their assessment. Thank you for your attention to this matter.

Cordially yours,



Mitzi Ng Clark

Enclosures

GRAS NOTICE FOR ML PRIME™ FOR USE IN MALOLACTIC FERMENTATION IN WINE PRODUCTION AT A MAXIMUM INOCULATION LEVEL OF 1.5 X 10^8 CFU/GRAM

Prepared for:

Office of Food Additive Safety (FHS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Campus Dr.
College Park, MD 20740

Submitted by:

Keller and Heckman LLP
Three Embarcadero Center, Suite 1420
San Francisco, CA 94111

On behalf of our client:

Scott Laboratories, Inc.
1480 Cader Ln.
Petaluma, CA 94954

Date:

July 19, 2023

Table of Contents

Part 1 - Signed Statements and Certification

1-1. Statement of Intent

In accordance with 21 C.F.R. 170, Subpart E, which includes regulations detailing Generally Recognized as Safe (GRAS) notifications, Scott Laboratories, Inc. (Scott Labs) has concluded, through scientific procedures, that ML Prime™ is GRAS and, therefore, is not subject to the U.S. Food and Drug Administration (FDA) premarket clearance requirements when used in malolactic fermentation of wine and musts at an inoculation level of 1.5×10^8 CFU/gram.

1-2. Name and Address of Notifier

Company:	Scott Laboratories, Inc.
Name:	Zachary Scott
Address:	1480 Cader Ln. Petaluma, CA 94954
Phone:	(415) 722-6216
Email:	zacks@scottlab.com

All communications on this matter are to be sent to Counsel for Scott Laboratories, Inc.:

Mitzi Ng Clark
Partner, Keller and Heckman LLP
Three Embarcadero Center, Suite 1420
San Francisco, CA 94111
Tel: (415) 948-2838
Email: clark@khlaw.com

1-3. Name of the Notified Substance

Lactiplantibacillus plantarum (*L. plantarum*) DSM 34613
Lactiplantibacillus plantarum ML Prime™
L. plantarum ML Prime™
L. plantarum DSM 34613
ML Prime™
Lactic acid bacteria

1-4. Applicable Conditions of Use of the Notified Substance

ML Prime™ is intended for use in wine production to induce malolactic fermentation (turning malic acid into lactic acid) and to prevent the growth of microorganisms that could cause off flavors in the finished product. A second dose may be added as needed to produce efficient malolactic fermentation, but the total use rate will not exceed 1.5×10^8 cfu/g. ML Prime™ has a higher alcohol tolerance than other *L. plantarum* strains; however, viability kinetics for ML Prime™ (**Appendix 1)** indicate that ML Prime™ viability is significantly reduced (~3 log reduction) within 8 days, under typical fermentation conditions.

1-5. Basis for the GRAS Determination

Scott Labs has concluded that ML Prime™ is GRAS through scientific procedures, in accordance with 21 C.F.R. 170.30 (b).

1-6. Exclusion from Premarket Approval

The notified substance is not subject to FDA's premarket clearance requirements of the Federal Food, Drug, and Cosmetics Act (FD&C Act) based on our conclusion that the notified substance is GRAS under the conditions of its intended use.

1-7. Availability of Data and Information

The information underlying this GRAS conclusion, including analytical data, published studies, and other information are available to FDA upon request, as required by 21 C.F.R. § 170.225(c)(7)(ii)(A) or (B), by contacting Keller and Heckman LLP at the below address.

Mitzi Ng Clark
Partner, Keller and Heckman LLP
Three Embarcadero Center, Suite 1420
San Francisco, CA 94111
Tel: (415) 948-2838
Email: clark@khlaw.com

1-8. Applicability of FOIA Exemptions

Scott Labs is not claiming any information in Parts 2 through 7 of this document as trade secret, confidential or financial information that is privileged or confidential. Thus, all information and data in this submission are not exempt from the Freedom of Information Act (FOIA), 5 U.S.C. Section 552.

1-9. Certification

We certify on behalf of our client, Scott Labs, that this GRAS conclusion is based on representative data from Scott Labs that is intended to demonstrate the safety and GRAS status of ML Prime™ for use in the production of wine. To the best of our knowledge, it is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the intended use of the substance.

1-10. Signature and Name and Title of the Person Signing this GRAS Notice:

Mitzi Ng Clark
Partner,
Keller and Heckman LLP

July 19, 2023
Date

Part 2 - Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

2-1. Scientific Data and Information that Identifies the Notified Substance

(a) Common or Usual Name:

Lactiplantibacillus plantarum (*L. plantarum*) DSM 34613
Lactiplantibacillus plantarum ML Prime™
L. plantarum ML Prime™
L. plantarum DSM 34613
ML Prime™
Lactic acid bacteria

2-2. Identity

The subject of this GRAS determination is a strain of the bacterial species, *Lactiplantibacillus plantarum,* designated as DSM 34613. The notified strain has been deposited with the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ) as DSM 34613.

Lactiplantibacillus plantarum was originally described in the literature by (Orla-Jensen) Bergey *et al.* in 1923 as nonmotile, Gram-positive rods that tend to become longer with increasing acidity. It was noted as early as 1923 that, while the natural habitat of *L. plantarum* was widely distributed across a variety of naturally fermented plant and animal products, the organism could also be isolated from other intentionally fermented dairy products, bread, and food products, such as pickles or sauerkraut. Recent molecular characterization techniques, including whole genome sequencing, have led to the genus *Lactiplantibacillus* being divided into 25 separate taxonomic genera, and *L. plantarum* was assigned to the *Lactiplantibacillus* genus as *Lactiplantibacillus plantarum* (Zheng *et al.* 2020). The taxonomic lineage of *L. plantarum* is described in **Table 1** below:

Table 1: Taxonomic Lineage of *L. plantarum* DSM 34613

Taxonomy	Taxonomic Assignment
Kingdom	Bacteria
Phylum	Firmicutes
Class	Bacilli
Order	Lactobacillales
Family	Lactobacillaceae
Genus	*Lactiplantibacillus*
Species	*Lactiplantibacillus plantarum*
Strain	*Lactiplantibacillus plantarum* DSM 34613

(a) Genomic Analysis of *L. plantarum* DSM 34613

A *de novo* genome sequence of *L. plantarum* DSM 34613 was generated and surveyed using publicly available bioinformatics tools to determine the presence or absence of genes known to be involved in conferring antimicrobial resistance (**Appendix 2**). The sequence was assembled and annotated by the Microbial Genome Sequencing Center, and the resulting sequence was screened for known antimicrobial resistance genes using the Comprehensive Antibiotic Resistance Database (CARD) v 5.2.0 (Alcock *et al.* 2019) using default settings and ResFinder v 4.1 (Bortolaia *et al.* 2020).

Analysis of the *de novo* genome sequence of *L. plantarum* using the CARD database yielded no matches for known antimicrobial resistance genes. Analysis using ResFinder returned a single match for an ATP-dependent protease, ClpL (2.1 kb full length match, 98.3% identity). ClpL has been shown to increase heat resistance in *L. monocytogenes* (Pontinen *et al.* 2017).

2-3. Raw Materials and Processing Aids

(a) Description of the Method of Manufacture

L. plantarum ML Prime™ is manufactured at a facility which complies with all relevant GMP and food safety (HAACP/HARPC) regulations.

A new stock culture of *L. plantarum* ML Prime™, stored at -80°C, is utilized to inoculate a pre-fermentation scaleup process prior to each production run. The small-scale process is then utilized to inoculate a fermentor containing culture media, consisting of other components that are safe and suitable for use as production aids for wine and musts.

Once the cell density reaches the required level, the biomass is separated, via centrifugation, and added to sterile trays for freeze-drying. Freeze-drying consists of a primary drying phase conducted under partial vacuum to remove free water, and a secondary drying phase under high vacuum to remove water directly associated with the biomass. The freeze-dried cultures are then bagged and stored under refrigeration until grinding.

Freeze-dried biomass is then ground prior to quality control (QC) analyses for viable cell concentration, malolactic activity, and absence of contaminants.

Finally, biomass is mixed with a maltodextrin carrier to reach the desired viable cell concentration prior to packing and frozen storage before shipping.

2-4. Product Specifications and Batch Analyses

(a) Physical, Chemical, and Microbiological Specifications

L. plantarum ML Prime™ is a lactic acid bacterium in powder form that is obtained by lyophilization and packaged in laminated foil. The powder is white to beige in color and has the slight odor of fermentation. The powder is made up of active, freeze-dried bacteria

Lactiplantibacillus plantarum sp. (*L. plantarum*) and maltodextrin as the carrier, giving the ML Prime™ freeze dried powder a shelf-life of 3 years when properly stored at -18 C degrees.

Table 2: Purity Specifications for Freeze Dried ML Prime™

Analyte	Limit	Analytical Method
Viable bacteria	> 10^{11} CFU/g	COEI-2-CONBAC
Dry matter	> 92%	Infrared-Loss on drying
Coliform	< 10^{2} CFU/g	ISO 4832
E. coli	Absent in 1 g	COEI-2-CONBAC
S. aureus	Absent in 1 g	ISO 6888-1
Salmonella	Absent in 25 g	ISO 6579
Acetic Bacteria	< 10^{4} CFU/g	COEI-2-CONBAC
Moulds	< 10^{3} CFU/g	ISO 6611:2004
Yeast	< 10^{3} CFU/g	ISO 6611:2004
Lead	< 2 mg/kg	OENO 18/2003
Mercury	< 1 mg/kg	OENO 18/2003
Arsenic	< 3 mg/kg	OENO 18/2003
Cadmium	< 1 mg/kg	OENO 18/2003

Table 3: Three Non-Consecutive Batch Analyses that are Proved

Analyte	Limit	Batch 1 727117277102	Batch 2 729917277106	Batch 3 813517278017
Viable bacteria	> 10^{11} CFU/g	5.60 x 10^{11} CFU/g	5.30 x 10^{11} CFU/g	5.40 x 10^{11} CFU/g
Dry matter	> 92%	99.3%	99.7%	99.6%
Coliform	< 10^{2} CFU/g	< 10^{2} CFU/g	< 10^{2} CFU/g	< 10^{2} CFU/g
E. coli	Absent in 1 g	Absent in 1 g	Absent in 1 g	Absent in 1 g

Analyte	Limit	Batch 1 727117277102	Batch 2 729917277106	Batch 3 813517278017
S. aureus	Absent in 1 g	Absent in 1 g	Absent in 1 g	Absent in 1 g
Salmonella	Absent in 25 g	Absent in 25 g	Absent in 25 g	Absent in 25 g
Acetic Bacteria	$< 10^4$ CFU/g	$<10^4$ CFU/g	$<10^4$ CFU/g	$<10^4$ CFU/g
Moulds	$< 10^3$ CFU/g	$<10^3$ CFU/g	$<10^3$ CFU/g	$<10^3$ CFU/g
Yeast	$< 10^3$ CFU/g	$<10^3$ CFU/g	$<10^3$ CFU/g	$<10^3$ CFU/g
Lead	< 2 mg/kg	<2 mg/kg	<2 mg/kg	<2 mg/kg
Mercury	< 1 mg/kg	<1 mg/kg	<1 mg/kg	<1 mg/kg
Arsenic	< 3 mg/kg	<3 mg/kg	<3 mg/kg	<3 mg/kg
Cadmium	< 1 mg/kg	<1 mg/kg	<1 mg/kg	<1 mg/kg

Part 3 – Dietary Exposure

3-1. Estimate of Dietary Exposure

L. plantarum ML Prime™ is intended to be used as a processing aid to reduce the presence of malic acid during wine production at a rate not to exceed 1.5×10^8 cfu/g in wine.

