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RE: Legal Opinion – FDA Compliance and Marketing of AC Oxyrase® (Respiratory Complex Enzyme Preparation Produced by *Acetobacter aceti*)

I. INTRODUCTION

This legal opinion addresses the Generally Recognized as Safe (GRAS) status of a food enzyme described as a "Respiratory Complex Enzyme Preparation Produced by *Acetobacter aceti*" and branded under the trade name "AC Oxyrase® (*hereinafter* AC Oxyrase®), a respiratory complex enzyme preparation produced by *Acetobacter aceti*, under the regulatory framework of the United States Food and Drug Administration (FDA). The opinion will analyze the current self-affirmed GRAS status of AC Oxyrase® and the pending GRAS submission.

II. REGULATORY FRAMEWORK

Under the Federal Food, Drug, and Cosmetic Act (FDCA), a substance is considered GRAS if it is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use. [1] The GRAS status can be self-affirmed by the manufacturer or notifier, or it can be affirmed by the FDA through a GRAS notification process.

Section 201(s) of the FDCA describes the two most common types of ingredients in conventional food: food additives and GRAS substances. Food additives require FDA approval before they can be marketed. GRAS substances do not. Both types are tied to their intended use. The same ingredient can be a food additive for one intended use and a GRAS substance for another.[2] A substance is GRAS under the conditions of its intended use only if it satisfies the safety standard for food additives under the FDCA.

Section 201(s), which excludes a GRAS substance from the definition of "food additive" and related premarket approval requirements, describes a GRAS substance as one that is generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in

[1] Oxyrase, Inc. Is hereby submitting a Generally Recognized as Safe (GRAS) notice in accordance with the provisions of 21 CFR part 170, subpart E., pg. 5, Oxyrase GRAS Petition _V4_05.06.24.pdf.

[2] In the preamble to the final rule (*see* 81 Fed. Reg. 54960, Aug. 17, 2016), the FDA explains that a GRAS notice can be an appropriate mechanism for informing the agency of a GRAS use for substance approved as a food additive for another use.

the case of a substance used in food prior to Jan. 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use.[3] According to this definition, experts can generally recognize a substance as safe through either (1) scientific procedures or (2) experience based on common use before Jan. 1, 1958. Some substances qualify under both prongs.

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 a reasonable certainty that the substance is not harmful under the conditions of its intended use; "Common knowledge" is based on "scientific procedures" or on experience based on common use of a substance in food prior to Jan. 1, 1958.

The FDA's GRAS notification procedure, finalized in 2016 but generally in place since 1997, allows companies to voluntarily notify the FDA of their own GRAS designations, without FDA oversight of the scientific procedures used to assess product safety.[4] Under this final rule, a company submits a notice stating its conclusion that the substance involved is GRAS for its intended use. If the FDA does not disagree, the agency sends a letter to the company stating that it has "no questions" regarding the company's GRAS conclusion.

III. CURRENT GRAS STATUS of AC OXYRASE®

AC Oxyrase® is currently self-affirmed as GRAS by Oxyrase, Inc. for its intended use in wine and beer to reduce oxygen to water, thereby replacing sulfites used in these beverages. [5] The self-affirmation is based on the provisions of 21 C.F.R. 170.30, which allows a company to determine whether a substance is GRAS through scientific procedures or, in the case of a substance used in food before 1958, through experience based on common use in food. The self-affirmation of GRAS status means that Oxyrase, Inc. has determined, based on scientific evidence and historical use, that AC Oxyrase® is safe for its intended use without requiring premarket approval from the FDA. [6] This self-affirmation allows the

[3] 21 U.S.C. § 321(s).

[4] The GRAS affirmation petition process has not been used since the FDA issued the proposed rule on the voluntary notification process in 1997. Since then, the FDA has followed what it has called its "interim pilot" program on voluntary notifications.

[5] Pursuant to 21 C.F.R. 170.30, Oxyrase, Inc. has determined that the enzyme complex, AC Oxyrase®, prepared from a pure culture of Acetobacter aceti, is GRAS for use to reduce oxygen to water in wine or beer., pg. 6, Oxyrase GRAS Petition _V4_05.06.24.pdf.

