April 27, 2018

Dr. Kristi O. Smedley
Center for Regulatory Services, Inc.
5200 Wolf Run Shoals Road
Woodbridge, VA 22192-5755

Re: GRAS Notice No. AGRN 24

Dear Dr. Smedley:

The Food and Drug Administration (FDA, we) completed our evaluation of AGRN 24. We received CJ CheilJedang Corporation's notice on July 17, 2017 and filed it on August 17, 2017. CJ CheilJedang Corporation submitted amendments to the notice on January 19, 2018 and March 19, 2018. The amendments provide a declaration that all substances used for the manufacture and formulation of the notified substance, L-methionine 90% produced by genetically engineered *Escherichia coli* K-12, are suitable for animal food, a list of raw materials used for the manufacture of the notified substance, including both fermentation steps, and verification of the method used to determine L-methionine content in the final ingredient.

The subject of the notice is L-methionine 90% produced by genetically engineered *Escherichia coli* K-12 for use as a source of L-methionine in animal diets according to current good manufacturing and feeding practices, incorporated into the diet at levels commensurate with the nutritional requirement. The notice informs us of CJ CheilJedang Corporation's view that the intended use of L-methionine 90% produced by genetically engineered *Escherichia coli* K-12 is generally recognized as safe (GRAS), through scientific procedures.

To address manufacturing chemistry of L-methionine 90% produced by genetically engineered *Escherichia coli* K-12, CJ CheilJedang Corporation provides information regarding the common name of the ingredient, conditions of use, raw ingredient and final ingredient specifications, general method of manufacture, packaging, analytical method for L-methionine content, and stability information. L-methionine is CAS number 63-68-3. The notified substance is produced by genetically engineered *Escherichia coli* K-12 in a two-step fermentation process which is tightly controlled. Following fermentation, the biomass undergoes various types of filtration, crystallization, washing with water, and drying. The notifier indicates that all materials used in the manufacture and formulation of the notified substance are suitable for use in animal food.

CJ CheilJedang Corporation provides a brief summary of the molecular techniques used to develop and characterize the two genetically engineered *Escherichia coli* K-12 organisms

($KCCM_{11252}P$ and $KCCM_{11340}P$). The notifier described the purification processes used in the preparation of the notified substance that remove any viable genetically engineered organisms and genomic deoxyribonucleic acid (DNA). The notifier states in a January 19, 2018 amendment to the notice that these purification processes are required to meet the stated specifications for the notified substance. FDA has no further questions regarding the genetic modifications that were used to develop the bioengineered organisms used in the manufacturing of L-methionine 90% based on its composition and the absence of genomic DNA and viable genetically engineered organisms as described in the notice and associated scientific literature.

CJ CheilJedang Corporation provides finished ingredient specifications: L-methionine (minimum 90.0%), water-loss on drying (maximum 1.5%), and ash (maximum 1.0%).

To address target animal safety and human food safety of the intended use of L-methionine 90% produced by genetically engineered *Escherichia coli* K-12, CJ CheilJedang Corporation provides information that L-methionine is an essential amino acid in all animal species and is incorporated into tissue proteins. The notifier included the report of an acute toxicity study in rats using L-methionine 90%, and the report did not reveal any adverse effects. Although this study was compliant with good laboratory practice (GLP) standards[1] , it is confidential and not publicly available; therefore, it can only corroborate the safety of the notified substance. In addition, this study is considered corroborative evidence because the rat is a non-target species. The notifier describes the purity of L-methionine 90% as sufficiently high that the concomitant impurities and contaminants are low enough that the probability of risk to human or animal health is reduced to a negligible level. The notifier also includes peer reviewed, publicly available references to support the safety of the source organism, *Escherichia coli* K-12. These references contained studies in chickens and cattle that showed that *Escherichia coli* K-12 is non-pathogenic and non-toxigenic.

To address the intended use of L-methionine 90% produced by genetically engineered *Escherichia coli* K-12, CJ CheilJedang Corporation states that methionine, being an essential dietary nutrient in all animals, is incorporated in animal diets to meet the nutritional requirements of the target animals as determined by animal nutritionists on a case-by-case basis, based on good feeding practices, thus it could be present at up to 0.3% in complete diets for animals. The notifier's strategy to address the intended use of L-methionine 90% is based on the identity of L-methionine in the notified substance, the relevance of L-methionine as the physiologically active form of the essential amino acid methionine, and the listing of methionine within Title 21 of the Code of Federal Regulations, part 582.5475 (21 CFR 582.5475) as a substance that is GRAS as a nutrient when used in accordance with good manufacturing and feeding practices.

Based on the totality of the data and information described above, CJ CheilJedang Corporation concludes that L-methionine 90% produced by genetically engineered *Escherichia coli* K-12 is GRAS for its intended use in animal food.

[1] 21 CFR 58

The Association of American Feed Control Officials (AAFCO) publishes a list of names and definitions for accepted animal food ingredients. FDA recognizes these names as being the "common and usual" names for animal food ingredients. FDA recognizes the name "L-methionine 90%" as the common and usual name for L-methionine 90% derived from the genetically engineered *Escherichia coli* K-12.

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 CJ CheilJedang Corporation's notice concluding that L-methionine 90% derived from the genetically engineered *Escherichia coli* K-12 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 L-methionine 90% derived from the genetically engineered *Escherichia coli* K-12. Accordingly, our response should not be construed to be a statement that foods containing L-methionine 90% derived from the genetically engineered *Escherichia coli* K-12, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that CJ CheilJedang Corporation provided, as well as other information available to FDA, we have no questions at this time regarding CJ CheilJedang Corporation's conclusion that L-methionine 90% produced by genetically engineered *Escherichia coli* K-12 is GRAS under the conditions of its intended use in animal food. The agency has not, however, made its own determination regarding the GRAS status of the subject use of L-methionine 90% produced by genetically engineered *Escherichia coli* K-12 in animal food under 21 CFR 570.35. Unless noted above, our review did not address other provisions of the FD&C Act. As always, it is the continuing responsibility of CJ CheilJedang Corporation to ensure that animal food ingredients that the firm markets are safe and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with 21 CFR 570.275(b)(1), the information in this notice in 21 CFR 570.225(c)(2) through (c)(5) will be accessible to the public on our website for the Current Animal Food GRAS Notices Inventory at https://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 24 in any future correspondence regarding this submission.

Sincerely,

/s/

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