EPA's Memorandum in Support of the Regulatory Decision for PNR 1427 (Seresto Pet Collar, EPA Reg. No. 11556-155)

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I. INTRODUCTION

This memorandum presents the outcome of the review of canine and feline incidents for pesticide product PNR1427 (Seresto or Seresto pet collar) and announces mitigation that is now incorporated to aid in the Agency's continued review and monitoring of the product. Seresto, registered originally by Bayer Animal Health (Bayer), but subsequently transferred to Elanco US Inc. (Elanco or the registrant) in 2020, was approved by the Environmental Protection Agency (EPA or the Agency) on March 16, 2012, under EPA Registration No. 11556-155.

Seresto includes two active ingredients, imidacloprid and flumethrin. Imidacloprid is a neonicotinoid insecticide and has been classified by the Insecticide Resistance Action Committee (IRAC)[1] as a Group 4(A) chemical that causes irreversible blockage of the postsynaptic nicotinic acetylcholine receptors in insects. Imidacloprid products can be used on a variety of agricultural crops, on non-agricultural use sites, in residential and commercial areas, as well as in pet spot-on and collar products.

Flumethrin is a pyrethroid insecticide categorized by the IRAC as a Group 3(A) chemical[1] and works by altering nerve function, causing paralysis in target insect pests, eventually resulting in death of the target pest. Flumethrin is used to formulate two products registered by EPA, the technical product and one end-use product, the Seresto pet collar.

The Agency received over 75,000 adverse event reports via the EPA Incident Data System (IDS), the EPA database that houses all adverse events reported to the Agency for all EPA-registered products, including 1,698 pet deaths, associated with the Seresto collar since it was registered in 2012. These pet incidents span an 8-year period, from when it was registered in 2012 through 2020.

In April 2021, EPA sent a letter pursuant to Section 6(a)(2) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and 40 CFR Part 159 to Elanco and Bayer, the current and former registrants of Seresto pet collars, respectively, reiterating the legal requirement under FIFRA to report incidents with this product and requiring them to provide additional data on reported adverse effects of Seresto pet collars. This additional information was more extensive than what pesticide registrants routinely reported to IDS, as the Agency typically receives reports in IDS only as incidents categorized into four severity codes (death, major, moderate, minor) as established in FIFRA 6(a)(2) and further defined in the PRN-98-3. EPA also required Elanco and Bayer to provide detailed sales data and data on annual incident rates and severity. The usefulness of these data in EPA's review is explained in detail below.

Over 120 documents were submitted for review and included adverse event reports for 2016-2020, toxicology and pharmacokinetic studies, and assessments and reviews conducted by the registrant. This document summarizes the Agency's review of those documents and additional information surrounding the Seresto canine and feline incidents and presents the regulatory decision made as a result of this review. EPA consulted with the Food and Drug Administration

[1] Insecticide resistance action committee. IRAC. (2023. April 18). https://irac-online.org.

Center for Veterinary Medicine (FDA CVM, hereafter referred to as FDA) on this review and incorporated methodologies often utilized in FDA's adverse event reviews.

II. ACTION DESCRIPTION

On April 27, 2021, EPA issued a letter to Elanco and Bayer requesting additional information on Seresto (EPA Reg. No. 11556-155) under FIFRA Section 6(a)(2) and 40 CFR § 159.160. Bayer responded by indicating they had transferred all the information on their former Animal Health business unit to Elanco in August of 2020, and thus did not have any information to provide to the Agency. Elanco provided over 120 documents for EPA to review. The documents included a variety of data specific to sales of the product, published articles, and enhanced incident data for dogs and cats.

On July 12, 2021, EPA sought public comment on a petition submitted by the Center for Biological Diversity (CBD) requesting that the Agency cancel Seresto and suspend the registration while the Agency moves forward with cancellation proceedings. The request for public comment was published in the Federal Register. 86 Fed. Reg. 36,546. The 60-day public comment period closed on September 10, 2021 with 5,477 comments received. These comments and the petition decision are discussed in the *Petition to Cancel Registration of PNR1427 (Brand Name Seresto) under the Federal Insecticide, Fungicide, and Rodenticide Act; Reg. No. 11556-155* (USEPA 2023b).

