February 13, 2023

Ms. Evangelia C. Pelonis
Keller and Heckman LLP
1001 G Street, N.W., Suite 500 West
Washington, D.C. 20001

Re: Animal Generally Recognized as Safe (GRAS) Notice No. 60 – Dried Fermentation Biomass

Dear Ms. Pelonis:

The Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM or we) refers to a generally recognized as safe (GRAS) notice, dated March 22, 2022, submitted on behalf of your client, Calysta, Inc. (the notifier)[1]. The subject of the notice is Dried *Methylococcus capsulatus* Product[2] (the notified substance) to be used as a source of protein in the diets of salmonid species at a level up to 18% of the diet. The submission informs us of the notifier's conclusion that the subject of the submission is GRAS through scientific procedures. Additionally, we received an amendment, dated May 25, 2022, providing more information for this submission. Mr. Melvin S. Drozen was notified in a letter dated June 2, 2022 that the GRAS notice, as amended, was acceptable for filing, and the notice was designated as animal GRAS notice number (AGRN) 60. We have completed our evaluation of AGRN 60 and have the following comments.

To address the identity, method of manufacture, and specifications of the notified Dried *Methylococcus capsulatus* Product, the notifier describes the common name of the ingredient, conditions of use, descriptions of manufacture and packaging, composition, analytical methods used to determine the contents of protein and other constituents, the process controls that ensure inactivation of the production organisms, and stability information. The notified substance is manufactured by continuous fermentation of *Methylococcus capsulatus* with three other microorganisms (*Cupriavidus* sp., *Aneurinibacillus danicus*, and *Brevibacillus agri*) that control fermentation byproducts. During the 12-week continuous fermentation cycle, the fermentation broth is harvested daily. The downstream processes consist of centrifugation, evaporation, heat treatment, and spray drying.

The notifier provides specifications for the notified substance as follows: Crude protein: ≥68%; Crude fat: ≥5%; Crude fiber: ≤1.0%; Ash: ≤12%; Moisture: ≤10.5%; Nickel: ≤7 ppm; Mercury:

[1] Prior to January 1, 2023, the GRAS notice and amendments were submitted by Mr. Melvin S. Drozen, Keller and Heckman LLP. In a November 29, 2022 letter from Mr. Tomas Belloso, Calysta, Inc., Ms. Evangelia C. Pelonis, Keller and Heckman LLP, was authorized as a new point of contact starting January 1, 2023.

[2] In a January 10, 2023 amendment, the notifier provided "Dried Fermentation Biomass" as a proposed common or usual name for the notified substance. "Dried Fermentation Biomass" will be referred to as the notified substance.

≤0.01ppm; Mesophilic aerobic plate count: ≤10,000 CFU/g; Molds: ≤250 CFU/g; Yeast: ≤250 CFU/g; Salmonella: Absent in 25g; and Listeria: Absent in 25g.

The notifier provides stability testing and packaging information for the notified substance.

To address the microbial safety of the notified substance, the notifier provides data showing that the methods in place are effective to destroy or inactivate the fermentation production organisms, including the source organism and other mesophilic organisms that may contaminate the final product.

To address the utility of the notified substance, the notifier provides a series of published studies showing the effects of the notified substance on the growth performance, body condition, hepatosomatic index and viscerosomatic index of Atlantic salmon and Rainbow trout. These studies also evaluated the digestibility of the notified substance. The experimental results show that the growth performance of salmonid fish fed the notified substance at 18 to 20% of the diet is comparable to salmonid fish fed fish meal, a common source of protein.

To address the target animal safety of the intended use of the notified substance, the notifier provides a series of published studies in Atlantic salmon and Rainbow trout fed the notified substance. The studies evaluated the effects of the notified substance on nutrient digestibility, performance parameters, survivability, and histology of the salmonid fish species. These studies demonstrated comparable results in salmonid fish fed a diet containing up to 18 to 20% the notified substance as compared with control animals fed fish meal. The notifier also includes five published studies, three unpublished studies, and a scientific opinion to address the immunogenicity potential of the notified substance for its intended use as a source of protein in diets for salmonid fish. The published and unpublished studies assess growth, immunoglobulin levels, and histopathology. For the published studies, four are conducted in Atlantic salmon and one is conducted in mice.

To address human food safety associated with use of the notified substance the notifier provides worst-case scenario calculations for mercury, benzene, and other natural gas constituents to demonstrate that there are no significant risks to consumers of the edible tissues of the salmon or trout raised exclusively on food containing the notified substance at the highest use levels. The notifier also describes that other components of the notified substance will be metabolized by the target species, and when incorporated in edible tissues will be indistinguishable from the same components derived from other sources.

The Association of American Feed Control Officials publishes in their Official Publication a list of names and definitions for accepted feed ingredients. FDA recognizes these names as being the “common or usual” names for feed ingredients. FDA recognizes “Dried Fermentation Biomass” as the common or usual name for the notified substance.

Section 301(ll) of the FD&C Act

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll) (1)-(4) applies. In our evaluation of the notifier’s notice, concluding that the notified substance, Dried Fermentation

Biomass, at a level up to 18% of the diet is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing the notified substance. Accordingly, our response should not be construed to be a statement that foods containing the notified substance if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusion

Based on the information contained in the notice and amendments submitted on behalf of Calysta, Inc., as well as other information available to the FDA, CVM has no questions at this time regarding the notifier's conclusion that Dried Fermentation Biomass is GRAS as a source of protein in the diets of salmonid species at a level up to 18% of the diet. The agency has not, however, made its own determination regarding the GRAS status of the intended use of the notified substance in animal food under 21 CFR 570.35. Unless noted above, our evaluation did not address other provisions of the Federal Food, Drug, and Cosmetic Act. As always, it is the continuing responsibility of Calysta, Inc. to ensure that animal food ingredients that the notifier markets are safe and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with 21 CFR 570.275(b)(2), the text of this letter responding to AGRN 60 is accessible to the public on our website for the Current Animal Food GRAS Notices Inventory at https://www.fda.gov/animal-veterinary/generally-recognized-safe-gras-notification-program/current-animal-food-gras-notices-inventory.

If you have any questions or comments, please contact Ms. Chelsea Cerrito at (240) 402-6729 or at chelsea.cerrito@fda.hhs.gov. Refer to AGRN 60 in any future correspondence regarding this notice.

Sincerely,

/s/
Timothy Schell, Ph.D.
Director
Office of Surveillance and Compliance
Center for Veterinary Medicine