[6] It is the view of Oxyrase, Inc. that the substance, AC Oxyrase®, is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act, based on the conclusion of Oxyrase, Inc. that the

company to market AC Oxyrase® without waiting for FDA review, provided that the data supporting the GRAS determination is available for FDA inspection upon request. [7]

Oxyrase, Inc. has submitted a GRAS notice to the FDA, which is currently pending review. [8] The submission includes comprehensive data on the identity, method of manufacture, specifications, and safety of AC Oxyrase®, as well as its intended use in food products. [9] The pending submission seeks to obtain FDA's affirmation of the GRAS status, which would provide an additional layer of regulatory assurance.

Description of the Notified Substance

1. **Common Name:** The notified substance is commonly known as the Respiratory Complex Enzyme Preparation Produced by *Acetobacter aceti*.
2. **Composition**: The Respiratory complex consists of enzymes and factors that facilitate electron transfer and promote proton translocation, ultimately resulting in the reduction of oxygen (O2) to water (2H2O).
3. **Source**: The complex is isolated from a pure culture of *Acetobacter aceti*, an aerobic microorganism recognized as GRAS, which is grown under controlled conditions in a fermenter.
4. **Trade Name**: The Respiratory complex is marketed as a suspension of particles under the Trade Name AC Oxyrase®.
5. **GRAS Notification**: A GRAS notification for AC Oxyrase® has been submitted with Tracking Number OLSGRN25458, indicating that it may lawfully be distributed.

More specifically, Oxyrase® consists of enzymes and factors that transfer electrons and promote proton translocation that result in reducing oxygen (O_2) to water (H_2O). This complex is isolated from a pure culture of *Acetobacter aceti*, a GRAS, aerobic microorganism, grown under controlled conditions in a fermenter. The primary activity of Oxyrase® is to reduce O_2 to H_2O. One unit of Oxyrase® activity reduces oxygen

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substance AC Oxyrase® is GRAS under the conditions of its intended use in wine or beer., pg. 6, Oxyrase GRAS Petition _V4_05.06.24.pdf.

[7] The data and information that are the basis for Oxyrase, Inc's GRAS determination is available for FDA's review, and copies will be provided to FDA upon request, in either electronic format or by paper copy. Request for copies and arrangements for review of materials cited herein may be directed to:, pg. 6, Oxyrase GRAS Petition _ V4_05.06.24.pdf.

[8] Oxyrase, Inc. Is hereby submitting a Generally Recognized as Safe (GRAS) notice in accordance with the provisions of 21 CFR part 170, subpart E., pg. 5, Oxyrase GRAS Petition _V4_05.06.24.pdf.

[9] 2.0 IDENTITY, METHOD OF MANUFACTURE, SPECIFICATIONS, AND PHYSICAL OR TECHNICAL EFFECT OF THE NOTIFIED SUBSTANCE, pg. 7, Oxyrase GRAS Petition _V4_05.06.24.pdf.

2.1. Identity of Notified Substance, pg. 7, Oxyrase GRAS Petition _V4_05.06.24.pdf.

concentration at the rate of 1.0 % per second at 37°C at its optimal pH. As pH moves away from optimal, the Oxyrase® activity decreases. As temperature increases, activity also increases to a point where enzyme conformation changes, then activity decreases until the protein becomes irreversibly altered or denatured, at which point activity is lost. As temperature decreases activity also decreases with a 2-fold decrease in activity for a 10°C drop.

The Oxyrase enzyme complex is produced in a controlled high energy, strictly aerobic standard fermentation of a selected, pure culture of *Acetobacter aceti*. The production process includes fermentation, recovery (downstream processing) and formulation of the final Oxyrase® product.

IV. CONCLUSION

The undersigned counsel respectfully opines that the AC Oxyrase® as presented (e.g. inclusive of the intended use in beer and wine beverages to reduce oxygen to water):

(1) Meets the definition of GRAS pursuant to 21 C.F.R. 170.30; and
(2) Oxyrase, Inc. may lawfully market AC Oxyrase®, as GRAS under the conditions of its intended use, without informing the FDA Center for Food Safety and Applied Nutrition (CFSAN) while CFSAN is evaluating the AC Oxyrase® GRAS notice.[10]

Undersigned counsel has reviewed the AC Oxyrase® product, its intended use and the relevant statutory and regulatory codifications including FDA guidance documents and case law to assess a compliant regulatory pathway for the marketing of AC Oxyrase® as a food enzyme preparation. It is the Opinion of undersigned counsel that AC Oxyrase® is GRAS and is not subject to the premarket approval requirements of the FDCA and is GRAS under the basis of scientific procedures and in accordance with the provisions of 21 CFR part 170, subpart E.

Very truly yours,

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[10] *See* Response 114, 81 Fed. Reg. 54960 at 55022.