To determine the estimated exposure to ML Prime™ from consumption of wine, Scott Labs commissioned Exponent, Inc. (Exponent) to conduct a dietary intake assessment. Specifically, Exponent's report analyzed the mean and 90th percentile daily intake of wine for use in three categories (red table wine, white table wine, and rose table wine), as well as total wine consumption. The consumption data are based on 2015-2018 NHANES data and are presented in **Table 3** below:

Table 4: Two-day Wine Consumption Among the Adult U.S. Population

Population-Adults 21+		Per User Two Day Intake (g/day)[b]	
Food Category	**N (users)[a]**	**Mean**	**90th Percentile**
Wine, total	626	160	315
Wine, red	381	149	302

Population-Adults 21+		Per User Two Day Intake (g/day)[b]	
Wine, white	268	151	257
Wine, rose	40[c]	115	214

[a] Unweighted number of users

[b] Based on 24-hour dietary recalls from NHANES 2015-2018

[c] The per user estimates at the mean and 90th percentile may not be statistically reliable due to an inadequate number of users

The estimated daily intake (EDI) was then calculated using the given maximum use rate for ML Prime™ of 1.5 x 10^8 cfu/g and the ML Prime™ specification for viable microbes of 10^{11} cfu/g. The calculated two-day mean and 90th percentile exposure to ML Prime™, from the proposed food uses, is described in **Table 4** below. The EDI is calculated for total wine consumption as the "worst-case" exposure scenario and is reported both in grams of ML Prime™ per day and cfu of ML Prime™ per day.

Table 5: EDI Calculations for ML Prime™

	Mean EDI		90th Percentile EDI	
	g/day	cfu/day	g/day	cfu/day
Wine, Total	0.24	2.4 x 10^{10}	0.47	4.7 x 10^{10}

The calculated EDI for ML Prime™ use in total wine is in line with the typically reported exposure to *L. plantarum* strains in other GRAS notices of 10^9-10^{11} cfu/day and is, therefore, GRAS for the proposed uses.

Part 4 - Self-Limiting Levels of Use

There are no self-limiting levels of use for *L. plantarum* ML Prime™.

Part 5 - Experience Based on Common Use in Food

Although *L. plantarum* has been a component of the human diet for thousands of years, the conclusion of this GRAS notification regarding ML Prime™ is based on scientific data and procedures and not common use in food before 1958.

Part 6 - Safety Narrative

6-1. Overview of Safety of *L. plantarum*

For much of recorded history, humans have consumed a variety of fermented fruits, vegetables, and meats. With the advent of modern microbiology techniques, many of the

microbes responsible for the fermentation of these foods have been identified, with one of the most common identified organisms being lactic acid bacteria (LAB). This includes *L. plantarum,* indicating that *L. plantarum* has been a component of human diets in the world for thousands of years (Behera, *et al.* 2018; Garcia-Gonzalez *et al.* 2021). The safety of the genus *Lactiplantibacillus* in general, and specifically, *L. plantarum* for use in food and probiotics, has been further established, via GRAS notice submissions and reviews by other authoritative bodies. As of April 2023, six GRAS notices have been submitted to FDA and, according to the Agency's website inventory of GRAS notices, these submissions received "no questions" letters for food ingredients containing *L. plantarum* specifically; an additional 20 GRAS notices describe other *Lactiplantibacillus* strains. These notices are listed below in **Table 5**. The information provided in this section, and elsewhere in this document, reflect FDA's confirmation that *L. plantarum* ML Prime™ is GRAS, by scientific procedures, for its intended use in wine production.

Table 6: GRAS Notices for *L. plantarum* and other *Lactiplantibacillus* Strains

GRN No.	GRAS Ingredient	Use	Use Level
GRAS Notices for *L. plantarum*			
953	*Lactiplantibacillus plantarum* strain CECT 7527, CECT 7528, and CECT 7529	General use in foods, yogurt, dairy products, etc.	4×10^9 -1.2×10^{12} cfu/serving
946	*Lactiplantibacillus plantarum* strain DSM 33452	Wine production	10^7 cfu/g
847	*Lactiplantibacillus plantarum* ECGC 13110402	General use in foods, excluding infant formula	10^{10} cfu/serving
722	*Lactiplantibacillus plantarum* Lp-115	General use in foods	10^{10} cfu/serving
685	*Lactiplantibacillus plantarum* strain 299v	General use in foods	10^{10} cfu/serving
378	Cultured foods cultured via many different possible strains including *L. plantarum* and other *Lactobacillus*	General use in foods as antimicrobial agent, including meat and poultry, excluding infant formula	0.1-4.5%
GRAS Notices for Other *Lactobacilli*			
1013	*Lactobacillus rhamnosus*	General use in foods, including infant formula	10^8-10^{11} cfu/g

GRN No.	GRAS Ingredient	Use	Use Level
957	*Lactobacillus johnsonii* strain ATCC PTA-124-124205	Snacks and other foods and beverages	Up to 10^{11} cfu/serving
871	*Lactobacillus acidophilus* DDS-1	General use in foods, excluding infant formula and meat and poultry	10^{9}-10^{11} cfu/serving
865	*Lactobacillus acidophilus* NCFM	Infant and toddler formula	10^{8} cfu/g
840	*Lactobacillus paracasei* strain F19	General use in foods excluding meat and poultry	At least 10^{9} cfu/serving
810	*Lactobacillus paracasei* subsp. *paracasei* strain F-19e	Infant formula	10^{9} cfu/day
760	*Lactobacillus curvatus* DSM 18775	Antimicrobial us in RTE foods	10^{6}-10^{7} cfu/g
758	*Lactobacillus helveticus* R0052, *Bifidobacterium longum* subsp. *infantis* R0033, and *Bifidobacterium bifidum* R0071	Infant formula	$5x10^{7}$ cfu/g
736	*Lactobacillus casei* subsp. *paracasei* Lpc-37	Yogurt and other snacks	At least 10^{10} cfu/serving
531	*Lactobacillus fermentum* CECT5716	Infant formula	10^{7} cfu/g
502	*Lactobacillus acidophilus* La-14	General use in foods	10^{9} cfu/serving
440	*Lactobacillus reuteri* strain NCIMB 30242	General use in foods	3.3×10^{8}-10^{10} cfu/serving
429	*Lactobacillus casei* strain Shirota	Fermented dairy products	4×10^{8} cfu/mL
410	*Lactobacillus reuteri* strain DSM 17938	Infant formula	10^{6}-10^{8} cfu/g
357	*Lactobacillus acidophilus* NCFM	Dairy products and snacks	10^{9} cfu/serving
288	*Lactobacillus rhamnosus* strain HN001	General use in foods	10^{9} cfu/serving

GRN No.	GRAS Ingredient	Use	Use Level
281	*Lactobacillus rhamnosus* strain HN001 produced in a milk-based medium	Infant formula	10^8 cfu/g
254	*Lactobacillus reuteri* strain DSM 17938	General use in foods	10^9 cfu/serving
240	Sugar cultured using *L. paracasei*	Antimicrobial in meat in poultry	4.8%
231	*Lactobacillus casei* subsp. *rhamnosus* strain GG	Infant formula	10^8 cfu/g

FDA has evaluated three new dietary ingredient (NDI) notifications for live *L. plantarum* strains; NDIN 171 for strain ATCC 202195, in combination with fructooligosaccharides (CFSAN, 2003), NDIN 764 for strain L-137, at a use level of $1.2x10^{10}$ cfu/day (CFSAN, 2012), and NDIN 900 for strain CJLP133, at a use level of $1x10^{10}$ cfu/day (CFSAN, 2016). All three notices were accepted by FDA. Further, the submitter has rigorously applied the decision tree recommended by Pariza, *et al.* 2015 "Decision Tree for Determining the Safety of Microbial Cultures to be Consumed by Humans or Animals" and determined that the notified strain is safe for human consumption. The decision tree is composed of thirteen questions which, when applied, provide a "comprehensive approach for determining the safety of microbial cultures that lack an established history of safe use for their intended new application." The decision tree is described below.

Has the strain been characterized for the purpose of assigning an unambiguous genus and species name using currently accepted methodology?

YES (go to 2)

Has the strain genome been sequenced?

YES (go to 3)

Is the strain genome free of genetic elements encoding virulence factors and/or toxins associated with pathogenicity?

YES (go to 4)

Is the strain genome free of functional and transferable antibiotic resistance gene DNA?

YES (go to 5)

Does the strain produce antimicrobial substances?

NO (go to 6)

Has the strain been genetically modified using rDNA techniques?

NO (go to 8a)

Was the strain isolated from a food that has a history of safe consumption for the species, to which the strain belongs, is a substantial and characterizing component?

YES (go to 9a)

Has the species to which the strain belongs undergone a comprehensive peer-reviewed safety evaluation and been affirmed to be safe for food by an authoritative group of qualified scientific experts?

YES (go to 10a)

Do scientific findings published since completion of the comprehensive peer-reviewed safety evaluation cited in question 9a continue to support the conclusion that the species, to which the strain belongs, is safe for use in food?

YES (go to 11a)

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?

NO (go to 12a)

Will the intended use of the strain expand intake of the species?

NO (go to 14a)

Based on the above decision tree analysis, the notifier respectfully submits that the strain is deemed to be safe for use in the manufacture of food, probiotics, and dietary supplements for human consumption.

Finally, the European Food Safety Authority (EFSA) maintains a list of microbes for which the agency has conducted thorough risk assessments for their use in human foods. This system proposed basing the safety assessment of a defined taxonomic group (*e.g.*, a genus or a species) on 4 pillars: established identity, body of knowledge, possible pathogenicity, and end use. If the taxonomic group does not raise safety concerns or, if safety concerns exist, but can be defined and excluded, the grouping is granted Qualified Presumption of Safety (QPS) status. Thereafter, "any strain of microorganism, the identity of which could be unambiguously established and assigned to a QPS group, would be freed from the need for further safety assessment other than satisfying any qualifications specified" (EFSA 2007, Herman *et al.* 2018). These risk assessments are all publicly available and are regularly updated to assess new information. To be granted QPS status, a microorganism must have a well-defined taxonomic identity, the available body of knowledge must be sufficient to establish safety, the lack of pathogenic properties must be established and substantiated, and its intended use must be clearly described.

In relation to the submission at hand, there are more than 20 organisms from the *Lactobacillus* genus, including *L. plantarum*, that have been assessed by EFSA and added to the QPS list, as of the most recent update published in December 2022 (EFSA 2023). Additionally, *L. plantarum* is included on the International Dairy Federation (IDF) list of microorganisms with technological or beneficial use (Bourdichon *et al.* 2012). The inclusion of *L. plantarum* on these lists provides strong support that any strains of *L. plantarum* are safe for human consumption and are GRAS by scientific procedures. Pariza, *et al*. (2015) agrees with this assertion and also discusses the QPS process, stating that "microorganisms listed on the IDF and/or QPS inventories meet the criteria for GRAS, for their traditional uses."