EPA and Elanco have had ongoing discussions on the findings of the Agency's review of the canine and feline incidents. The Agency and Elanco have worked closely to come to an agreement on label mitigation. Also on June 9th, 2023, Elanco submitted regulatory requests in response to the Agency's findings. The resulting revisions to the Seresto registration are discussed in detail in Section V below.

III. USE PROFILE

The Seresto collar is impregnated with the insecticide active ingredients imidacloprid and flumethrin. Before Elanco's amendment request, each collar was labeled to provide 8 months of control for fleas, ticks, and lice on dogs and puppies 7 weeks of age and older, and for fleas and ticks on cats and kittens 10 weeks of age or older. The use on cats has now been incorporated into a new product that is registered for use on cats only. The collar is designed with a mechanical release system that is intended to allow for quick release of the collar in situations where the animal is at risk of strangulation due to the collar catching on an object. The labels indicate that existing fleas on dogs and cats will be killed within 24 hours whereas reinfesting fleas will be killed within 2 hours. Efficacy against existing ticks on dogs and cats begins within 48 hours, whereas reinfesting ticks will be killed within 6 hours of application of the collar. Further, the dog label indicates that the product is water resistant, though the duration of efficacy drops down to 5 months (fleas) and 7 months (ticks) for dogs that swim more than once a month. Duration of efficacy may also be reduced for dogs that are bathed more than once a month. The label does not specify water resistance claims when the product is used on cats.

IV. EVALUATION

A. Assessment of Risks to Companion Animal Health

EPA assessed risks to companion animal health by evaluating the canine and feline incidents (or adverse events) reported to the EPA associated with the Seresto flea/tick pet collar. Below is a summary of the findings of that review; details of the analysis can be found in *Canine and Feline Adverse Event Review for the Seresto Collar (EPA Reg No. 11556-155)* (USEPA 2023a). EPA consulted with FDA on this review and incorporated methodologies often utilized in FDA's reviews.

1. Data Analysis

Several data sets associated with the registration of this collar and the reported adverse events were included in the review, including a review of the companion animal studies submitted in support of the collar registration, a review of the toxicological data set on the two active ingredients (imidacloprid and flumethrin), an analysis of available data on release rates of active ingredients from the collar, and studies measuring plasma or serum levels of these compounds after both oral and collar exposure in dogs and cats.

Many external factors can influence whether incidents are reported to EPA (and with what level of detail and/or data) which can make it difficult to predict the true rate of adverse incidents for Seresto and other EPA-regulated pet products. To help minimize potential bias, EPA focused on two other Elanco products that both contain imidacloprid (K9 Advantix II and Advantage II) as the comparison group, because enhanced reporting data were available for these products and were based on the same Elanco monitoring program and EPA reporting protocols. Using data EPA had on K9 Advantix II and Advantage II, EPA conducted a disproportionality analysis, which is a method used to establish a possible causal relationship between a product and reported adverse events and helps to detect when there is a higher-than-expected number of adverse reactions with one drug compared to other reactions reported in a pharmacovigilance database. This is often referred to as "signal detection". Two indices often applied in pharmacovigilance monitoring were used, the Proportional Reporting Ratio (PRR) and the Incidence Rate Ratio (IRR). PRRs are used to compare the number of adverse events reported to the total adverse event reports for all or several other products, and IRRs are used to compare the number of adverse events reported to product sales data. These ratios were determined using specific clinical signs reported in each case; for example, the rate of reported deaths for one product versus others, or the rate of seizures reported for one product versus others. PRR and IRR were used to help evaluate if Seresto was associated with a disproportionate number of adverse incidents relative to other EPA-regulated flea and tick products for dogs/cats. Additional information on these indices can be found in the *Canine and Feline Adverse Event Review for the Seresto Collar (EPA Reg No. 11556-155)* document (USEPA 2023a).

EPA also analyzed the frequency of reported canine and feline incidents from 2016 to 2021 in the IDS database based on severity categories (death, major, moderate, minor). Comparisons were made between total reported cases and reporting frequencies in each category of Seresto

canine and feline incidents compared to canine and feline incidents associated with spot-ons and non-Seresto collars.

