January 26, 2015

Mr. Melvin S. Drozen
Keller and Heckman LLP
1001 G Street, N.W.
Suite 500 West
Washington D.C. 20001

Re: GRAS Notice No. AGRN 000016

Dear Mr. Drozen:

The Food and Drug Administration (FDA) is responding to the notice, dated December 3, 2013 that you submitted on behalf of Metabolic Explorer under FDA's Center for Veterinary Medicine (CVM) Pilot Program for substances Generally Recognized As Safe (GRAS) added to food for animals (See 75 FR 31800; June 4, 2010). FDA's Center for Veterinary Medicine received the notice on December 3, 2013, filed it on January 2, 2014 and designated it as GRAS Notice No. AGRN 000016.

The subject of your notice is L-methionine 85% produced by a bioengineered *Escherichia coli* K-12. The notice informs FDA of the view of Metabolic Explorer, that L-methionine 85% produced by a bioengineered *Escherichia coli* K-12 is GRAS, through scientific procedures when used as a nutrient at levels up to 0.3% in animal feed.

Metabolic Explorer provides information about the identity, specifications, method of manufacture, and conditions of use of L-methionine 85% (L-methionine is CAS number 63-68-3).

Metabolic Explorer provides information about the genetic engineering of the source organism, *Escherichia coli* K-12, and the manufacture of L-methionine. The notified substance is produced through a fermentation which is tightly controlled. Following fermentation, the biomass undergoes various types of filtration, crystallization, washing with water, and drying. Metabolic Explorer indicates all materials added to the final formulations are of suitable quality for feed and in compliance with FDA regulations. Raw ingredients and final product specifications were also included in the submitted materials. Metabolic Explorer includes analytical methodology to determine L-methionine of the final ingredient. Metabolic Explorer also provides stability, homogeneity, and packaging information for the notified substance.

Metabolic Explorer provides finished product specifications: L-methionine (minimum 85%), loss on drying (maximum 3%), ash (maximum 3%), fat (maximum 0.2%), and residual sugars (maximum 0.5%).

Metabolic Explorer provides information on an *Escherichia coli* K-12 strain that was bioengineered to produce L-methionine 85% with the same chemical characteristics as L-methionine. Metabolic Explorer provides a description of the safety of the host and gene donor organisms (also *Escherichia coli* K-12 strain), and a summary of the genetic changes that were made. Metabolic Explorer provides published and unpublished information to support genetic modifications that were performed during the development of the source organism strain.

Metabolic Explorer provides published information to support the intended use of L-methionine 85% produced by a bioengineered *Escherichia coli* K-12 when used as a nutrient at levels up to 0.3% in animal feed. Published articles were referenced to support that methionine is recognized as the first limiting amino acid in poultry and high-yielding dairy cows and as the second or third limiting amino acid in swine.

Metabolic Explorer provides published and unpublished information to support target animal safety of L-methionine and L-methionine 85% produced by a bioengineered *Escherichia coli* K-12. Pivotal published articles cited to support safety of the L-methionine 85% for its intended use were: Albert et al. 1992; Benevenga, and Steele, 1984; Falkow et al., 1976; Harter, and Baker, 1978; Hayashi et al., 2001; Johnson et al., 2006; Mengel, and Klavins, 1967; Smith, 1974; and Toue et al., 2006.

To address human food safety, the notice states that the primary consideration is the safety of the production organism. Metabolic Explorer also states that L-methionine 85% and any of the residual impurities (which includes low levels of other amino acids) will be metabolized when the animal consumes and digests its food (like other amino acids); therefore, the L-methionine 85% derived from the bioengineered *Escherichia coli* K-12 will be indistinguishable from methionine derived from other sources. Metabolic Explorer provides unpublished information that included *in vivo* genotoxicity studies, a subchronic oral toxicity study, an acute oral toxicity study, and a developmental toxicity study to support the safety of any potential human dietary exposure to L-methionine 85%.

Based on the information provided by Metabolic Explorer, as well as other information available to FDA, the agency has no questions at this time regarding Metabolic Explorer's conclusion that this L-methionine 85% derived from the bioengineered *Escherichia coli* K-12 is GRAS under the stated intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of this L-methionine 85% derived from the bioengineered *Escherichia coli* K-12. As always, it is the continuing responsibility of Metabolic Explorer to ensure that food ingredients that the firm markets are safe and are otherwise in compliance with all applicable legal and regulatory requirements.

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 "L-methionine 85%" as the common and usual name for L-methionine 85% derived from the bioengineered *Escherichia coli* K-12.

In addition, in our review of Metabolic Explorer's notice for L-methionine 85%, FDA did not review whether food containing L-methionine 85% derived from the bioengineered *Escherichia coli* K-12 would violate section 301(ll) of the Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. 331(ll)], or whether any of the exemptions in section 301(ll) apply to foods containing L-methionine 85% derived from the bioengineered *Escherichia coli* K-12. Section 301(ll) of the FDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FDCA, 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 accordance with the Federal Register notice announcing the CVM Pilot Program, a copy of the text of this letter, as well as a copy of the information in this notice that conforms to the information described in your GRAS exemption claim is available for public review and copying via the FDA home page at http://www.fda.gov. To view or obtain an electronic copy of this information, follow the hyperlinks from the "Safe Feed" webpage (www.fda.gov/safefeed) under the Seek Ingredient Approval section to "Generally Recognized as Safe (GRAS) Notification Program" where the Animal Food GRAS Inventory is listed.

If you have any questions about this letter, please contact Dr. M. Thomas Hendricks at 240-453-6869 or by email at thomas.hendricks@fda.hhs.gov. Please reference AGRN 000016 in any future correspondence regarding this submission.

Sincerely,

/s/

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

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