The genus *Lactobacillus* has been the subject of several safety assessments and has in every case been found to be a safe genus with limited concern regarding adverse effects (Salminen & Tuomola 1998; Borriello, *et al*. 2003; Bernardeau, *et al.* 2006; Bernardeau, *et al.* 2008). *Lactobacillus,* including *L. plantarum,* are widely used as probiotics in the dairy industry where they have a long history of safe use (Bourdichon, et al., 2012). There have been extremely rare cases of negative effects linked to the consumption of *Lactobacillus rhamnosus* as a probiotic; two cases of sepsis in preterm infants (Dani, *et al*. 2015) and two cases of *Lactobacillus* spp. abscesses in immunocompromised elderly patients (Saarela, *et al.* 2002). After extensive literature searches, we were unable to find any cases in which the consumption of *L. plantarum* was linked to infection. Opportunistic infections by *Lactobacillus* spp. are described, but they are extremely rare and restricted to severely immuno-compromised individuals (Sullivan & Nord 2006; *Salminen,* et al. 2004; Dani, *et al*. 2015; Doron, *et al.* 2015). Infection or pathology linked to *L. plantarum* species is even more rare. In a review of 89 cases of patients with confirmed *Lactobacillus* infection, *L. plantarum* was only found as the infecting organism one time, in a case of endocarditis stemming from poor oral hygiene, and it was noted that 82% of patients had severe or fatal comorbidities (Salminen, *et al*. 2004). A second review followed 45 cases of *Lactobacillus* bacteremia over 15 years, where the researcher concluded that *Lactobacilli* are avirulent pathogens that produce bacteremia, only in patients with serious underlying illnesses and have received antibiotic therapy that may select out for the organism (Husni, *et al.* 1997). In both studies, *L. plantarum* infection was only found as an opportunistic infection and was not linked to its consumption in food or as a food ingredient.

A search for publicly available literature conducted in April 2023 returned several repeat-dose animal and human studies, which involved exposure to various strains of *L. plantarum*. Studies that involve healthy animals or humans are summarized in **Table 6** below. It should be noted that many more studies than are summarized here were found, although these additional studies focus on participants with underlying conditions (constipation, antibiotic treatment, high cholesterol, etc.) The studies below focus on beneficial effects of *L. plantarum* and/or other *Lactobacilli* strains, rather than on reporting the negative effects of exposure. These studies typically report no adverse effects, though this was not the focus of these studies.

Table 7: Animal and Human Studies on *L. plantarum* Consumption

Subjects	Dosage and Duration	Results	Reference
Animal Studies			
5-week-old SD male rats	0, 0.6, 1.2, and 2.4 x 10^9 cfu/day; 60 days	Reduced weight gain in highest dose group; no other adverse effects	Kim *et al.* 2014
Crl:CD(SD) rats	0, 5.5 x 10^{10}; 1.9 x10^{11} cfu/kg bw/day; 90 days	No adverse effects reported for any group	Mukerji *et al.* 2016
Human Studies			
Healthy adults	0, 3 x 10^9 (reduced to 1.2 x 10^9); 12 weeks	No adverse effects reported	Fuentes *et al.* 2013; Fuentes *et al.* 2016
Healthy adults	10^{10} cfu/day; 6 weeks	No adverse effects reported	Bukowska *et al.* 1998
Healthy adults	2 x 10^{10} cfu/day; 21 days	No adverse effects reported	Johansson *et al.* 1998
Healthy children (6 mo-3 years)	10^{10} cfu/day; 3 months	No adverse effects reported	Ribeiro and Vanderhoof 1998
Healthy children (6 mo-3 years)	Not reported; 13 days	No adverse effects reported	Kingamkono *et al.* 1999
Healthy adult males	10^{11} cfu/day; 6 weeks	No adverse effects reported	Huang *et al.* 2018
Healthy adults	2 x 10^9 cfu/day; 6 weeks	No adverse effects reported	Montero *et al.* 2017

On the basis of the above, the notifier asserts that *L. plantarum* ML Prime™ is GRAS.

6-2. Allergenicity

L. plantarum ML Prime™ has been produced without the food or their derivatives that account for the majority of human food allergies named in Section 201(qq)(1) of FD&C Act.

6-3. Summary of Basis for GRAS Determination

Scott Labs has determined that *L. plantarum* ML Prime™ is GRAS for the intended use in wine production, based on the following:

- *L. plantarum* ML Prime™ is manufactured under cGMP for food (21 C.F.R. Part 117) and meets appropriate food grade specifications;
- Potential contaminants, such as heavy metals and pathogenic microbes, are either absent (not detected) or below toxicological and regulatory limits;
- The intended uses and the estimated consumption of *L. plantarum* ML Prime™;
- The long history of safe use of the organism, *Lactiplantibacillus plantarum,* in the industrial scale production of food, and data supporting the organism's non-pathogenic and non-toxigenic nature;
- The results of specific toxicological studies undertaken using *L. plantarum*; and
- Long history of safe consumption of many different *L. plantarum* strains.

Part 7 - List of Supporting Data and Information

7-1. References

Alcok BP, *et al.* (2020) Card 2020: antibiotic resistome surveillance with the comprehensive antibiotic resistance database. *Nucleic Acids Research*. 48 (D1): D517-D525. https://doi.org/10.1093/nar/gkz935

Behera SS, *et al.* (2018) *Lactobacillus plantarum* with functional properties: an approach to increase safety and shelf-life of fermented foods. *BioMed Research International*. https://doi.org/10.1155/2018/9361614

Pederson CS (1935) A study of the species *Lactobacillus plantarum*. *Journal of Bacteriology*. 31(3):217-224.

Bernardeau M, *et al.* (2006) Beneficial lactobacilli in food and feed: long-term use, biodiversity and proposals for specific and realistic safety assessments. *FEMS Microbiology Reviews*. 30(4):487-513. https://doi.org/10.1111/j.1574-6976.2006.00020.x

Bernardeau M, *et al.* (2008) Safety assessment of dairy microorganisms: the *Lactobacillus* genus. *International Journal of Food Microbiology*. 126(3):278-285. https://doi.org/10.1016/j.ijfoodmicro.2007.07.015

Borriello SP, *et al*. (2003) Safety of probiotics that contain Lactobacilli or Bifidobacteria. *Clinical Infectious Diseases*. 36(6):775-780. https://doi.org/10.1086/368080

Bortolaia V, *et al.* (2020) ResFinder 4.0 for predictions of phenotypes from genotypes. *Journal of Antimicrobial Chemotherapy*. 75(12):3491-3500. https://doi.org/10.1093/jac/dkaa345

Bourdichon F, *et al.* (2012) Safety demonstration of microbial food cultures (MFC) in fermented food products. *Bulletin of the International Dairy Federation*. 455/2012. Bulletin455.pdf (ukidf.org)

Bourdichon F, *et al.* (2012) Food fermentations: microorganisms with technological beneficial use. *International Journal of Food Microbiology.* 154(3):87-97. https://doi.org/10/1016/j.ijfoodmicro.2011.12.030

Bukowska, *et al.* (2002) Effect of *Lactobacillus plantarum* 299v on cardiovascular disease risk factors in smokers. *The American Journal of Clinical Nutrition*. 76(6):1249-1255. https://doi.or/10.1093/ajcn/76.6.1249

CFSAN. 2003. NDIN 171, Lactobacillus plantarum and Fructooligosaccharides

CFSAN. 2012. NDIN 764, Lactobacillus plantarum HK-LP_137, Immuno-LP20.

CFSAN. 2016. NDIN 900, Lactobacillus plantarum CJLP133.

Dani C, *et al.* (2015). Lactobacillus Sepsis and Probiotic Therapy in Newborns: Two New Cases and Literature Review. *American Journal of Perinatology Reports*. e25-e29.

Doron S and Snydman DR, (2015) Risk and safety of probiotics. *Clinical Infectious Diseases.* 60(S2):S129-S134. https://doi.org/10.1093.cid/civ085

EFSA (2007). Introduction of a qualified presumption of safety ("QPS") approach for assessment of selected microorganisms referred to EFSA: opinion of the scientific committee. Appendix A: Assessment of gram-positive non-sporulating bacteria. *EFSA J* 587.

EFSA (2023) Update of the list of qualified presumption of safety ("QPS") recommended microorganisms intentionally added to food or feed as notified to EFSA. *EFSA J*. 21(1):e07747

Fuentes MC, *et al*. (2013) Cholesterol-lowering efficacy of *Lactobacillus plantarum* CECT 7527, 7528 and 7529 in hypercholesterolaemic adults. *Br J Nutr* 109:1866–1872

Fuentes MC, *et al.* (2016) A randomized clinical trial evaluating a proprietary mixture of Lactobacillus plantarum strains for lowering cholesterol. *Medit J Nutr Metab* 9:125–135.

Garcia-Gonzalez N, *et al.* (2021) Health-promoting role of *Lactiplantibacillus plantarum* isolated from fermented foods. *Microorganisms*. 9(349) https://doi.org/10.3390/microorganisms9020349

Huang WC, *et al.* (2018) Effect of Lactobacillus plantarum TWK10 on improving enduranceperformance in humans. *Chin J Physiol* 61:163–170.

Husni R, *et al.* (1997) Lactobacillus Bacteremia and Endocarditis: Review of 45 Cases. *Clinical Infectious Diseases*. 1048-1055.

Johansson ML, *et al.* (1998) Survival of *Lactobacillus plantarum* DSM 9843 (299v), and effect on the short-chain fatty acid content of faeces after ingestion of a rose-hip drink with fermented oats. *Int J Food Microbiol* 42:29–38.

Kim DH, *et al*. (2014) Effect of mixture of *Lactobacillus plantarum* CECT 7527, 7528, and 7529 on obesity and lipid metabolism in rats fed a high-fat diet. *J Kor Soc Food Sci Nutr* 43:1484–1490.

Kingamkono R, *et al*. (1999) Enteropathogenic bacteria in faecal swabs of young children fed on lactic acid-fermented cereal gruels. *Epidemiol Infect* 122:23–32

Montero E, *et al.* (2017) Clinical and microbiological effects of the adjunctive use of probiotics in the treatment of gingivitis: arandomized controlled clinical trial. *J Clin Periodontol* 44:708–716

Mukerji P, *et al*. (2016) Safety evaluation of AB-LIFE® (*Lactobacillus plantarum* CECT 7527, 7528 and 7529): antibiotic resistance and 90-day repeated-dose study in rats. *Food Chem Toxicol* 92:117–128

Pariza MW, *et al*. (2015) Determining the safety of microbial cultures for consumption by humans and animals. *Regul Toxicol Pharmacol* 73:164–171.