Although signal detection can help identify potential issues of concern, more in-depth clinical review and veterinary medical judgement was used to further evaluate possible safety signals and assess causality. In a causality assessment, several factors are considered when evaluating adverse event reports for potential association with product use, including the timing of the event compared to the application, concurrent medications or disease, and pre-existing condition of the pet. Causality categories included ratings of definitely, probably, possibly, or unlikely related to product use, or insufficient information to assess the case.

2. Major Conclusions

The most frequently reported clinical sign for Seresto in dogs was pruritis (itchy skin) and was reported in 54% of the reported incident cases (of 49,000 cases). This was followed by lethargy and anorexia, each of which was reported in approximately 10% of cases. For cats, application site hair change was the most frequently reported sign (32% of 16,000 cases) followed by application site lesions and pruritis, each of which was reported in approximately 25% of cases. More severe clinical signs (for example, convulsions) were reported much less frequently and appeared to be similar across the three Elanco products that were compared.

PRR values for Seresto generally did not exceed a value of 2, a common threshold used in pharmacovigilance evaluations and also used by the FDA as a signal of disproportionate reporting, the exceedance of which will usually trigger further evaluation of adverse event reports. For both PRR and IRR, Seresto had values greater than 1 (but less than the threshold of 2) compared to the other Elanco products, indicating greater frequency of death and some neurological signs for Seresto when compared to the two other Elanco products (K9 Advantix II and Advantage II). Limitations of this comparison include using only two other products for comparison (two for canine and one for feline) and that imidacloprid is a common active ingredient in all three products, which could mask any detectable differences if associated with the active ingredient. Despite the lack of exceedance of this commonly used threshold, EPA further analyzed cases that reported death and some neurological signs by completing individual case reviews.

To help expand the product comparisons to other active ingredients, the Agency also analyzed all canine and feline incidents related to collars and spot-ons reported from 2016 to 2021 in the IDS database, regardless of whether those incidents were attributable to Seresto. The comparisons were made between counts and reporting frequencies of Seresto canine and feline incidents compared to canine and feline incidents associated with spot-ons and non-Seresto, EPA-registered collars. For reported deaths, Seresto had a similar reporting frequency to spot-ons for both dogs and cats (2.7% for Seresto, 3% for cat spot-ons, 2.3% for dog spot-ons). The reporting frequency of deaths for Seresto was higher than other collars in dogs and lower than other collars in cats (2.7% for Seresto, 6.7% for other cat collars, 0.8% for other dog collars). For the major severity category, Seresto had a higher reporting frequency of incidents compared to all other spot-ons or non-Seresto collars in both dogs and cats. For the moderate severity category, Seresto

was higher than the other spot-ons, but varied when compared against other collars. Reporting frequency in the minor severity category was generally similar across all products.

The severity categories (death, major, moderate, minor) are subjective, and interpretation of incidents may vary widely across registrants. A clearer understanding of these comparisons would require detailed information on each incident from each company. This information is not currently available in EPA's IDS. Once the company becomes aware of an event, they are reported to the Agency through IDS. Additional characterization of these comparisons can be found in the Canine and Feline Adverse Event Review for the Seresto Collar (EPA Reg No. 11556-155) document. (USEPA 2023a).

EPA also examined studies on the levels of imidacloprid and flumethrin found in the plasma (bloodstream) of animals after oral administration of the active ingredients at concentrations that approximated the Lowest Observed Adverse Effect Concentration (LOAEC) and compared that to plasma concentrations of animals after collar wear. Because exposure to the collar is likely through dermal (primarily) but also through oral exposure (due to licking and grooming behavior), it is difficult to make a direct comparison to oral or dermal laboratory studies based on the dose used in the study. Thus, the plasma concentrations are used for comparison. In this comparison, the maximum concentration of the active ingredients detected in plasma in dogs after oral administration were generally 10x higher than the concentration measured in dogs after wearing the collar. This suggests that systemic exposure to the active ingredients in dogs that wear the collar are lower than the levels at which adverse effects are potentially anticipated. Limitations of this analysis include the fairly limited number of animals included in the studies and the inability to complete the analysis for cats, as no data measuring plasma levels in cats after oral exposure was available.

