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Discuss Seresto Incident Profile

Elanco (EAH) Participants:
Sabine Bongaerts; Vice President Regulatory Affairs and Pharmacovigilance
Niels Krebsfaenger; Executive Director Global Pharmacovigilance
Will Heeb; Director Pharmacovigilance North America
Jennifer Schofield; Principal Scientist Regulatory Affairs

SafetyCall International (SCI) / Pet Poison Helpline / University of Minnesota Participants:
Rick Kingston, Pharm D; President, Regulatory and Scientific Affairs/Sr. Clinical Toxicologist
Ahna Brutlag, DVM, MS, DABT, DABVT; Director, Veterinary Services & Senior Veterinary Toxicologist

EPA Participants:
Edward Messina; Acting Director, Office of Pesticide Programs
Michael Goodis; Acting Deputy Director, Office of Pesticide Programs
Marietta Echeverria; Acting Director, Registration Division
Catherine Aubee; Associate Director, Registration Division
Jennifer Saunders; Branch Chief, IVB1
Jamey Shuler; Risk Manager, IVB1
Dana Vogel; Director, Health Effects Division
David Miller; Branch Chief, Chemistry and Exposure
Aaron Niman; Chemistry and Exposure
Shana Recore; Chemistry and Exposure
Cathryn Britton; Branch Chief, RMIB V
Rachel Fletcher; Chemical Review Manager, RMIB V

Ed Messina opened the discussion. Meeting objective is to exchange ideas around recent activities and press articles. There is pressure from EPA Management with a briefing in the coming weeks to inform on strategy to resolve/mitigate. EAH acknowledged the pressure on OPP as expressed in both opening and closing remarks. EPA expressed concerns around how to address scrutiny from the public, Congress and Management.

Following brief introductions from both EAH and EPA, the EAH presentation was initiated as moderated by Will Heeb. The following are highlights of presentation content and discussion:

Product Benefits:

EAH provided a brief summary of product benefits including the importance of flea and tick products in protection of both animals and humans from vector-borne disease (e.g., bartonellosis, ehrlichiosis, Lyme disease, Rocky Mountain Spotted Fever [RMSF]). Specifically, EPA-regulated topically acting products which can "fight the bite" are important tools in this regard. For example, Seresto was implemented singularly and in a multi-factorial approach by the Centers for Disease Control (CDC) to decrease tick infestations in a community with a high human fatality rate from RMSF (CDC RODEO project, see online journal article HERE). The program was successful in decreasing the tick population as intended. (Slides 2-5.)

Reporting Bias:

Rick Kingston noted that there can be a difference in reporting between companies with products containing the same active ingredients (e.g., more sensitive surveillance efforts lead to a large amount of "background noise" – events that occur concurrently and coincidentally during product use that have nothing to do with the product). Further, well-known reporting biases were discussed, such as product price and time in market. It was noted that the absolute number of incident reports must be put into context of these biases and, most importantly, the units sold (slide 7). Further, it was pointed out that spontaneous incident reports require further medical expert evaluation, in particular as related to causality.

Reporting Rate Overall:

Cases reported versus product distribution was presented graphically with a decrease in overall adverse event reporting rate from approximately Ex. 4 CBI in 2013 to Ex. 4 CBI in 2020 (slide 8). For the 2013 to 2020 time period, EAH provided that total collars distributed was approximately Ex. 4 CBI with an average reporting rate of approximately Ex. 4 CBI Specifically, from 2019 to 2020, sales increased from approximately Ex. 4 CBI collars to approximately Ex. 4 CBI collars while the reporting rate declined from just less than Ex. 4 CBI to below Ex. 4 CBI The graphic included all incidents reported, regardless of causality or severity. EAH concluded there is no established link between death and exposure to the active ingredients contained in Seresto. [*Post-meeting note:* According to EAH data, AEs classified as minor and moderate account for >92% of adverse event reports received for Seresto dog in the US from 01 Jan 2013 to 31 Dec 2020. Again, this is for reports received without causality considerations. Stratifying the data for A (probable) and B (possible) product-related cases according to international ABON causality coding practices, >97% of adverse event reports are minor or moderate. (For further information on ABON, see page 41, Section 4.5.10: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-9/vol_9b_2011-10.pdf.)]