Pontinen AB, *et al.* (2017) Screening of the two-component-system histidine kinases of *Listeria monocytogenes* EGD-e. LiaS is needed for growth under heat, acid, alkali, osmotic, ethanol, and oxidative stresses. *Food Microbiology*. 65 https://doi.org/10.1016/j.fm.2017.01.018

Ribeiro H and Vanderhoof JA. (1998) Reduction of diarrheal illness following administration of *Lactobacillus plantarum* 299v in a daycare facility. *J Pediatr Gastroenterol Nutr* 26:561

Saarela, M, *et al.* (2002). Safety Aspects of Lactobacillus and Bifidobacterium Species Originating from Human Oro-gastrointestinal Tract or from Probiotic Products. *Microbial Ecology in Health and Diseases*. 14:233-240 https://doi.org/10.1080/08910600310002127

Salminen M, *et al*. (2004) Lactobacillus Bacterimia, Clinical Significance, and Patient Outcome, with Special Focus on Probiotic *L. rhamnosus* GG. *Clinical Infectious Diseases.* 38(1):62-69. https://doi.org/10.1086/380455

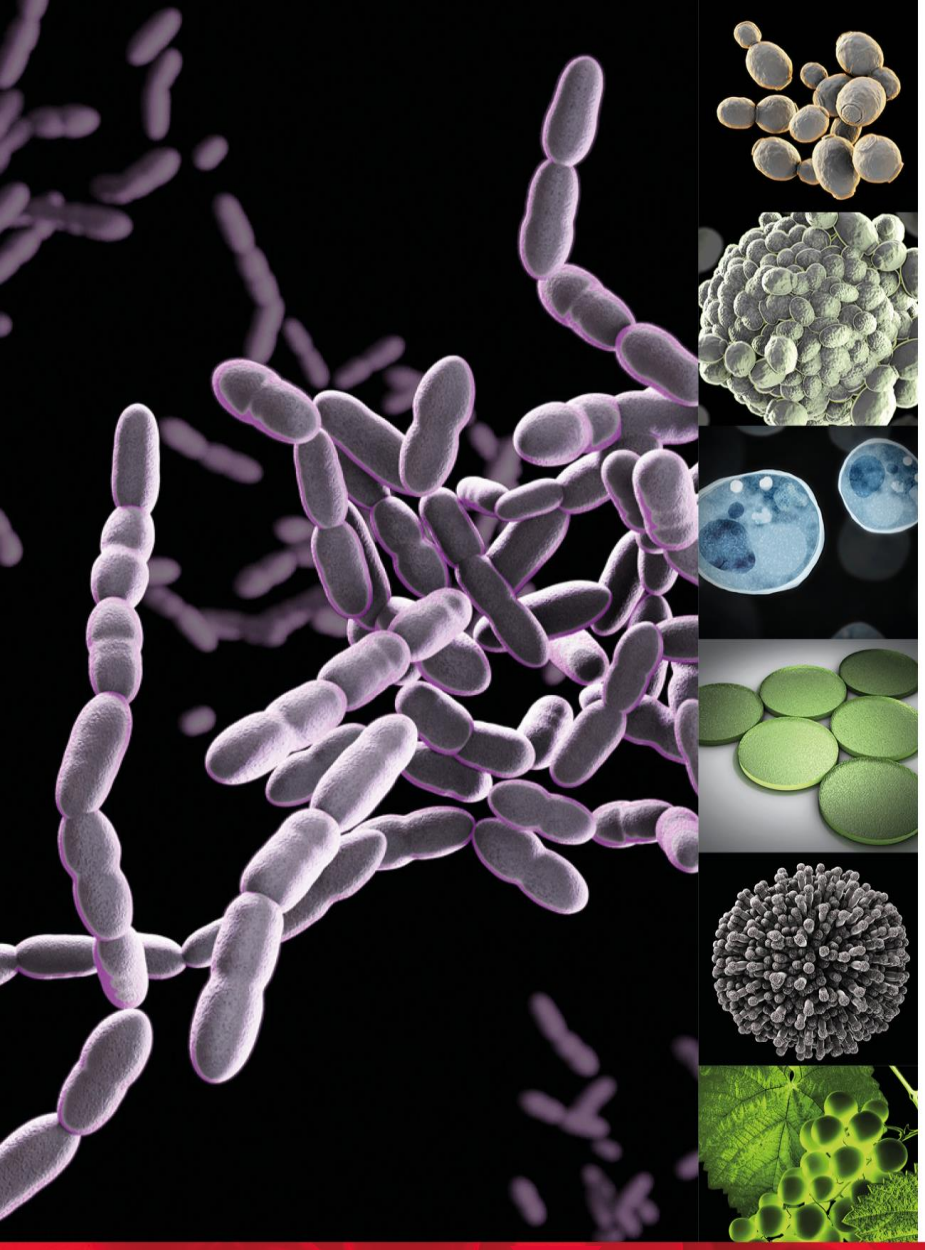
Salminen S and Tuomola E. (1998) Adhesion of some probiotic and dairy Lactobacillus strains to Caco-2 cell cultures. *International Journal of Food Microbiology*. 41(1):45-51. https://doi.org/10.1016/s0168-1605(98)00033-6

Sullivan A and Nord C. (2006) Probiotic lactobacilli and bacteraemia in Stockholm. *Scandinavian Journal of Infectious Diseases*. 38(5):327-331. https://doi.org/10.1080/00365540500449826

Zheng J, *et al.* (2020) A taxonomic note on the genus *Lactobacillus*: description of 23 novel genera, emended description of the genus *Lactobacillus* Beijerinck 1901, and union of *Lactobacillaceae* and *Leuconostocaceae*. *International Journal of Systematic and Evolutionary Microbiology*. 70(4):2782-2858. https://doi.org/10.1099/ijsem.0.004107

7-2. Tables

Appendix 1



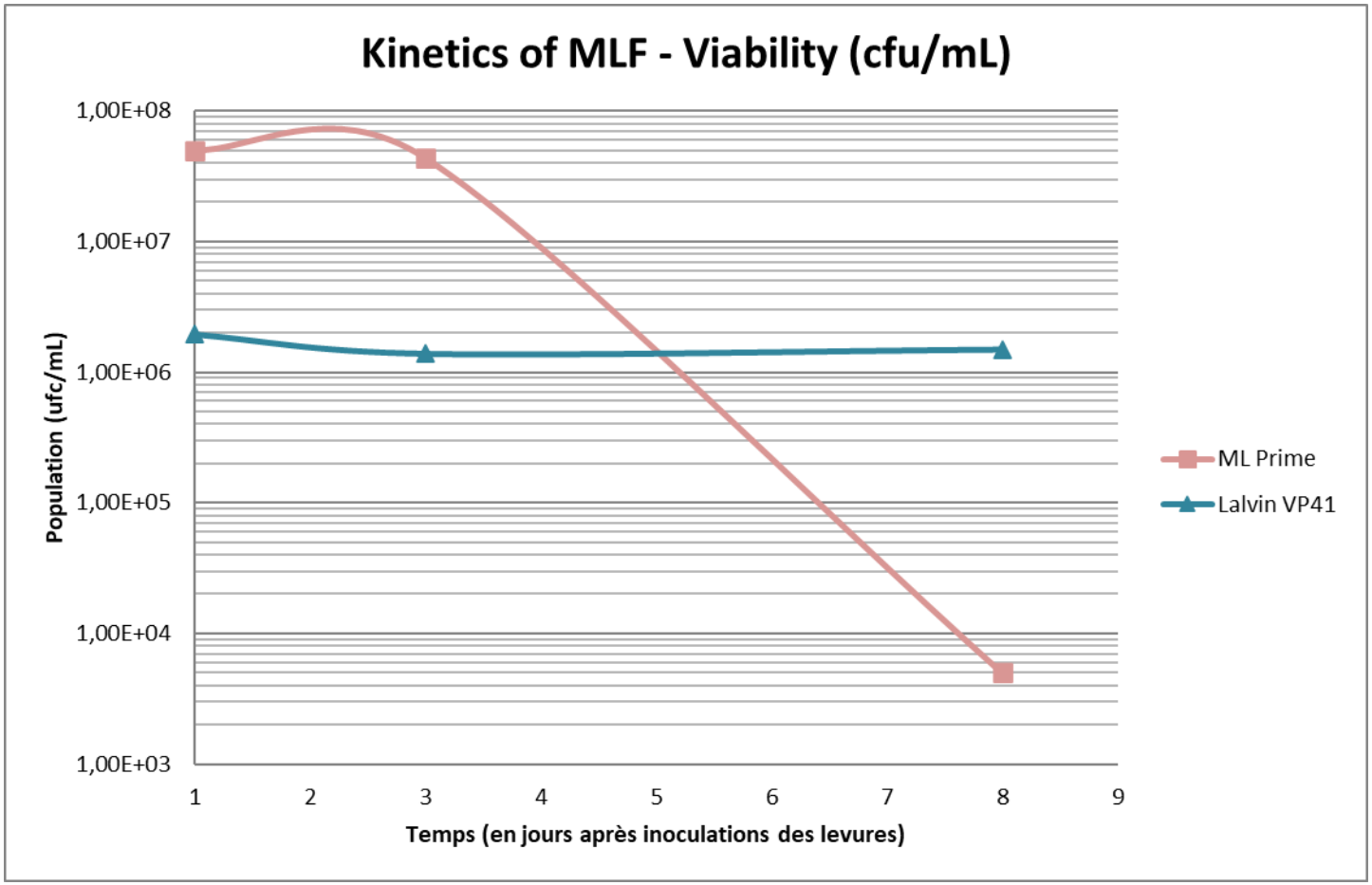
ML Prime Malolactic Fermentation Kinetics -

malic acid degradation

viability decrease

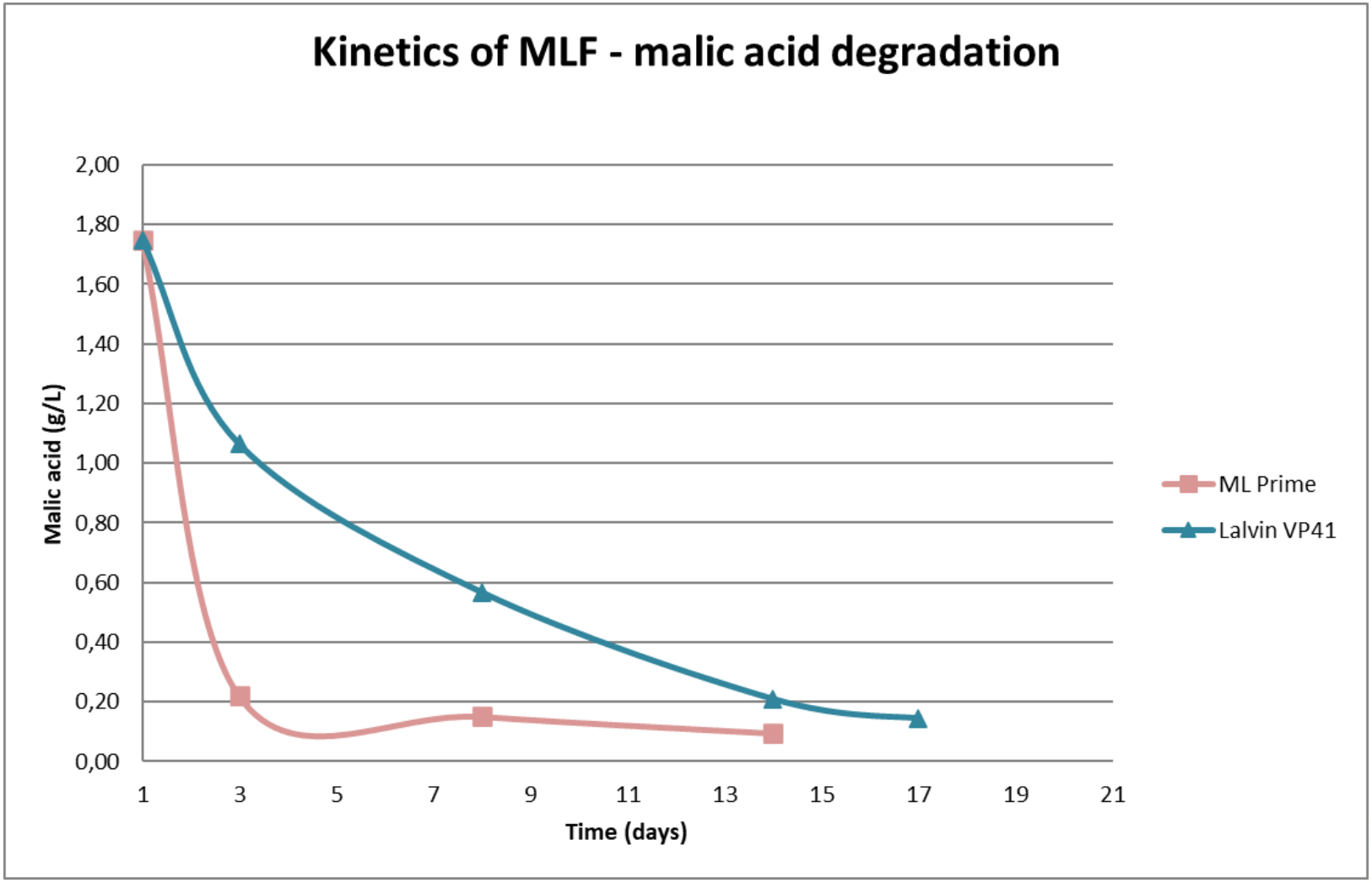
Blagnac Laboratory
Malolactic Fermentation Kinetics