EPA, in consultation with the FDA, also conducted case reviews for all death cases to assess causality for death and other reported severe clinical signs, as well as for a subset of non-death cases where neurological signs were reported, about 1700 cases. Most of these cases were assessed as being possibly caused by Seresto products but had a low level of confidence in those determinations because of various confounding factors, often typical of adverse event causality review. A large percentage of cases were also assessed as having insufficient information to determine causation, particularly in reported death cases. Specific confounding factors in case narratives included a lack of additional data around death reports (*e.g.*, only claim was collar was placed on pet and then, at a later date, the pet died) or the case narrative reported that the pet was in "unknown condition" prior to the collar application which made it difficult to assess causality. All the reported death cases that were found to be probably or definitely related to the Seresto product use (4 canine and 9 feline out of 1477 cases reviewed) were associated with mechanical strangulation or trauma caused by the collar, often associated with a failure of the release mechanism.

B. Usage and Benefits Assessment

1. Usage Data

EPA's analysis of adverse canine and feline incident reports associated with Seresto relied on the reported sales data of Seresto and the other two Elanco spot-on products, Advantage II (contains imidacloprid and pyriproxyfen) and K9 Advantix II (contains imidacloprid and permethrin). Available data from both registrant product distribution data and proprietary survey data on pesticide sales to consumers provide independent lines of evidence for increased distribution and sales of Seresto collars between 2017 and 2019/2020, which suggest increased levels of usage are likely to have occurred during and shortly after that period. The number of Seresto collars distributed by Elanco annually does not necessarily reflect the number of collars purchased or used by consumers each year. For example, products distributed towards the end of a given year may not move through distribution channels and reach the consumer market until the following calendar year. Further, those products might not be used immediately following purchase, despite being captured in the survey-based sales data. Therefore, usage will lag both the distribution and sales numbers reported in a given year. Consistent annual increases in both distribution and sales values may, however, be considered a reliable indication of rising demand for the product.

The use of collars impregnated with insecticides, including but not limited to Seresto, increased from less than 5% to about 12% of the pet insecticide market from 2017 to 2019. For both cats and dogs, collars accounted for about one-third of flea and tick control product sales in 2019. Still, liquid insecticide products including shampoos, dips, and topical spot-on treatments continue to represent the leading market share of sales, accounting for approximately 70% of the pet insecticide market in 2019. The use of pet insecticides for lice prevention or control is not described in these recent surveys of pet insecticide usage.

2. Assessment of Pest Management Benefits & Alternatives

EPA reviewed extension literature developed by entomologists and veterinarians as well as pet insecticide usage data obtained from proprietary market research data and the sole current registrant of Seresto, Elanco, to evaluate the role of Seresto as a pest management tool and the availability of efficacious alternative insecticides.

Pests Targeted by Seresto Collars

Each Seresto collar provides protection for 8 months against fleas and ticks. All pet protection products that are registered for public health pests are required to meet certain minimum efficacy standards as stated in 40 CFR Part 158, subpart R. Fleas and ticks are considered public health pests.

Fleas are the most common insect ectoparasites of domesticated cats and dogs in the US and worldwide. While several species can attack both animals, the cat flea (*Ctenocephalides felis felis*) is the most common species.

All ectoparasitic arthropod pests, including fleas, ticks, and lice, may cause serious skin irritation that can lead to bacterial or fungal infections and bleeding due to excessive itching. Depending on the species, ticks may transmit Lyme disease, Rocky Mountain spotted fever, anaplasmosis, tularemia, Ehrlichiosis, and many other disease pathogens that affect both companion animals and humans.

Diseases carried by fleas and ticks are widespread and some, such as Lyme disease, are easily encountered by pet cats and dogs, and consequently their human family members. In the U.S. in 2020, there were almost 900,000 cases of tick-borne disease reported in dogs. Ticks carry pathogens that can lead to at least sixteen different human diseases. Therefore, preventive protection from a collar such as Seresto is particularly advantageous because it greatly reduces the chance of repeated and extended feeding by fleas and ticks.