Additional clarity was requested by EPA regarding chart details:

- Cumulative? Each cross-section of data represents independent sales per year. For example, in 2020 there were almost Ex. 4 CBI collars sold. This resulted in approximately Ex. 4 CBI case reports for every collar sold or Ex. 4 CBI collars.
- Units distributed? Represents what has left the EAH warehouse; this is the best means industry has to capture product in the market – consistent although imperfect.
- Clarification of rate requested: Does Ex. 4 CBI (number of case reports per unit distributed) equate to Ex. 4 CBI case reports/10,000 collars? EAH confirmed. EPA noted this is above the threshold of concern of 1/10,000 PMRA uses in their analysis. EAH clarified that 1/10,000 is the commonly accepted threshold as a signal for individual clinical signs (e.g., 1 report of an individual clinical sign per 10,000 collars sold). Importantly, an incident reporting rate >1/10,000 is generally not regarded as a serious safety concern. It is rather regarded as a potential trigger for further investigation. Such investigation may or may not confirm a safety risk that may or may not lead to regulatory action/mitigation measures (EMEA/CVMP/900/03 – FINAL; https://apvma.gov.au/node/314).
- Of note, as per the reporting biases mentioned above, EAH anticipates an increase in reports due to recent media coverage; we are currently seeing increased call volume overall.

Pet Death Reports:

David Miller requested clarification around the 1,700 fatalities reported in the press. EAH believes that number is representative of the number of fatalities reported to EPA by EAH, irrespective of causality or relationship.

The fatality reporting rate is precipitously declining while annual sales continue to rise. For example, as derived from slide 11, in 2013, 85 deaths were reported of Ex. 4 CBI collars sold, resulting in a reporting rate of Ex. 4 CBI deaths/10,000 collars. In 2020, 165 deaths were reported and **Ex. 4 CBI** collars were sold, resulting in a reporting rate of Ex. 4 CBI **deaths/10,000 collars irrespective of causality**.

EAH further explained that all incident reports received, including those from the US, are evaluated within the global pharmacovigilance system and causality assessment (ABON coding, see reference above) is applied by trained medical experts. EAH's analysis for all reported deaths in dog reports received in the US between 2013 and 2020 established no link between death and exposure to the active ingredients contained in Seresto. Out of all reports received by EAH, 12 were classified "A – probably" or "B – possibly" product related. Out of those 12, 10 were related to collar entrapment (slide 10).

The continued increase in sales, coupled with the corresponding decrease in reported fatalities, supports a lack of causal relationship between Seresto usage and death as concluded from more detailed analysis (see below).

Clarification was requested by EPA around the peak in the absolute number of reported deaths (2018). Factors involved:

- D-A assignment changed based on interpretation of 6a2 and PR98-3 as related to death; e.g., A client's dog passed away a few days after Seresto was placed due to unrelated causes. The pet owner kept the collar in a baggie and later called EAH to determine if they could use the collar on a different dog. There was no allegation that the collar harmed the dog or caused the death. Prior to July 2018, EAH would have reported this case as a D-A. Note that reporting mechanisms remain the same in 2019, 2020, and 2021 following that 2018 change.
    - From 07-2019 meeting minutes: It was noted that Bayer's original coding practices were very conservative (i.e., events coded at the highest severity category) and that the 2018 change resulted in more appropriate categorization of events. It was further noted that Bayer captures and reports every call that comes in regardless of potential (lack of) causality. "On 27 July 2018, BAH implemented a change in interpretation of adverse effect severity classification. This change was initially communicated to EPA during discussion with Will Heeb and Rick Kingston on 26 Mar 2018. Included in that discussion was a general consensus that there was a need for harmonization across industry and with the Agency in severity classifications and this was a positive initial step in that direction. Comments on the proposal were provided by EPA, for which BAH was grateful. The feedback (including, but not limited to, separation between human and animal listings and consideration of practices of other organizations for harmonization) was taken under advisement for implementation."
    - Rick Kingston noted that the peak of fatalities may also be due in part to the Weber effect with a large spike of reports early in market presentation and then a drop off with time; duration of the drop-off may be specific to the particular product, in some instances prolonged in line with peak sales and growing market access.