Example 1: Red must – 248g/L sugars – pH=3.37
Yeast ICV D254 25g/hL + GFP – Temperature=25°C



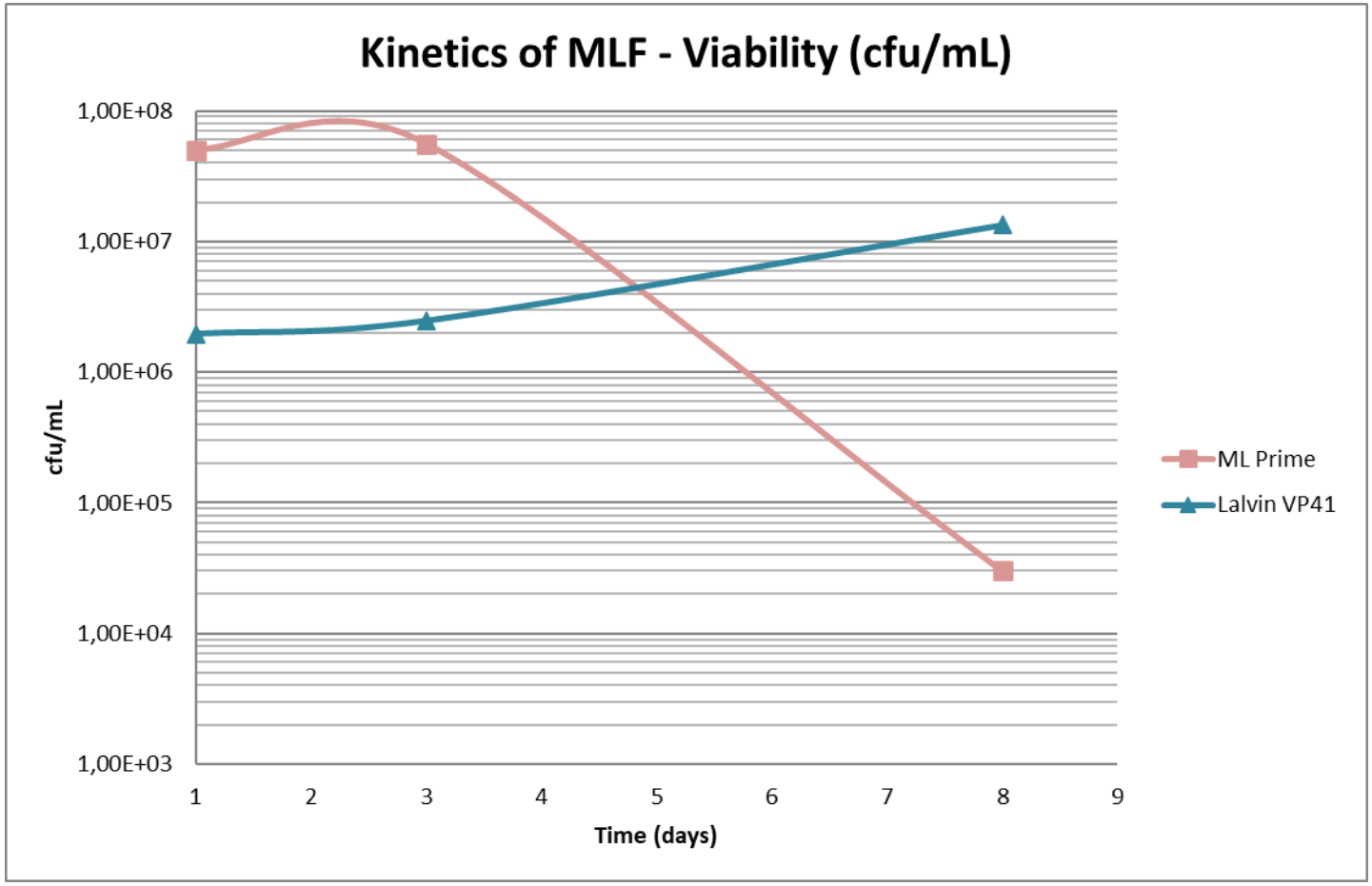
LALLEMAND
LALLEMAND OENOLOGY
Original by culture

Example 1: Red must – 248g/L sugars – pH=3.37
Yeast ICV D254 25g/hL + GFP – Temperature=25°C



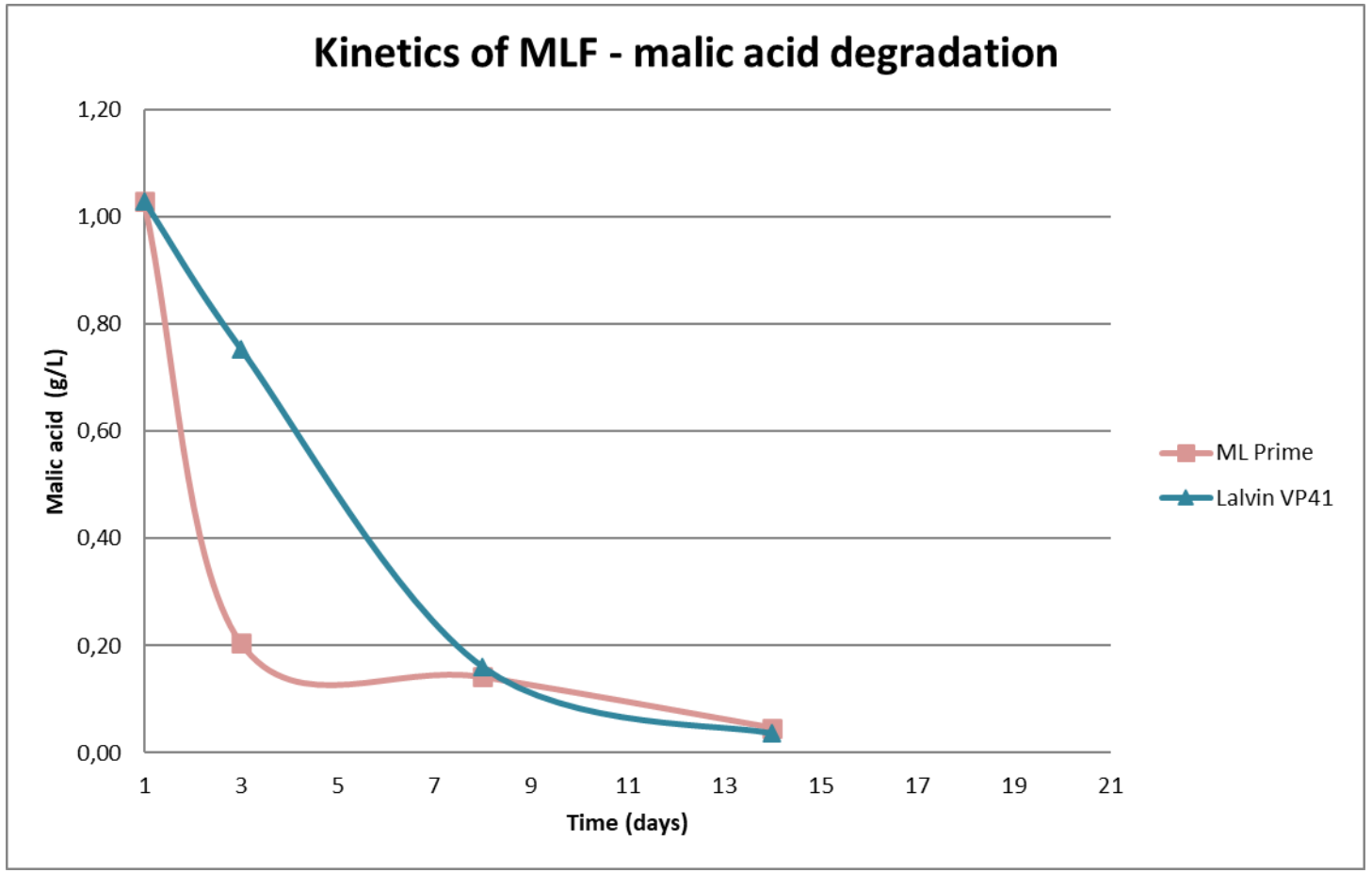
LALLEMAND
LALLEMAND OENOLOGY
Original by culture

Example 2: Red must – 242g/L sugars – pH=3.68
Yeast ICV D254 25g/hL + GFP – Temperature=25°C



LALLEMAND
LALLEMAND OENOLOGY
Original by culture

Example 2: Red must – 242g/L sugars – pH=3.68
Yeast ICV D254 25g/hL + GFP – Temperature=25°C



LALLEMAND
LALLEMAND OENOLOGY
Original by culture

Appendix 2

MASCOMA

MAS22-46	Bioinformatics Group
Lactiplantibacillus plantarum ML PRIME™ – whole genome sequencing and AMR analysis Rintze Zelle, Pier-Luc Desgagné, Matt Perisin, Petra Deane	

Project Details

Project ID	OP22-42
Report Date	2022-04-09
Prepared by	Rintze Zelle
Requested by	Oenology

0. Executive summary

A *de novo* genome sequence of *Lactiplantibacillus plantarum* ML PRIME™ was created and screened for the presence of antimicrobial resistance (AMR) genes using the CARD and ResFinder databases. ResFinder identified a high-similarity match to an ATP-dependent protease ClpL gene, which had been found in *Listeria monocytogenes* and shown to improve heat resistance in that species. Neither CARD nor ResFinder reported hits to antibiotic resistance genes.