Lice that attack dogs or cats do not feed on humans the way fleas and ticks can. However, they can be serious health problems for affected animals if left uncontrolled.

Comparison of Seresto with Available Alternatives

When comparing Seresto with other registered alternatives, EPA draws a distinction between "preventive" and "curative" products. Collars such as Seresto are mainly intended to prevent infestation by target pests. Other preventive options include EPA regulated collars and spot-on topical treatments containing various active ingredients, including synthetic pyrethroids, the organophosphate tetrachlorvinphos (TCVP), the neonicotinoids imidacloprid and dinotefuran, and the phenylpyrazole fipronil. Additionally, chewable (ingestible) formulations are available with various active ingredients such as afoxolaner and lotilaner that are regulated by the FDA and require a prescription from a veterinarian. In contrast, products intended to be "curative" claim to eradicate target pests that have already infested a pet animal. Such products include sprays and shampoos. Active ingredients in these products frequently include pyrethroids and botanically derived pyrethrins, TCVP, soaps, and essential oils.

The benefits of Seresto compared to available alternatives can be summarized as a matter of easy-to-use and long-lasting protection. Seresto collars are available without a prescription, and therefore offer consumers the ability to obtain pest protection without the cost of a veterinarian visit. All pet protection products except ingestible (chewable) formulations are available without a prescription, though many do not offer the benefit of the longevity of the protection offered with Seresto. Seresto collars provide protection for 8 months, while other preventive protection products provide efficacy for periods ranging between 1 week to 7 months. Of these, the only alternative that provides the 7-month protection are collars containing the organophosphate insecticide tetrachlorvinphos (TCVP). TCVP collars claim control of both fleas and ticks and are available for both cats and dogs. While these products all meet minimum efficacy standards as required by EPA, TCVP is currently undergoing registration review, and is the subject of a petition to cancel the registered collar(s) which is still under review (docket EPA-HQ-OPP-2009-0308 contains additional information on TCVP).

Seresto offers ease of application as consumers need only to affix a collar to the pet once every 8 months. A collar is easier to administer than spot-ons, sprays, or shampoos, because the animal must remain still during application of spot-ons and other topical treatments. Chewable pesticides may be easier to administer than these topical alternatives to Seresto, but their feasibility also depends on the ability of an individual animal to accept and swallow the oral formulation.

Preventive protection products like Seresto may also help users to reduce the need for indoor residential treatments such as perimeter sprays and foggers containing pyrethroids or neonicotinoids to eradicate ticks and fleas that are carried indoors on animals.

V. RATIONALE FOR FINAL REGULATORY DECISION AND RISK MITIGATION

The Agency is adjusting the regulatory requirements for this registration of Seresto pet collars (EPA Reg. No 11556-155). Elanco applied to amend the registration to incorporate additional necessary mitigation that will aid in the Agency's continued review of this product; help to raise awareness in the veterinary and consumer community about potential risks from pesticide products used on pets; recommend actions to prevent potential severe signs from developing after the use of the Seresto collar; and provide information on how and where to report adverse events when they occur. Further the Agency is working to improve its process for adverse event review; included in these efforts is the use on cats will be removed from the Seresto registration (EPA Reg. Np. 11556-155) and the agency has registered a cat only collar.

During the review of the reported cases of potential deaths associated with the collar the Agency found that critical details of incidents were often missing from case narratives, often preventing the Agency from determining the cause of the incident. Where sufficient details were provided, there were no cases where high confidence existed in a correlation between the collar use and the death, often due to confounding factors such as concurrent medical conditions. In addition, the rate of deaths reported, based on the comparative statistical analyses performed, was similar between Seresto and other available pet products. Detailed case narrative reviews were not conducted for those other products.

In a number of cases with moderate or severe clinical signs, removal of the collar often seemed to alleviate symptoms, and/or reapplication of the collar coincided with a reoccurrence of symptoms. For these reasons, through the implemented mitigation measures, Elanco will develop an outreach program that is intended to raise awareness in the veterinary and consumer communities on the risks of pesticide use and outline the proper steps to take in the event of a reaction. Incorporated label changes highlight clinical signs that have been reported most frequently to the EPA, and clearly state where to report these types of adverse events and provide instructions for collar removal.

