

July 20, 2017

Michael L. Lindinger, Ph.D.
The Nutraceutical Alliance
Lindenfarne Horse Park
10526 4th Line Nassagaweya
Campbellville, ON Canada L0P 1B0

Re: GRAS Notice No. AGRN 19

Dear Dr. Lindinger:

The Food and Drug Administration (FDA, we) completed our evaluation of AGRN 19. We received Freedom Health, LLC's notice on February 17, 2016 and filed it on March 22, 2016. Freedom Health, LLC submitted amendments to the notice on November 17, 2016 and July 3, 2017, which included new references, and information related to utility, and chemistry, manufacturing and controls.

The notified substance is L-glutamine for use as an ingredient in an equine feed supplement for consumption by post-weaning horses at levels not to exceed 4 grams per day, or approximately 9 mg / kg body wt / day, above the L-glutamine level already present in a horse's typical forage and grain diet. The intended nutritive effect is to support the cellular metabolism of intestinal epithelial cells. The notice informs us of Freedom Health's view that the use of L-glutamine in an equine feed supplement is generally recognized as safe (GRAS) through scientific procedures.

Freedom Health describes the common name of the ingredient, conditions of use, the general method of manufacture of L-glutamine, specifications and analytical methods, analysis of lots, physical description, stability, homogeneity, and method of manufacture of L-glutamine for animal food supplements. Public information included general manufacturing methods.

Freedom Health provides information that L-glutamine is manufactured by a fermentation process using *Corynebacterium glutamicum* (*Brevibacterium flavum*). The notified substance is produced through a fermentation which is tightly controlled. Following fermentation, the substance undergoes various types of filtration, crystallization, purification, and drying. Freedom Health indicates all materials added to the final formulations are of suitable quality for animal food and in compliance with FDA regulations.

Freedom Health provides finished product specifications that include: L-glutamine (99-101%), identification (FT-IR) complies, specific rotation (D-line 20° H₂O) +6.3 to +7.3 degrees, specific rotation (D-line 20° HCl) +31.5 to +33 degrees, loss on drying (maximum 0.3%), and residue on ignition (maximum 0.1%).

To address intended nutritive effect, Freedom Health cites 23 publically available reports of the different roles of L-glutamine in metabolism. Some reports indicate that under some conditions, such as periods of increased metabolic rates to support fetal development, neonatal growth, or growth during lactation, L-glutamine may not be synthesized in sufficient amounts. Other cited

publically available reports study animal disease models (mice, rats, and swine) and suggest that high concentrations of intracellular and extracellular L-glutamine are associated with reduction in infection, sepsis, severe burn wounds, cancer and other pathologies. Other cited publically available reports indicate that L-glutamine is an energy substrate for immune and epithelial cells, and is important for intestinal development and function. The notice cites publically available reports showing a beneficial effect of L-glutamine supplementation (1% of the diet) in piglets and lactating sows.

Freedom Health cites ten publically available reports supporting the idea that exercise in horses induces proteolysis, and supplementing protein and amino acid mixtures may decrease post-exercise proteolysis. The notice cites three publically available reports regarding the supplementation of L-glutamine in exercising rodents and humans at levels of 0.9 g/kg of body weight or more.

To address target animal safety, as a part of the GRAS notice, the notifier provided the report of a panel of individuals (Freedom Health's GRAS panel) who evaluated the data that are the basis for the notifier's GRAS conclusion. Freedom Health considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of food ingredients. The conclusion of Freedom Health's GRAS Panel, that the substance is safe for its intended use, was based on published data.

Publically available information is presented in the notice indicating that supplemental L-glutamine is well tolerated in humans and did not cause severe adverse side effects when orally supplemented below 40 gram per day in humans. The notifier also provides publically available information showing that L-glutamine is considered non-mutagenic based on standardized *in vitro* assays. Other publically available information presented in the notice shows that the NOAEL for L-glutamine in rats is 3.8 and 4.5 g/kg body mass/day in male and female rats, respectively. Based on the information provided in the notice, the exposure level to glutamine in horses would be approximately 0.44 g/kg body weight considering all sources of L-glutamine in the diet and the supplemental L-glutamine administered in the supplement. Exposure to L-glutamine only from the notified L-glutamine in the supplement would be approximately 0.008 g/kg of body weight considering a 450 kg horse. Therefore, exposure to L-glutamine from the notified use as a supplemental source of L-glutamine in horses is approximately 380-450 fold lower than the NOAEL established in rats. Information on the effects of L-glutamine supplementation in horses, rabbits, and poultry is also presented in the notice.

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-glutamine" as the common and usual name for L-glutamine derived by a fermentation process using *Corynebacterium glutamicum* (*Brevibacterium flavum*).

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 way. We question whether the information provided in the notice substantiates that L-glutamine supports the cellular metabolism of intestinal epithelial cells when used at levels not to exceed 4 grams per day (or approximately 9 mg/kg body weight/day) above that already present in typical forage and grain diets of post-weaning horses. If products containing L-glutamine bear

any claims on the label or in labeling regarding the function of the notified substance, these claims must 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 Federal Food, Drug, and Cosmetic Act (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 your notice concluding that L-glutamine 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 L-glutamine. Accordingly, our response should not be construed to be a statement that foods containing L-glutamine, 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 amendment submitted by Freedom Health, as well as other information available to the Agency, we have no questions at this time regarding Freedom Health's conclusion that L-glutamine is GRAS under its intended conditions of use. This letter is not an affirmation that the notified substance is GRAS under 21 CFR 570.35. Unless noted above, our evaluation 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.

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 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 19 in any future correspondence regarding this submission.

Sincerely,

/s/

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