February 22, 2017

Dr. James La Marta
DSM Innovation Inc.
45 Waterview Boulevard
Parsippany, New Jersey 07054

Re: GRAS Notice No. AGRN 20

Dear Dr. La Marta:

The Food and Drug Administration (FDA, we) completed our evaluation of AGRN 20. We received DSM Innovation Inc.'s notice on March 25, 2016 and filed it on April 29, 2016. DSM Innovation Inc. submitted an amendment to the notice dated October 31, 2016, clarifying the intended use of inactivated modified *Saccharomyces cerevisiae* (IMSC) and the type of substrates that will be used in the biofuel fermenter. In an amendment dated December 12, 2016, the notifier clarified the notifier's name and provided revisions to the target animal safety section of the notice.

The subject of the notice is inactivated modified *Saccharomyces cerevisiae* (IMSC) for use as a nutrient source in animal food. The yeast has the ability to metabolize 5-C sugars and is utilized during the production of fuel ethanol and the byproducts from this process, including the inactivated yeast alone, or as a component of Distillers Dried Grains (DDG) or DDG with Solubles (DDGS) at a level(s) of up to 20% of the dry solids, and the dried yeast, DDG, or DDGS will be used as ingredients in animal food in accordance with good feeding practices. The notice informs us that IMSC is used as a nutrient source in diets for pets, poultry (broilers, layers and breeding chickens; turkeys), swine (piglets, growers, finishers, gestating and lactating sows), bovine (beef and dairy), fish (salmonoids, catfish, tilapia), and minor species such as ducks, quail, sheep, and goats. The notice further informs us of DSM Innovation Inc.'s view that IMSC when sold alone as yeast or as a component of Distillers Dried Grains (DDG) or DDG with Solubles (DDGS) is GRAS through scientific procedures when used as a nutrient source for the stated animal species.

As a part of the GRAS notice, DSM provides the report of a panel of individuals (the GRAS panel) who evaluated the data and information that are the basis for the notifier's GRAS conclusion. DSM considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of animal food ingredients. The conclusion of the GRAS panel, that the IMSC is safe for its intended use, is based on published data and information.

DSM provides a description of the genetic modifications. A combination of contour-clamped homogenous electric field gel electrophoresis (CHEF), Southern blotting, polymerase chain reaction (PCR) amplification, and nucleotide sequencing were used to verify the genetic material that was introduced into the bioengineered organism. DSM concludes that adequate information is provided in the notice and related publications to establish the safety of its

bioengineered strain of *S. cerevisiae*, which is capable of metabolizing xylose to ethanol. Public information included scientific literature pertaining to the molecular techniques used to develop and characterize the bioengineered *S. cerevisiae* strain.

DSM describes the common name of the ingredient, conditions of use, fermentation media composition, the general method of manufacture of yeast, specifications of the live modified yeast and analytical methods, inactivation of the modified *S. cerevisiae*, analysis of lots, and physical description. Public information included general manufacturing methods for yeast and DDG(S).

DSM provides specifications for the modified *Saccharomyces cerevisiae* liquid concentrate: appearance (turbid cream yeast (concentrated broth) with a white/beige color), dry matter (15-20%), pH (3.8-4.5), glucose ($\leq$ 0.5g/l), microbial contamination: total bacterial count ($\leq 10^6$ CFU/mL), and microscopic observation in the EOF broth (conform).

To address intended nutritive effect, DSM cites multiple publications to document the nutrient content of baker's yeast and conventional DDG(S) and its use in animal food. This was compared to proprietary data showing the nutrient content of the inactivated bioengineered yeast and the DDG(S) produced by the bioengineered yeast. DSM also provided proprietary analysis of total tract nutrient digestibility, amino acid content, amino acid digestibility, and True Metabolizable Energy corrected for nitrogen (TMEn). No public citations were provided for these components. DSM compiled these supportive data to further demonstrate feeding value and substantial equivalence.

To address target animal safety, DSM provides a narrative and corresponding references indicating that the use of toxicity data for *S. cerevisiae*, also known as baker's or brewer's yeast (CAS # 68876-77-7), is appropriate to support the toxicity profile of IMSC. DSM also provides data showing that no changes occurred in the metabolic pathways of the bioengineered IMSC when compared to the parent *S. cerevisiae* strain that could lead to accumulation of toxic metabolites and alteration of the yeast viability, confirming that IMSC is phenotypically and compositionally comparable to commercial strains of *S. cerevisiae*. DSM states that the amount of IMSC in DDG/DDGS or animal food will not be higher than the amount of conventional *S. cerevisiae* already found in animal food or DDG/DDGS, as a byproduct of conventional ethanol distillation.

To address human food safety, DSM states that the inactivated modified *S. cerevisiae* will be metabolized during animal digestion into essential compounds consisting mainly of proteins and carbohydrates and not present a hazard to human health from the consumption of food from production animals fed the inactivated modified *Saccharomyces cerevisiae*.

The Association of American Feed Control Officials (AAFCO) publishes a list of names and definitions for accepted feed ingredients. FDA recognizes these names as being the "common and usual" names for feed ingredients. FDA recognizes the name "*Saccharomyces cerevisiae* expressing xylose isomerase from *Piromyces* sp. E2" as the common and usual name for modified *Saccharomyces cerevisiae* yeast.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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 your notice concluding that inactivated modified *Saccharomyces cerevisiae* 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 inactivated modified *Saccharomyces cerevisiae*. Accordingly, our response should not be construed to be a statement that foods containing inactivated modified *Saccharomyces cerevisiae*, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that DSM Innovation Inc., provided, as well as other information available to FDA, we have no questions at this time regarding DSM Innovation Inc.'s conclusion that inactivated modified *Saccharomyces cerevisiae* is GRAS under its intended conditions of use. This letter is not an affirmation that inactivated modified *Saccharomyces cerevisiae* is GRAS under 21 CFR 570.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

The conclusion is based upon yeast (modified *Saccharomyces cerevisiae*) fermenting fiber liberated from grain pericarp. No other sources of fiber (e.g., wood, stover, straw, Switchgrass, or other such sources of cellulosic biomass) were evaluated, and are, therefore, excluded from this GRAS notice evaluation.

In accordance with 21 CFR 570.275(b)(1), the information in this notice described in 21 CFR 570.225(c)(2) through (c)(5) will be accessible to the public on our website for Animal Food GRAS Notices Inventory at http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/GenerallyRecognizedasSafeGRASNotifications/ucm243845.htm .

If you have any questions about this letter, please contact Dr. M. Thomas Hendricks at 240-402-5925 or by email at Thomas.hendricks@fda.hhs.gov. Please reference AGRN 20 in any future correspondence regarding this submission.

Sincerely,

/s/

Daniel G. McChesney, Ph.D.
Director
Office of Surveillance and Compliance
Center for Veterinary Medicine