EPA also conducted a review of the benefits of Seresto in comparison to other pet products available for flea and tick control. Although alternatives to Seresto do exist, some of these may be associated with shorter durations of action and/or less convenient, not be available for cats, or potentially lack the efficacy of the Seresto collar. The availability of safe and effective flea and

tick control options for pets is also a fundamental part of protecting pet health, due to the protection they provide against disease transmission and quality of life for both pets and their owners. These factors were also considered in the proposed mitigations for the Seresto collar, and EPA's goal through these mitigations is to continue to allow products on the market that can protect pets while simultaneously minimizing any risk associated with the use of the Seresto collar, and other pesticide pet products. EPA is committed to continuing to actively improve the process by which pet products are assessed and adverse events are considered in the registration and registration review of these products.

Based on these considerations, the Agency has approved the following mitigation measures on the registration of Seresto:

1. The Seresto dog product and the Seresto cat product are subject to a time-limited registration of 5 years, which will expire on July 13, 2028. Elanco US Inc. may request extension of the time-limited registration, or removal of the expiration date. An amendment request for these changes must be submitted at least one year prior to the expiration date and is subject to EPA review.

2. Elanco US Inc. must submit annual enhanced incident reports and annual sales information in doses sold for this product in the EPA developed templates found at https://www.epa.gov/pesticides/use-standardized-templates-report-pet-spot-incidents-conclusion-pilot-and-implementation. The data are to be provided no later than the end of the first quarter of the following year (e.g., 2023 data no later than 31 Mar 2024).

3. Elanco US Inc. must submit an annual report, similar to a modified Food and Drug Administration (FDA) Annual Periodic Drug Experience Report, which provides an update on stewardship efforts and analysis of safety information collected the preceding year. This additional analysis must be submitted together with Elanco US Inc.'s annual submission of detailed case data (Item #2) and will include:
    a. Update on execution of stewardship efforts.
    b. Brief summary of the incidence rates of reports of adverse effects during the preceding year.
    c. Detailed analysis of any serious adverse effects that have increased in frequency during the preceding year.
    d. Overall evaluation of the benefit-risk profile of the product, taking into account adverse effect data and any other new or emerging safety information.

4. Elanco US Inc. must develop and implement additional efforts regarding case follow-up, referrals, and necropsies as medically indicated. Annually, Elanco US Inc. must review and update training materials, frequency of training, and technical solutions for collecting and providing data related to the pets involved in adverse event (AE) reports for all Elanco US Inc. staff responsible for taking in these data. Elanco US Inc. will, to the fullest extent possible, include the following information for each AE:
    a. Pre-existing medical conditions (e.g., hypothyroidism, diabetes), including previous history of reported condition.
    b. Medications concomitantly administered.
    c. Pet's prior experience with the product.

d. Pet health status.

Elanco US Inc. must report on these efforts one year from the registration and has committed to continuing these efforts moving forward.

5. Elanco US Inc. must develop and implement a communications initiative to ensure the US veterinary community is informed of risks and benefits associated with use of pesticides in pet products, including Seresto, and the importance of reporting AEs. Those communications will include, at a minimum:
    a. A discussion of pesticide products in pet health – risks and AE reporting (including phone numbers relevant to reporting for Elanco US Inc. products).
    b. A reminder that a Post Approval Experience (PAE) section is now on the label, including reported adverse events as listed below, and the owner is recommended to remove the collar and consult their veterinarian if these symptoms occur.
        i. AEs in dogs are listed in decreasing order of reporting frequency: pruritus (itchy skin), vomiting, lethargy, behavioral disorders, application site reactions (dermatitis, inflammation, eczema, alopecia or lesions), anorexia, hyperactivity, muscle tremor, vocalization, convulsion, ataxia (problems with balance and coordination).
        ii. AEs in cats are listed in decreasing order of reporting frequency: Application site reactions (hair change, lesions, pruritus, erythema, inflammation, hemorrhage, burns, self-trauma, ulcers), behavioral disorders, lethargy, anorexia, vomiting, alopecia, hyperactivity, skin disorders, vocalization, skin lesion, hypersalivation.
    c. An update on outcomes of EPA's Seresto review
    d. Elanco US Inc. will utilize the following items for delivery:
        i. Submission of an educational article to a veterinary trade publication (e.g., DVM360, Vet Practice News)
        ii. Submission of information to the Veterinary Information Network (VIN)
        iii. Letter to pet health Doctors of Veterinary Medicine (DVMs)
        iv. Email "blast" to drive DVMs to a webpage
        v. Elanco US Inc. Web content with Frequently Asked Questions (FAQs) for DVMs
        vi. White paper which can be accessed online or sent out upon request by our pharmacovigilance (PV) call center

