U.S. FOOD & DRUG ADMINISTRATION

September 15, 2025

Royal Canin US, Inc.
Attention: William Sanders, Ph.D.
Senior Regulatory Approvals Manager
500 Fountain Lake Blvd. Suite 100
St. Charles, MO 63301

Re: GRAS Notice AGRN 75 – Tagetes (Aztec Marigold) Extract

Dear Dr. Sanders:

The Food and Drug Administration's (FDA, the Agency) Center for Veterinary Medicine (CVM or we) refers to a generally recognized as safe (GRAS) notice, dated January 14, 2025, submitted on behalf of Royal Canin US, Inc. (Royal Canin or the notifier). The subject of the notice is Tagetes (Aztec marigold) extract as a source of lutein in food for puppies at levels up to 20 mg/kg dry matter (DM) lutein, and in food for kittens, adult cats, and adult dogs at levels up to 80 mg/kg DM lutein. The submission informs us of the notifier's conclusion that the subject of the submission is GRAS through scientific procedures. You were notified in a letter dated February 13, 2025 that the GRAS notice was acceptable for filing, and the notice was designated as animal GRAS notice number (AGRN) 75. On June 5, 2025, CVM received an amendment from the notifier containing information to address questions identified during evaluation of the notice. On June 18, 2025, CVM received an amended notice which modified the intended use of the notified substance to a source of lutein. We have completed our evaluation of AGRN 75 and have no questions at this time.

To address the identity, method of manufacture, and specifications of the notified substance, the notifier provides information on the identity of lutein in the notified substance, manufacturing process, specifications for the marigold oleoresin and the marketed formulations, and analytical methods used to determine the levels of total xanthophylls, lutein, zeaxanthin, impurities, and contaminants. The notified substance is produced from dried marigold (*Tagetes erecta*) flowers which are extracted with hexane to obtain the carotenoid enriched marigold oleoresin after removal of hexane. The marigold oleoresin may undergo saponification and is blended with carriers and preservatives to produce the commercial products. The notifier provides specifications for the marigold oleoresin, which include color of yellow to brownish, total carotenoids/xanthophylls ≥125 g/kg, % lutein of total carotenoids ≥70%, % zeaxanthin of total carotenoids ≥4%, moisture ≤20%, ash ≤15%, fatty acids ≤45%, waxes/resins ≤4%, and non-xanthophylls plant materials ≤45%. The notifier also provides specifications for impurities and contaminants such as heavy metals, microbials, and dioxins/furans. The notifier also provides stability information.

To address the target animal safety of the intended use of the notified substance, the notifier provides a toxicological risk assessment for the primary constituent components of the notified substance: xanthophylls – primarily lutein, free fatty acids, and non-xanthophyll (NX) plant

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material. The other components, moisture, and ash, pose no toxicological concerns. The notifier compares the estimated dietary intake (EDI) of lutein and NX material resulting from inclusion of the notified substance in pet foods at the maximum intended use levels with intakes from pivotal safety studies in the scientific literature. The EDI of lutein resulting from the inclusion of the notified substance at levels which provide up to 80 mg lutein/kg DM in adult dogs, adult cats, and kittens, and up to 20 mg lutein/kg DM in puppies, are less than the National Research Council's (NRC) Presumed Safe Intake (PSI) for lutein in the respective species. The EDI of NX material exceed the calculated exposures in the studies on which the PSIs for lutein are based but are well below the exposure that was tolerated by dogs in a study not considered in the NRC evaluation. The notifier also describes how the possible components of the NX material such as waxes, fiber, and nitrogen free extracts are commonly consumed by the target species and would be included at less than 0.1% of finished pet foods, making adverse effects unlikely. The remaining material in the notified substance, free fatty acids, are also commonly consumed by the target species and pose no safety concerns.

The notifier also provides contaminant data to demonstrate that heavy metals, residual hexane, dioxins and furans, and microbial pathogens should not be present in the notified substance at levels that would pose safety concerns to the target species.

The notifier uses information from two representative commercial formulations of the notified substance, from two different suppliers, to construct the safety narrative. The notifier also explains that there is no difference in safety conclusions between versions of marigold extract due to the presence of enzymes that will hydrolyze lutein and lutein esters in the gastrointestinal tracts of the target species.

The notifier concludes that information on the physical or other technical effect of the notified substance is not necessary because use of the notified substance as a source of lutein does not impact target animal safety.

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 particular. The notifier did not provide any information to demonstrate that the notified substance functions as intended because the notifier has concluded that the intended use of the notified substance would not be expected to impact safety. Therefore, we did not evaluate whether the notified substance would achieve the effect claimed for it. However, please note that if products containing the notified substance bear any claims on the label or in labeling regarding the function of the notified substance, these claims should 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(ll) of the Federal Food, Drug, and Cosmetic 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 the notifier's notice, as amended, concluding that the notified substance 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 the notified substance. Accordingly, our response should

not be construed to be a statement that foods containing the notified substance, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

CONCLUSION

Based on the information contained in the notice and amendments, submitted on behalf of Royal Canin, and other information available to the FDA, we have no questions at this time regarding the notifier's conclusion that Tagetes (Aztec marigold) extract is GRAS under the intended conditions of use. The Agency has not, however, made its own determination regarding the GRAS status of the intended use of the notified substance in animal food under 21 CFR 570.35. Unless noted above, our evaluation did not address other provisions of the Federal Food, Drug, and Cosmetic Act. As always, it is the continuing responsibility of Royal Canin to ensure that animal food ingredients that the notifier 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 75 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-notificationprogram/current-animal-food-gras-notices-inventory.

If you have any questions or comments, please contact Ms. Megan Hall at animalfood-premarket@fda.hhs.gov.

Sincerely,

/s/
Jeanette B. Murphy, M.S.
Acting Director
Office of Surveillance and Compliance
Center for Veterinary Medicine