1. Material and methods

1.1 Whole Genome Sequencing and Annotation

An annotated *de novo* assembled genome sequence of *L. plantarum* ML PRIME™ was generated by the Microbial Genome Sequencing Center (MiGS; https://www.migscenter.com/; Pennsylvania, USA) from supplied inoculated agar plates. MiGS extracted high-molecular weight DNA from the cell material (QIAGEN DNeasy Blood & Tissue Kit), followed by multiplexed Oxford Nanopore Technologies (ONT) sequencing on a MinION DNA sequencer (R9.4.1 flowcell, Ligation Sequencing Kit SQK-LSK109, Native Barcoding Expansion 1-12 kit EXP-NBD104), and Illumina sequencing on a NextSeq 2000 sequencer with 2x151 bp paired-end reads. Libraries were prepared as described in Baym *et al.* (2015). ONT sequence data was basecalled with Guppy v5.0.16 and adapters were trimmed with porechop v0.2.3_seqan2.1.1 (default parameters). Illumina sequence reads were adapter-trimmed with bcl2fastq2 v2.20.0.445. Demultiplexed trimmed sequence reads were assembled with Unicycler v0.4.8 in a hybrid assembly with default parameters, including polishing with Pilon v1.23. Gene annotations were generated with Prokka v1.14.5 (Seemann, 2014).

1.2 AMR screening with CARD

The *de novo* genome sequence of *L. plantarum* ML PRIME™ in FASTA format was screened against the Comprehensive Antibiotic Resistance Database (CARD) (Alcock et al., 2019) using the online CARD's Resistome Gene Identifier (RGI) version 5.2.0 and CARD database version 3.1.4 (https://card.mcmaster.ca/analyze/rgi), at default settings ("Select Data Type": "DNA sequence", "Select Criteria": "Perfect and Strict hits only", "Nudge >=95% identity Loose hits to Strict": "Exclude nudge", and "Sequence Quality": "High quality/coverage").
For interpretation of the hit categories "Perfect", "Strict", and "Loose", we refer to CARD's Resistance Gene Identifier documentation:

"The RGI analyzes genome or proteome sequences under three paradigms: Perfect, Strict, and Loose (a.k.a. Discovery). The Perfect algorithm is most often applied to clinical surveillance as it detects perfect matches to the curated reference sequences and mutations in the CARD. In contrast, the Strict algorithm detects previously unknown variants of known AMR genes, including secondary screen for key mutations, using detection models with CARD's curated similarity cut-offs to ensure the detected variant is likely a functional AMR gene. The Loose algorithm works outside of the detection model cut-offs to provide detection of new, emergent threats and more distant homologs of AMR genes, but will also catalog homologous sequences and spurious partial hits that may not have a role in AMR. Combined with phenotypic screening, the Loose algorithm allows researchers to hone in on new AMR genes."
https://github.com/arpcard/rgi/blob/6e2befe808d3a86e07f063078fef170269dbd2ac/README.rst

1.3 AMR screening with ResFinder

The *de novo* genome sequence of *L. plantarum* ML PRIME™ in FASTA format was screened against the ResFinder database (Bortolaia et al., 2020) for acquired antimicrobial resistance genes using the online ResFinder 4.1 service (https://cge.cbs.dtu.dk//services/ResFinder/) with software version 2022-03-10 and ResFinder database version 2022-02-04. The analysis was run against all available antibiotics (i.e. Aminoglycoside, Beta-lactam, Colistin, Disinfectant, Fluoroquinolone, Fosfomycin, Fusidic Acid, Glycopeptide, "MLS - Macrolide, Lincosamide and Streptogramin B", Nitroimidazole, Oxazolidinone, Phenicol, Rifampicin, Sulphonamide, Tetracycline, and Trimethoprim) with "Select threshold for %ID" set to 70% (down from the default 90%), "Select minimum length" to the default 60%, "Select species" set to "Other", and "Select type of your reads" set to "Assembled Genome/Contigs".

2. Results and discussion

2.1 Whole-genome sequencing

ML PRIME™ was whole-genome sequenced with both Illumina and Oxford Nanopore (ONT) platforms. Assembly of 1.3 gigabases of ONT read data (N50 of 2.7 kb) and 1.0 gigabases of Illumina read data (2x151 bp paired end reads) resulted in a 3.6 megabase assembly consisting of one circular contig of 3.5 megabase and five small circular contigs ranging from 11 and 71 kb. The genome size agrees with the median genome length of 3.6 megabase observed for *L. plantarum* (see https://www.ncbi.nlm.nih.gov/genome/?term=txid1590%5bOrganism:exp%5d).

2.2 CARD (Comprehensive Antibiotic Resistance Database)

Analysis of the *L. plantarum* ML PRIME™ genome sequence with CARD's Resistome Gene Identifier yielded no hits in either the "Perfect" or "Strict" categories.

2.3 ResFinder

Analysis of the *L. plantarum* ML PRIME™ genome sequence with ResFinder to detect acquired antimicrobial resistance genes showed one hit, of a full-length 2.1 kb match with 98.3% sequence identity to an ATP-dependent protease ClpL (https://www.ncbi.nlm.nih.gov/nuccore/CP023753), which had been found in *Listeria monocytogenes* and shown to improve heat resistance in that species (Pöntinen et al., 2017) (Table 1). Whereas ClpL was found on a plasmid in the *Listeria monocytogenes* AT3E strain

(Pöntinen et al., 2017), its homologue in *L. plantarum* ML PRIME™ was found on the 3.5 Mbase chromosome. Beyond this hit associated with heat tolerance, no hits were reported for antimicrobial resistance genes.

Table 1. ResFinder results for *L. plantarum* ML PRIME™.

Phenotype	Resistance gene	Identity	Alignment Length / Gene Length	Contig position	PMID	Accession number
temperature	ClpL	98.3	2115/2115 / 954	1:3356663..3358777	29104933	CP023753

3. References

Alcock, B.P., Raphenya, A.R., Lau, T.T.Y., Tsang, K.K., Bouchard, M., Edalatmand, A., Huynh, W., Nguyen, A.-L.V., Cheng, A.A., Liu, S., et al. (2019). CARD 2020: antibiotic resistome surveillance with the comprehensive antibiotic resistance database. Nucleic Acids Res. https://doi.org/10.1093/nar/gkz935.

Baym, M., Kryazhimskiy, S., Lieberman, T.D., Chung, H., Desai, M.M., and Kishony, R. (2015). Inexpensive Multiplexed Library Preparation for Megabase-Sized Genomes. PLOS ONE *10*, e0128036. https://doi.org/10.1371/journal.pone.0128036.

Bortolaia, V., Kaas, R.S., Ruppe, E., Roberts, M.C., Schwarz, S., Cattoir, V., Philippon, A., Allesoe, R.L., Rebelo, A.R., Florensa, A.F., et al. (2020). ResFinder 4.0 for predictions of phenotypes from genotypes. J. Antimicrob. Chemother. *75*, 3491–3500. https://doi.org/10.1093/jac/dkaa345.

Pöntinen, A., Aalto-Araneda, M., Lindström, M., and Korkeala, H. (2017). Heat Resistance Mediated by pLM58 Plasmid-Borne ClpL in Listeria monocytogenes. MSphere *2*, e00364-17. https://doi.org/10.1128/mSphere.00364-17.

Seemann, T. (2014). Prokka: rapid prokaryotic genome annotation. Bioinformatics *30*, 2068–2069. https://doi.org/10.1093/bioinformatics/btu153.

GRAS Notice (GRN) No. 1158 Amendments

From: Clark, Mitzi Ng
To: Deng, Kaiping
Cc: Haas, Lauren; Fulmer, Preston A.
Subject: [EXTERNAL] RE: Intended use_GRN 001158
Date: Wednesday, November 8, 2023 10:22:32 PM
Attachments: image001.png

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

Dear Dr. Deng,

We appreciate your inquiry and can confirm that *Lactiplantibacillus plantarum* DSM 34613 is not intended for use in infant formula, products under the jurisdiction of the United States Department of Agriculture, or in foods where standards of identity preclude its use. *L. plantarum* DSM 34613 is intended solely for use in wine production to induce malolactic fermentation and to prevent the growth of microorganisms that could cause off flavors in the finished product. Any other referenced uses for *Lactobacillus* are not relevant to Scott Laboratories' proposed GRAS notice.

Please do not hesitate to contact us if you have any additional questions.

Sincerely,

Mitzi Ng Clark
Partner
direct 415.948.2838 clark@khlaw.com
Keller and Heckman LLP | Three Embarcadero Center, Suite 1420 | San Francisco, CA 94111
Washington, DC Brussels San Francisco Shanghai Boulder

khlaw.com
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From: Deng, Kaiping <Kaiping.Deng@fda.hhs.gov>
Sent: Saturday, November 4, 2023 2:53 AM
To: Clark, Mitzi Ng <clark@khlaw.com>
Subject: Intended use_GRN 001158

** EXTERNAL EMAIL **

Dear Ms. Clark,

This is Kaiping Deng. I am the Regulatory Review Scientist assigned to the GRAS notice dated July 19, 2023, that you submitted on behalf of Scott Laboratories, Inc.. The subject of the notice is *Lactiplantibacillus plantarum* DSM 34613. Would you please confirm whether the subject is intended for use in infant formula, products under the jurisdiction of the United States Department of Agriculture, or in foods where standards of identity preclude its use?

Thank you, and we look forward to hearing from you.

Best regards,

Kaiping

Kaiping Deng, Ph.D.
Regulatory Review Scientist
Regulatory Review Branch
Division of Food Ingredients
Office of Food Additive Safety
FDA/CFSAN
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Writer's Direct Access
Mitzi Ng Clark
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March 8, 2024

Via Electronic Mail

Kaiping Deng, Ph.D.
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

Re: Scott Laboratories, Inc.: GRAS Notice GRN 001158 for *Lactiplantibacillus plantarum* DSM 34613; Our File No. SC18878.00002

Dear Dr. Deng:

On behalf of Scott Laboratories, Inc. (Scott Labs or the Company), this letter and its attachments respond to questions posed in FDA's February 9, 2024 correspondence, regarding GRAS Notice (GRN) 001158. As you know, the Notice speaks to the use of *Lactiplantibacillus plantarum* DSM 34613 for use at a maximum level of 1.5 x 10^8 colony forming units (CFU/g) in wine production to induce malolactic fermentation (turning malic acid into lactic acid) and to prevent the growth of microorganisms that could cause off flavors in the finished product. For ease of reference, we reproduce each question below in italics, followed by the relevant response.

1. *In part 2-3 (page 6), the notifier describes the manufacture of L. plantarum DSM 34613. Please indicate that all raw materials and processing aids are food grade and are used in accordance with U.S. regulations, are GRAS for their intended use, or are the subject of an effective food contact notification.*

Response: We confirm that all raw materials and processing aids used in the manufacture of *L. plantarum* 34613 are either GRAS or cleared food additives for their respective uses under Part 21 of the U.S. Code of Federal Regulations.

2. *In Table 3 (pages 7-8), the notifier lists the specifications for L. plantarum DSM 34613 and provide the results from the analyses of three non-consecutive batches. Please indicate that all analytical methods have been validated for their intended use. We note that the results*

for lead, mercury, arsenic and cadmium are the same as the corresponding specification limits. Please indicate the limit of detection for the method used to analyze for these heavy metals and report the actual values for the analyses for heavy metals. We further note that the specifications for heavy metals are higher than is typically seen for a fermentation-derived ingredient produced in accordance with good manufacturing practices. Please lower the specifications for heavy metals be as low as possible to align with FDA's Closer to Zero initiative of reducing dietary exposure to heavy metals from food.

Response: All analytical methods used to provide the analysis results of three non-consecutive batches of *L. plantarum* DSM 34613 have been validated for their intended use. We are *producing L. plantarum* DSM 34613 to be used solely in wine fermentation, and our customers expect us to comply with the limits set by the Oenological Codex (OIV). While we agree that the heavy metal limits listed in the OIV are high, in the absence of regulatory limits, we adapt our specifications to our customer usage and international standards so that our quality management systems are easy to understand and meet the needs of our customers.