    Elanco US Inc. must report on these efforts one year from the registration and provide a commitment to continuing these efforts moving forward. EPA may make recommendations to improve the outreach efforts after the 1-year review.

6. Elanco US Inc. must evaluate and summarize known characteristics of the release mechanism of the collar including testing performed to assess performance.
    a. Elanco US Inc. must assess potential modifications of the release mechanism to optimize performance without compromise to collar retention under normal conditions of use.
    b. Elanco US Inc. must report on these efforts one year from the registration and provide a commitment to continuing these efforts moving forward.

7. Seresto has been split into two registrations, one for cats and one for dogs. This split aligns the product registrations with that of most other EPA-registered impregnated pet collars and will make comparison of incident data across products easier and more relevant in the future.

8. Label warnings, similar to FDA label warnings, have been added to the Directions for Use sections of the dog and cat labels. The warnings discuss common adverse effects that have been reported, along with instructions to remove the collar if those effects occur. The label warnings outline frequent clinical signs based on adverse events associated with the product. and encourage the end user to report the incident.

    a. The label warning for the dog product is as follows:

"The following adverse events are based on adverse event reporting. Not all adverse reactions are reported to EPA. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data. The following adverse events in dogs are listed in decreasing order of reporting frequency: pruritus (itchy skin), eczema, lethargy, behavioral disorders, application site reactions (dermatitis, inflammation, eczema, alopecia or lesions), anorexia, hyperactivity, muscle tremor, vocalization, convulsion, ataxia (problems with balance and coordination). Remove the collar if these symptoms occur and consult with your veterinarian. Report suspected adverse events by calling Elanco [1-800-422-9874] {or} [1-800-255-6826] or the EPA website at https://www.epa.gov/pesticide-incidents/report-pesticide-exposure-incidents-affecting-pets-or-domestic-animals."

    b. The label warning for the cat product is as follows:

"The following adverse events are based on post registration adverse event reporting on cats. Not all adverse reactions are reported to EPA. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data. The following adverse events in cats are listed in decreasing order of reporting frequency: Application site reactions (hair change, lesions, pruritus (itchy skin), erythema (reddening of the skin), inflammation, hemorrhage, burns, self-trauma, ulcers), behavioral disorders, lethargy, anorexia, vomiting, alopecia, hyperactivity, skin disorders, vocalization, skin lesion, hypersalivation. Remove the collar if these symptoms occur and report suspected adverse events to Elanco at 1-800-422-9874 or the EPA website at https://www.epa.gov/pesticide-incidents/report-pesticide-exposure-incidents-affecting-pets-or-domestic-animals."

VI. SUPPORTING DOCUMENTS

All supporting documents can be found in docket ID number EPA-HQ-OPP-2021-0625 at regulations.gov.

USEPA 2023a. Canine and Feline Adverse Event Review for the Seresto Collar (EPA Reg No. 11556-155). Office of Pesticide Programs, July 10, 2023, DPs 464137, 464138, 464768.

USEPA 2023b. Response to Petition to Cancel Registration of PNR1427 (Brand Name Seresto) under the Federal Insecticide, Fungicide, and Rodenticide Act; Reg. No. 11556-155. Office of Pesticide Programs, Pesticide Reevaluation Division, July 13, 2023.

USEPA 2023c. Usage, Benefits, and Impacts of Potential Mitigation for Seresto® Pet Protection Collars Containing Imidacloprid (PC Code 129909) and Flumethrin (PC Code 036007). Office of Pesticide Programs, Biological and Economic Analysis Division, May 30, 2023. DP 465946.