U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

January 21, 2022

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

Re: GRAS Notice No. AGRN 48

Dear Dr. Smedley:

The Food and Drug Administration, (FDA, we) completed our evaluation of animal GRAS notice number (AGRN) 48. We received CJ CheilJedang Corporation's ("CheilJedang" or notifier) notice on April 1, 2021 and filed on May 14, 2021. CheilJedang submitted an amendment on September 14, 2021 that provided revised results of an Antibiotic Minimal Inhibitory Concentration test. On October 15, 2021 CheilJedang submitted another amendment to address questions on chemistry, manufacturing and controls and molecular biology of notified substance.

The notified substance is Dried L-Valine Fermentation Product (≥72% L-valine) produced by bioengineered *Corynebacterium glutamicum* KCCM80240. The notice informs the FDA of CheilJedang's view that the notified Dried L-Valine Fermentation Product is Generally Recognized as Safe (GRAS), through scientific procedures, for use as a source of L-valine in livestock and poultry diets at a level consistent with good feeding practices for the target species.

CheilJedang provided information about the identity, method of manufacture, specifications, analytical methods, contaminants, and stability of the notified substance and the intended use. The notified substance is Dried L-Valine Fermentation Product produced by a bioengineered strain *C. glutamicum* KCCM80240. CheilJedang also addressed - the method of manufacture, composition, analytical methods used to determine the contents of L-valine and other constituents in the notified substance, and method to inactivate the production organism. Dried L-Valine Fermentation Product is manufactured by fermentation of the genetically engineered strain *C. glutamicum* KCCM80240. At the end of the fermentation, the production organism is inactivated by lowering the pH and applying heat. The sterilized liquid is concentrated prior to granulation, drying and particle sizing. CheilJedang presented specifications for the finished product which include: L-valine (≥72% on dry matter basis), Moisture (≤5%), and absent of

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viable cells of production strain *C. glutamicum* KCCM80240. CheilJedang also presented stability and packaging information for the notified substance.

To address the utility of the intended substance, CheilJedang submitted published pivotal data and information generated through a bioavailability study in poultry using the notified substance to support the notified intended use. The notified substance, Dried L-Valine Fermentation Product, is intended to serve as a bioavailable source of L-valine, an essential amino acid in diets for livestock and poultry when fed in accordance with good feeding practices. Body weight gain was the parameter used to evaluate the intended use of the notified substance reported in Wensley et al. (2020). Secondary supporting evidence used this parameter that is available from another published study conducted in swine by Oliveira et al. (2019). The notifier used data in broiler chickens to extrapolate bioavailability of the notified substance to other animal species.

To address target animal safety (TAS) of the intended use of substance, Dried L-Valine Fermentation Product, CheilJedang submitted the following public available information: a) safety of the host organism (*C. glutamicum*) and donor organism (*L. delbrueckii*); b) safety of the genetic modifications in the production strain *C. glutamicum* KCCM 80240; c) safety of L-valine; d) safety of the notified substance; and e) safety assessment of impurities and/or potential contaminants in the notified substance.

To address the TAS safety of the host organism (*C. glutamicum*) and donor organism (*L. Delbrueckii*), CheilJedang provided publicly available information documenting its safe use in industrial production of amino acids for use in animal food. To address the safety of the genetic modifications introduced to the production strain *C. glutamicum* KCCM 80240, the notifier described these modifications and provided information on the lack of potential spillover effects on cell metabolism of the production strain *C. glutamicum* KCCM 80240 compared to the wild-type strain (*C. glutamicum* ATCC 14067), and parental strain (*C. glutamicum* CA08-0012). The spillover information included a) summary information on the safety of the production and host organisms; b) metabolic flux analysis of the wild type, the parent and production strains; and c) a comparison of the levels of extracellular amino acids, organic acids, and biogenic aminesin the fermentation media from the wild type, the parent, and production strains.

To address the safety of L-valine, CheilJedang cited publicly available information to support its supplemental use in animal food. The notifier included the results of an acute study in rats and a bacterial reverse mutation assay. The notifier also included information that showed viable cells of the production strain *C. glutamicum* KCCM 80240 are not detected in the notified substance, and that the dietary contribution of amino acids (other than L-valine), total minerals and heavy metals associated with the maximum inclusion level of 0.5% of the notified substance is not significant and does not raise safety concerns in the target species.

To address the human food safety of the notified substance, CheilJedang stated that L-valine is a required nutrient for humans. The notified substance is intended for use in livestock and poultry feeds only as a nutritional source of the essential amino acid L-valine. The notifier stated there is no additional exposure to L-valine above the natural basal content for the consumer raised by digested meat produced from animals fed a diet supplemented by the notified substance. Consumption of food produced from animals fed a diet supplemented by the notified substance

does not represent a safety concern for human food safety.

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 the name "Dried L-Valine Fermentation Product" as the common or usual name for the Dried L-Valine Fermentation Product (≥72% L-valine) produced by bioengineered *Corynebacterium glutamicum* KCCM80240.

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 CheilJedang's notice, concluding that Dried L-Valine Fermentation Product 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 Dried L-Valine Fermentation Product. Accordingly, our response should not be construed to be a statement that foods containing Dried L-Valine Fermentation Product, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusion

Based on the information contained in the notice, including amendments submitted by CheilJedang, as well as other information available to FDA, we have no questions at this time regarding CheilJedang's conclusion that Dried L-Valine Fermentation Product as a source of L-valine in livestock and poultry diets is GRAS. The agency has not, however, made its own determination regarding the GRAS status of the intended use of the Dried L-Valine Fermentation Product as a source of L-valine in livestock and poultry diets 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 CheilJedang 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 48 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) 402-5758 or by e-mail at wasima.wahid@fda.hhs.gov. Please reference AGRN 48 in any future correspondence regarding this GRAS notice.

Sincerely,

/s/

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

References

Wensley, M., J. Woodwoth, J. DeRouchey, S. Dritz, M. Tokach, R. Goodband, H. Walters, B. Leopold, C. Coufal, K. Haydon, and J. Lee. 2020. Effects of amino acid biomass or feed grade amino acids on growth performance of growing swine and poultry. Translational Animal Science 4:52.

Oliveira, M., J. Htoo, J. Gonzalez-Vega, and H. Stein. 2019. Bioavailability of valine in spray-dried L-valine biomass is not different from that in crystalline L-valine when fed to weanling pigs. Journal of Animal Science. 97:4227-4234.