In practice, we are committed to keeping heavy metal contamination to be as low as possible to align with FDA's Closer to Zero initiative of reducing dietary exposure to heavy metals from food. Heavy metal contamination is not a potential hazard in our process or bacteria starter culture products. Confirmation that heavy metals are not present in our raw materials occurs for all raw materials through vendor questionnaires and/or vendor testing of raw materials prior to receipt. Potable water is used in our process, which complies with heavy metal limits for drinking water. Seed materials are grown with those same standards and are inoculated into the fermentations at extremely low levels, which suggests that their contribution to heavy metal contamination of a production batch is exceedingly small. There are no other sources of potential heavy metal contamination.

As an act of caution, we monitor for heavy metals by performing testing annually. Our bacteria starter culture production site in St. Simon, France, submits representative food cultures to be tested. Testing is performed by one external lab that is certified COFRAC 1-1488 and accredited to run heavy metal testing on food matrices. The methods that are being used have been validated for the purpose, as it is validated for all food matrices per the testing lab. Limits of detection for the heavy metals method used by this external lab are:

- Lead: <0.01 mg/kg
- Mercury: <0.005 mg/kg
- Arsenic: < 0.05 mg/kg
- Cadmium: <0.005 mg/kg

L. plantarum DSM 34613 results of heavy metal testing:

Heavy Metal	OIV spec	Batch 1 727117277102	Batch 2 729917277106	Batch 3 813517278017
Lead	<2mg/Kg	< 0,01 mg/kg	< 0,01 mg/kg	< 0,01 mg/kg
Mercury	<1mg/Kg	0,011 ± 0,0033 mg/kg	0,006 ± 0,0018 mg/kg	0,010 ± 0,0030 mg/kg
Arsenic	<3mg/Kg	0,05 ± 0,016 mg/kg	0,04 ± 0,013 mg/kg	0,04 ± 0,013 mg/kg
Cadmium	<1mg/Kg	0,029 ± 0,0087 mg/kg	0,030 ± 0,0090 mg/kg	0,050 ± 0,0150 mg/kg

3. *On page 8, the notifier reference consumption data "presented in Table 3 below". We note that Table 3 contains batch analyses and Table 4 contains wine consumption data. Please address this discrepancy.*

Response: We agree that the passage on page 8, which refers to "Table 3," should in fact reference "**Table 4** below." The title for the table, itself, is correctly labeled as "**Table 4: Two-day Wine Consumption Among the Adult U.S. Population**." We have addressed this discrepancy in the attached, revised pages of the GRAS notice (**Attachment 1**).

4. *In Part 3 (pages 8-9), the notifier provides a dietary exposure estimate for L. plantarum DSM 34613 from the consumption of wine by adults in the United States aged 21 years and older. Please provide a statement why it is appropriate not to provide a dietary exposure estimate for the total US population aged 2 years and older in this case*.

Response: Due to state and federal laws related to the sale of alcoholic beverages to those under the age of 21, NHANES does not collect or report data on consumption of such beverages by those under the age of 21. As there is no legal consumption of alcoholic beverages in the under 21 age group, consumption of or exposure to food ingredients intended solely for use in alcoholic beverages (as we have here) is not included in the GRAS assessment for such ingredients.

5. *In Part 2-2 (page 5), the notifier states that L. plantarum DSM 34613 could be isolated from other intentionally fermented dairy products, bread, and food products, such as pickles or sauerkraut. For the administrative record, please clarify where the stock strain*

that the notifier use for manufacturing L. plantarum DSM 34613 is isolated from, and briefly specify how the purity of the L. plantarum DSM 34613 inoculum for the manufacturing process is ensured.

Response: *L. plantarum* DSM 34613 was isolated from an Italian red wine fermentation. The stock strain inoculum material is pure *L. plantarum* DSM 34613, which is validated by genetic profile and compared to the reference *L. plantarum* DSM 34613 at our Lallemand SAS bacteria production facility. This bacteria production facility currently operates under the Food Safety System Certification FSSC 22000 (**Attachment 2**). The seed preparation is tested for purity prior to freezing. During this first purity check, the inoculum is tested for microbial contaminants. A DNA analysis is also run to ensure stability of the strain, which consists of analysis of four variable number tandem repeat (VNTR) loci to ensure purity and identity of the seed culture.

6. *In Part 2-3 (page 6) and Appendix 2, the notifier states that a de novo genome sequence of L. plantarum DSM 34613 was generated and surveyed using publicly available bioinformatics tools. The notifier conclude that no antimicrobial resistance genes are identified. For the administrative record, please clarify if the genome data is available in a public domain, e.g., a NCBI accession number.*

Response: Due to the proprietary nature of the *L. plantarum* DSM 34613 isolate, we consider this strain as our intellectual property and have not deposited its genome data in a public domain.

7. *In Part 6-3 (page 16), the notifier states that "the long history of safe use of the organism, Lactiplantibacillus plantarum, in the industrial scale production of food, and data supporting the organism's non-pathogenic and non-toxigenic nature".*

   Please provide genotypic or phenotypic analysis on L. plantarum DSM 34613, in order to prove that the strain is non-pathogenic and non-toxigenic.

   - *Genotypic analysis should include homology search for virulence factors and biogenic amine producing genes.*

   - *Ethyl carbamate (EC) is a food processing contaminant in fermented foods and beverages and has been classified as probably carcinogenic to humans. Many factors influence the occurrence of EC in wine, including the presence of precursors. Citrulline can serve as an EC precursor. Certain wine lactic acid*

bacteria can form small amounts of citrulline during arginine biosynthesis through the arginine deiminase (ADI) pathway. The genome sequence of L. plantarum DSM 34613 should be analyzed for genes encoding the enzyme arginine deiminase, the first enzyme in the ADI pathway that catalyzes the degradation of arginine to citrulline and ammonia.

- *Please clarify whether the fermentation of L. plantarum DSM 34613 will generate any other undesirable secondary metabolites during its use in production of wine and musts.*

- *Phenotypic analysis of L. plantarum DSM 34613 may include in vitro cytotoxicity test and enterotoxin production test.*

Response: Based on plating results using the methodology described in the attached document (**Attachment 3**), Biogenic Amines Analysis Report, no biogenic amines of concern were detected above the limit of detection for the strain *L. plantarum* DSM 34613 (ML PRIME), which are known for their negative consequences on the health of sensitive humans. Virulence factors are not an issue in wine due to the high acid and alcohol wine environment (Azevedo, Battaglene, & Hodges, 2016).[1]

It should also be noted that, during malolactic fermentation, indigenous bacteria often produce biogenic amines from amino acids. *L. plantarum* DSM 34613 has been selected for malolactic fermentation because it is unable to produce biogenic amines. Furthermore, since *L. plantarum* speeds up malolactic fermentation, other indigenous organisms that could produce biogenic amines are less likely to grow (Krieger-Weber, Heras, & Suarez, 2020).[2]

The genome sequence of *L. plantarum* DSM 34613 was analyzed for genes encoding the enzyme arginine deiminase, the first enzyme in the ADI pathway that catalyzes the degradation of arginine to the ethyl carbamate precursor citrulline. It was found that the strain *L. plantarum* DSM 34613 does not harbor genes encoding for the arginine deiminase enzyme.

---

[1] Azevedo S, Battaglene T, Hodson G. (2016) Microbiologically, wine is a low food safety risk consumer product. *BIO Web of Converences*. 7, 04003. Doi:10.1051/bioconf/20160704003.

[2] Krieger-Weber S, Heras JM, and Suarez C. (2020) *Lactobacillus plantarum,* a new biological tool to control malolactic fermentation: a review and outlook. *Beverages*. 6;23: doi:10.3390/beverages6020023.

L. plantarum DSM 34613 has been used at levels up to 1.5 x 10^8 CFU/gram to conduct the malolactic fermentation in wines by commercial wineries in Europe and elsewhere in the world for over 10 years. During this time no production of undesired metabolites are reported to be generated by *L. plantarum* DSM 34613 during the production of wine and musts.

8. *Please clarify that the fermentation process is continuously monitored for contaminants.*

Response: The fermentation process of our *L. plantarum* DSM 34613 is continuously monitored for contaminants during its preparation in a HACCP-controlled sterile environment at our Lallemand SAS bacteria production facility. This bacteria production facility currently operates under the Food Safety System Certification FSSC 22000. The seed preparation is tested for purity prior to freezing. During this first purity check, the inoculum is tested for microbial contaminants, and a DNA analysis is also run to ensure stability of the strain. Because the inoculum is the starter material for larger fermentations, any microbial contaminant would be amplified and grown along with the intended culture. Each batch of culture is put through rigorous microbiological quality testing before it is sold into the market. If any contaminating microorganisms were present in the inoculum, they would be amplified through fermentation and found in the finished product. As part of our quality control program, an investigation is conducted on any lot that does not meet the product specifications; an investigation would identify contaminated inoculum material.

9. *Please provide updated information on the literature search(es) performed to prepare the notice. This includes the date(s) (e.g., month and year) of the search(es), the resource database(s) used (e.g. PubMed), the principal search terms used, and the time period that the search spanned.*

Response: The initial search for literature as described in GRN 1158 was conducted in April 2023 and included all relevant publications available on or before April 1, 2023. Primary search terms included, alone or in combination: *Lactobacillus plantarum*; *L. plantarum*; *Lactiplantibacillus plantarum*; *Lactiplantibacillus*; malolactic fermentation; pathogenicity; safety; toxicity; and wine and must production. The following databases were searched: PubMed; Google Scholar; SciFinder; TOXNET (now PubChem-NLM/NCBI). An update to this search was performed in March 2024 covering the intervening time (April 2023-March 2024) and utilized the same search terms and publication databases. No relevant studies, which would impact the safety of *L. plantarum* or would otherwise impact the GRAS conclusion based on scientific procedures as described in GRN 1158, were identified in the updated search.

10. *In part 6-1 (page 10), the notifier states that the safety of the genus Lactiplantibacillus in general, and specifically, L. plantarum for use in food and probiotics has been further established, via GRAS notice submissions and reviews by other authoritative bodies." In general, submissions should not include discussion of purported benefits or language implying dietary supplement uses (e.g., "probiotic," dose, capsule, sachet, efficacy as an endpoint, health benefit). It should be noted that this claim should not have been included in a notification which should focus on identity, safety and intended uses in conventional food.*

Response: We understand and are aware of FDA's position regarding description of efficacy rather than safety in GRAS notices. Scott Labs did not intend to imply that the uses described herein constituted a "probiotic" use or effect. The references to "probiotic" in GRN 1158 are an artifact of how the ingredient is typically described in the reviewed safety studies and were not intended to constitute a claim regarding its use as a probiotic in this instance.

* * *

We appreciate the Agency's continued review of this GRAS Notice. Please let us know if you have any other questions or if you need any additional information.