Further details on EAH investigation into reported death cases (2012 – 2015) which totaled 305 dog and 100 cat reports (slide 12):

- 57% of total cases were confirmed or reasonably assumed to involve *other* causes of death or euthanasia for an underlying condition such as cancer or due to traumatic incident
- For 42% of total cases, no specific cause death or euthanasia was determined including 23% of which were inquiries unrelated to the death of the animal (slide 12).
- Clinical signs reported were variable and heterogenous, inconsistent with a product-related scenario in which signs would be focused on one or very few clinical phenomena.
- Similarly, annual rates of death exist for the general US population of dogs and cats (numbering in the millions), contributing to background noise in reporting.
- Ahna Brutlag described SCI's review of fatality data (same period: 2012 – 2015). A board-certified veterinary toxicologist individually reviewed the raw data under masked conditions for 282 death cases (~75% canine, 25% feline). Using standard factors of association such as temporality, toxicologic plausibility, etc. Each case was individually reviewed and assessed for the strength of association for a relationship between Seresto and the reported effects. The relationship with Seresto was then coded as being probable, possible, or unlikely. Five deaths were determined to have probable or possible association. These findings aligned well with those of Bayer Animal Health's causality analysis. For those cases deemed to have an unlikely relationship, there were no identifiable signals, trends, or patterns.

For both deaths and neurologic signs, there was discussion around comparison with other products including odds and incident ratios, disproportionality analysis (e.g., deaths following convulsion/seizure), PRR and relative risk. EAH noted that they are open to further discussion around such analyses and their appropriate use.

Rick Kingston made the comment that, based on their experience in conducting post-market surveillance for numerous companies in this and other product markets, the Seresto incidence rates and nature of spontaneously reported effects including reports of death did not, in their view, trigger a safety signal.

Neurologic Signs:

EAH provided rates for Preferred Terms (PT) from the Neurologic System Organ Class (SOC) noting that there has been a general decrease in rates for all neurologic PTs over time (slide 14). EPA asked about the rank order of convulsions. EAH confirmed that convulsions are the second most common PT in the Neurologic SOC specifically, with a 2020 rate of Ex. 4 CBI reports/10,000 collars distributed. [*Post-meeting note:* Convulsions are the 23rd most frequently reported PT overall for Seresto in 2020.] EAH noted that seizures/convulsions are reported very rarely for Seresto-treated pets with further discussion around background noise (epilepsy is reported to occur in 0.5 to 2.0% of the dog population) as well as potential temporal relationship (slides 15, 16).

EPA asked for confirmation of animal numbers in the companion animal safety studies conducted for registration; EAH confirmed standard EPA CAS study group numbers of 12 animals per treatment group, split gender (OPPTS 870.7200). Studies were conducted in both adult and pediatric animals for both species as well as with and without collar reflectors. [*Post-meeting note:* The safety of the Seresto collar was evaluated at 5x on 12 pediatric and 12 adult animals per species (split gender). 3x safety was also

evaluated in pediatrics (6 animals per gender per species). Additional studies including VICH-compliant Target Animal Safety studies and field safety and efficacy trials were conducted for global registration purposes.]

EAH noted pharmacokinetic studies in dogs and cats wearing the Seresto collar showed limited systemic exposure to the active ingredients; the exposure was not of toxicological relevance. Further, adverse events reported following chewing and/or ingestion of (parts of) the collar are generally related to gastrointestinal signs and not to serious neurological signs (slide 16).

Rick Kingston noted that idiosyncratic reactions are difficult, if not impossible, to predict and are usually not realized until the product is in the marketplace. All such reactions occur at a very rare frequency and are not included in label language for other regulated products.

Marietta Echeverria referenced the European label which contains some additional warnings; EAH was asked if they were willing to explore additional label language. Niels Krebsfaenger explained the EU label and neurological signs, when and how they were added as requested at the end of the 2016 reporting period. Data were further internally analyzed per standard processes without confirmation of a validated signal and, thus, no requirement for modification of labels globally.

General:

There was conversation around a data driven discussion as key to consideration of potential changes to the label. EAH expressed concerns around changes in other areas of the label unrelated to current discussion as discussed prior with the EPA. Marietta Echeverria indicated that EPA management is interested in discussing any label changes EAH considers making to product labels and that these potential changes are likely outside of those normally reviewed by EPA for other more routine label amendments.

EAH has the technical capacity to provide data in the enhanced reporting format. The data provided would look similar to that of our spot-on products. David Miller later noted that a good start would be use of the standardized template.

Final comments included a statement from Ed Messina requesting assistance and data from EAH to ensure correct interpretation of the incident numbers.

EPA will regroup internally and formalize data needs with further discussion (and requests) to follow. EAH agreed to provide an initial draft of the minutes for EPA review and comment as well as a proposal as to which type of data and analyses could support comprehensive understanding by EPA.