



November 22, 2022

Kristi O. Smedley, Ph.D.
Center for Regulatory Services, Inc.
5200 Wolf Run Shoals Road
Woodbridge, VA 22192

Re: Animal Generally Recognized as Safe Notice No. 45 – dried fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550)

Dear Dr. Smedley,

The Food and Drug Administration's (FDA or the agency) Center for Veterinary Medicine (CVM or we) refers to a generally recognized as safe (GRAS) notice, dated February 4, 2021, submitted by Native Microbials, Inc. (Native Microbials or the notifier). The subject of the submission is dried fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550) to be used as a viable microorganism in diets of beef cattle at an intended use rate of 1×10^8 colony forming units (CFU)/head/day. The submission informs us of the notifier's conclusion that the subject of the submission is GRAS through scientific procedures. Following an initial evaluation, you were notified in a letter dated March 16, 2021 that the GRAS notice was acceptable for filing, and the notice was designated as animal GRAS notice number (AGRN) 45. During the evaluation, we received an amendment, dated August 11, 2021, in response to our July 21, 2022 request for more information. We have completed our evaluation of AGRN 45.

To address the chemistry, manufacturing and controls of the notified substance the notifier provides information about the identity, method of manufacture and specifications of the notified substance. The notified substance, viable source of dried fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550), is produced through a sorbitol fed-batch anaerobic fermentation process. After the fermentation, the biomass is harvested by centrifugation, and mixed with cryoprotectants followed by freeze drying. The freeze-dried cell concentrate is encapsulated with hydrogenated glycerides or other fat to produce the final product, viable fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550). The notifier provides specifications for the finished product which include: viable cell counts no less than 2×10^7 CFU/g, coliforms less than 10 CFU/g, *Escherichia coli* less than 10 CFU/25g, *Salmonella* negative in 25g, and *listeria* negative in 25g. The notifier also provides the stability, homogeneity, and packaging information for the finished product, dried fat encapsulated *S. dextrinosolvens* strain ASCUSBF53 (NRRL B-67550).

To address the molecular biology, the notice includes a description of the whole genome sequence analysis conducted for the notified substance viable source of dried fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550). The notifier used both Illumina Miseq (short reads sequencing) and Oxford Nanopore (long reads sequencing) platforms to sequence whole genome of *S. dextrinosolvens* strain ASCUSBF53. Subsequently the sequenced genome was processed for downstream analyses. The taxonomic identification

was carried out using 16S rRNA analysis and whole genome Average Nucleotide Identity analysis. Further, a series of bioinformatics tools and online databases were used to analyze the coding sequence of the *S. dextrinosolvens* strain ASCUSBF53 genome for the presence of potential plasmids, antimicrobial resistance genes, and pathogenicity and virulence related genes.

In order to support identity and microbial safety, the notifier provides a narrative based on scientific data and literature that addresses different aspects, including genomic analysis, the presence of the microbial species in animals, pathogenicity, toxin production, and published literature, to support its conclusion that the dried fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550) is safe for the intended use as a supplemental source of viable microorganisms in dairy cattle feed to “support normal rumen digestion”.

To address the target animal safety of the notified substance, the notifier provides a narrative, including scientific data and literature, addressing different aspects, including genomic analysis, the prevalence of the genus species in several environments, information that the genus species is a commensal ruminal microbe, toxigenicity and pathogenicity, published literature, and an unpublished beef cattle study report, to support their conclusion of that use of viable source of dried fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550) as a supplemental source of viable microorganisms in beef cattle feed is safe.

To address the human food safety of the notified substance, the notifier states that no transfer of the viable encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550) from the rumen to edible tissues is anticipated under the conditions of intended use as a direct fed microbial in the feed of beef cattle. The strain has been characterized as viable encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 and whole genome sequence analysis indicates the absence of any genetic element sequences that code for virulence factors or protein toxins.

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 *Succinivibrio dextrinosolvens* Fermentation Product” as the common or usual name for the notified substance.

Section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any particular order. The notifier did not provide any information to demonstrate that the notified substance functions as intended because Native Microbials concluded that the intended use would not be expected to impact safety. Therefore, we did not evaluate whether the notified substance, dried fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550), would achieve the effect claimed for it. However, please note that if products containing the notified substance, dried fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550), bear any claims on the label or in labeling regarding the function of the notified substance, these claims should be supported by appropriate data and information. FDA may take enforcement action if any claims on labels or labeling are found to be false or misleading.

Section 301(II) of the FD&C Act

Section 301(II) 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(II) (1)-(4) applies. In our evaluation of Native Microbials' notice, concluding that the notified substance, its viable source of dried fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550) to be used in diets of beef cattle at an intended use rate of 1×10^8 colony forming units (CFU)/head/day is GRAS under its intended conditions of use, we did not consider whether section 301(II) 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 viable dried fat encapsulated *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550) to be used as a source of viable microorganism in diets of beef cattle at an intended use rate of 1×10^8 colony forming units (CFU)/head/day if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusion

Based on the information contained in the notice and the amendments, submitted on behalf of Native Microbials, Inc, as well as other information available to FDA, we have no questions at this time regarding the notifier's conclusion that *Succinivibrio dextrinosolvens* strain ASCUSBF53 (NRRL B-67550) to be used as a source of viable microorganism in diets of beef cattle at an intended use rate of 1×10^8 colony forming units (CFU)/head/day is GRAS. 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 Title 21 of the *Code of Federal Regulations* (21 CFR) part 570.35. Unless noted above, our evaluation did not address other provisions of the FD&C Act. As always, it is the continuing responsibility of Native Microbials to ensure that animal food ingredients that it 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 45 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 about this letter, please contact Ms. Wasima Wahid at (240) 402-5857 or at wasima.wahid@fda.hhs.gov.

Sincerely,

/s/

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