Cordially yours,

Mitzi Ng Clark

Attachments:

Attachment 1: Updated Pages of GRN 001158

Attachment 2: FSSC 22000 Certification

Attachment 3: Biogenic Amine Analysis

Attachment 1

GRAS NOTICE FOR ML PRIME™ FOR USE IN MALOLACTIC FERMENTATION IN WINE PRODUCTION AT A MAXIMUM INOCULATION LEVEL OF 1.5 X 10^8 CFU/GRAM

Prepared for:

Office of Food Additive Safety (FHS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Campus Dr.
College Park, MD 20740

Submitted by:

Keller and Heckman LLP
Three Embarcadero Center, Suite 1420
San Francisco, CA 94111

On behalf of our client:

Scott Laboratories, Inc.
1480 Cader Ln.
Petaluma, CA 94954

Date:

July 19, 2023

Analyte	Limit	Batch 1 727117277102	Batch 2 729917277106	Batch 3 813517278017
S. aureus	Absent in 1 g	Absent in 1 g	Absent in 1 g	Absent in 1 g
Salmonella	Absent in 25 g	Absent in 25 g	Absent in 25 g	Absent in 25 g
Acetic Bacteria	$< 10^4$ CFU/g	$<10^4$ CFU/g	$<10^4$ CFU/g	$<10^4$ CFU/g
Moulds	$< 10^3$ CFU/g	$<10^3$ CFU/g	$<10^3$ CFU/g	$<10^3$ CFU/g
Yeast	$< 10^3$ CFU/g	$<10^3$ CFU/g	$<10^3$ CFU/g	$<10^3$ CFU/g
Lead	< 2 mg/kg	<2 mg/kg	<2 mg/kg	<2 mg/kg
Mercury	< 1 mg/kg	<1 mg/kg	<1 mg/kg	<1 mg/kg
Arsenic	< 3 mg/kg	<3 mg/kg	<3 mg/kg	<3 mg/kg
Cadmium	< 1 mg/kg	<1 mg/kg	<1 mg/kg	<1 mg/kg

Part 3 – Dietary Exposure

3-1. Estimate of Dietary Exposure

L. plantarum ML Prime™ is intended to be used as a processing aid to reduce the presence of malic acid during wine production at a rate not to exceed 1.5×10^8 cfu/g in wine.

To determine the estimated exposure to ML Prime™ from consumption of wine, Scott Labs commissioned Exponent, Inc. (Exponent) to conduct a dietary intake assessment. Specifically, Exponent's report analyzed the mean and 90th percentile daily intake of wine for use in three categories (red table wine, white table wine, and rose table wine), as well as total wine consumption. The consumption data are based on 2015-2018 NHANES data and are presented in **Table 4** below:

Table 4: Two-day Wine Consumption Among the Adult U.S. Population

Population-Adults 21+		Per User Two Day Intake (g/day)[b]	
Food Category	**N (users)[a]**	**Mean**	**90th Percentile**
Wine, total	626	160	315
Wine, red	381	149	302

Attachment 2

BUREAU VERITAS Certification

FSSC 22000

The Food Safety Management System of

LALLEMAND SAS

At

4 CHEMIN DU BORD DE L'EAU
15130 SAINT SIMON - FRANCE

Has been assessed and determined to comply with the requirement of

Food Safety System Certification 22000
FSSC 22000

Certification scheme for food safety management systems consisting of the following elements:
ISO 22000:2018
ISO TS 22002-1: 2009 Prerequisite programmes on food safety Part 1: Food manufacturing
And Additional FSSC 22000 requirement (version 5.1)

This certificate is applicable for the scope of:

PRODUCTION BY FERMENTATION/CONCENTRATION/FREEZING/LYOPHILIZATION OF MICROORGANISMS IN POWDER ON FROZEN FORM, IN BULK OR IN UNIT DOSIS (POUCH OF 1 G TO 20 KG) FOR USE AS FOOD INGREDIENT.

PRODUCTION PAR FERMENTATION / CONCENTRATION / CONGELATION / LYOPHILISATION DE MICROORGANISMES SOUS FORME DE POUDRES OU CONGELEES, EN VRAC OU CONDITIONNES EN DOSES UNITAIRES (SACHETS DE 1 G A 20 KG) UTILISES COMME INGREDIENT POUR L'INDUSTRIE ALIMENTAIRE.

Food Chain Subcategory: K- Production of (Bio) Chemicals

Certificate of registration number: FR078757-1
Contract number: **10644075**
Initial certification date: **04/06/2015**
Issued by another certification body before the date: **21/11/2022**
Expiry date of previous cycle: **03/06/2021**
Certification cycle start date: **04/06/2021**
Valid until : **03/06/2024**

Paris La Défense, on 21/11/2022

For the President, Laurent Croguennec

Signature

cofrac
CERTIFICATION DE SYSTEMES DE MANAGEMENT
Accréditation N°4-0572
Portée disponible sur www.cofrac.fr

Issued by : Bureau Veritas Certification France, Le Triangle de l'Arche - 9 cours du Triangle 92937 Paris-la-Défense cedex – Puteaux | France.

The authencitity of this certificate can be verified in the FSSC 22000 database of Certified Organizations available on www.fssc22000.com

Attachment 3

MASCOMA

Analysis Report - January 16, 2023

Goal

Utilizing the strain ML Prime, analyze for the presence of biogenic amines after the growth of the organism on MRS at pH 4.8.

Analysis Method

Biogenic amines
The ML Prime strain was plated to isolate individual colonies on MRS and incubated anaerobically at 28°C overnight. The next day three colonies were anaerobically grown in 5 mL MRS broth pH 4.8 to provide inoculum. Five mL of MRS pH 4.8 was added to an anaerobic pressure bottle, the cultures were inoculated at an OD 600 nm = 0.05 and grown in a sealed bottle at 28°C and sampled at 34 and 63 hours. Samples were diluted 20 times and 100 µL of sample was mixed with dansyl chloride (100 µL of 0.01 g/L in acetone). Saturated Na2CO3 (50 µL) was added, along with internal standard (10 µL of 1,7-heptanediamine at 0.5 ppm), and samples were held at 40 °C for 60 min. After derivatization, 20 µL of NH4OH was added, followed by 500 µL of acetonitrile. Diluted samples were filtered and 10 µL of acetonitrile was injected onto a Thermo LC-MS for analysis. Compounds were separated on a Zorbax C18 column eluted with 0.1% formic acid in water and 0.1% formic acid in acetonitrile at 0.3 mL/min. Analytes were quantified based on the response of extracted mass to charge ratios normalized to the ISTD.

Results

Below are the results of the biogenic amines. The data is the average for each of the 3 colonies with the media blanks subtracted.

	averages corrected for background (mg/L)						
	Phenylethyl_amine	Putrescine	Cadavarine	Histamine	Tyramine	Spermidine	Spermine
M14336_34hrs	0.0	0.0	0.0	0.0	0.0	0.0	0.0
M14336_63hrs	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Conclusions

Based on the above results, no biogenic amines were detected above the LOD of the strain ML PRIME, which are known for their negative consequences on the health of sensitive humans.

Analyst: Justin Jasper PhD, Scientist
Reviewer: Erin Wiswall PhD, Senior Director R&D

Keller & Heckman

Serving Business through Law and Science®

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Keller and Heckman LLP
Three Embarcadero Center
Suite 1420
San Francisco, CA 94111

Writer's Direct Access
Mitzi Ng Clark
(415) 948-2838
clark@khlaw.com

April 15, 2024

Via Electronic Mail

Kaiping Deng, Ph.D.
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

Re: Scott Laboratories, Inc.: GRN 001158 for *Lactiplantibacillus plantarum* DSM 34613; Our File No. SC18878.00002

Dear Dr. Deng:

On behalf of Scott Laboratories, Inc. (Scott Labs), this letter and its attachment summarizes the April 5, 2024 ZOOM conversation between FDA, Scott Labs, and Keller & Heckman, LLP regarding GRAS Notice (GRN) 001158. As you know, the Notice speaks to the use of *Lactiplantibacillus plantarum* (*L. plantarum*) DSM 34613 for use at a maximum level of 1.5 x 10^8 colony forming units (CFU/g) in wine production to induce malolactic fermentation (turning malic acid into lactic acid) and to prevent the growth of microorganisms that could produce off flavors in the finished product.

This letter memorializes Scott Labs' decision to reduce the specification data for the heavy metal content of *L. plantarum* DSM 34613 to < 0.1 mg/kg. Accordingly, we provide below the updated specification data (we have also reproduced the batch data in full, for ease of reference):

Heavy Metal	Specification	Batch 1 727117277102	Batch 2 729917277106	Batch 3 813517278017
Lead	< 0.1 mg/kg	< 0.01 mg/kg	< 0.01 mg/kg	< 0.01 mg/kg
Mercury	< 0.1 mg/kg	0.011 ± 0.0033 mg/kg	0.006 ± 0.0018 mg/kg	0.010 ± 0.0030 mg/kg
Arsenic	< 0.1 mg/kg	0.05 ± 0.016 mg/kg	0.04 ± 0.013 mg/kg	0.04 ± 0.013 mg/kg
Cadmium	< 0.1 mg/kg	0.029 ± 0.0087 mg/kg	0.030 ± 0.0090 mg/kg	0.050 ± 0.0150 mg/kg

Additionally, following our discussion, we are attaching the updated Scott Labs' Food Safety System Certification (FSSC) 22000, which is valid until June 3, 2027.[1]

* * *

We appreciate the Agency's continued review of this GRAS Notice. Please let us know if you have any other questions or if you need any additional information.

Cordially yours,

Mitzi Ng Clark

Enclosures:

Attachment 1: Updated FSSC 22000 Certification

[1] Please note that the FSSC 22000 Certification included in our March 8, 2024, letter as Attachment 2, is valid through June 3, 2024, which is depicted in the common EU format (day/month/year).

Attachment 1

Bureau Veritas Certification

FSSC 22000

The Food Safety Management System of

LALLEMAND SAS

4 CHEMIN DU BORD DE L EAU
15130 - ST SIMON - FRANCE

COID: FRA-1-0343-597266

Has been assessed and determined to comply with the requirement of

Food Safety System Certification 22000
FSSC System 22000

Certification scheme for food safety management systems consisting of the following elements
ISO 22000:2018

ISO TS 22002-1: 2009 Prerequisite programmes on food safety Part 1: Food manufacturing

And Additional FSSC 22000 requirement (version 5.1)

This certificate is applicable for the scope of:

PRODUCTION BY FERMENTATION, CONCENTRATION, FREEZING, LYOPHILIZATION OF MICROORGANISMS IN POWDER ON FROZEN FORM, IN BULK OR IN UNIT DOSIS (POUCH OF 1 G TO 20 KG) FOR USE AS FOOD INGREDIENT

PRODUCTION PAR FERMENTATION, CONCENTRATION, CONGELATION, LYOPHILISATION DE MICROORGANISMES SOUS FORME DE POUDRES OU CONGELEES, EN VRAC OU CONDITIONNES EN DOSES UNITAIRES (SACHETS DE 1 G A 20 KG) UTILISES COMME INGREDIENTS POUR L'INDUSTRIE ALIMENTAIRE

Food Chain Subcategory: K- Production of (Bio) Chemicals

Initial Certification Date :	**21 November 2022** (Issued by another certification body since the date: 04/06/2015)
Expiry date of previous cycle:	03 June 2024
Certification decision date:	05 April 2024
Certification Cycle Start Date:	**04 June 2024**
Valid until:	**03 June 2027**

Certificate of registration number: **FR087990** Version: 1
Contract number : **18548267**

Paris La Défense, on : 10 April 2024
For the President, Samuel DUPRIEU Signature

Issued by : Bureau Veritas Certification France
1 place Zaha Hadid 92400 COURBEVOIE France

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