UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND

POLLUTION PREVENTION

MEMORANDUM

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SUBJECT: Spot-On Enhanced Reporting Pilot Template Development Synopsis

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I. ACTION REQUESTED

Registration Division's Invertebrate and Vertebrate Branch I requested that Health Effects Division finalize the Spot-on Enhanced Reporting template. This template was developed to standardize submission of enhanced reporting data on both sales data and adverse event incidents across spot-on registrants. The remainder of the memorandum provides background on the development of the template and an overview of the framework that will be used to analyze enhanced reporting data required as a condition of registration.

II. BACKGROUND

In 2008-2009, an increase in the number of reports of pet incidents involving Spot-on flea and tick control products were reported to EPA's Incident Data System (IDS). In response, EPA required Spot-on registrants to submit enhanced incident reports for 2008 incidents to be reviewed by EPA. An analysis of this enhanced data was conducted in 2009 and released in 2010. As a result of the 2010 analysis, EPA implemented several mitigation measures including a requirement that registrants continue to perform enhanced quarterly incident reporting to EPA.[1] EPA recently compiled some of the enhanced incident reports for the years 2008 to 2014 into an electronic format to perform statistical analysis. In reviewing the data, EPA found a number of deficiencies that made it difficult to analyze the data and evaluate potential risks that might be associated with Spot-on products and the effects that earlier mitigation actions may have had. These deficiencies included:

- Inconsistent formatting both between companies and within a company over time;
- Missing incident information in the data file (e.g., missing EPA Reg. Nos.; missing data fields);
- No data for some quarters/years;
- Not all companies submitted data;
- Some data formats were unreadable by statistical software;
- Incomplete sales data or sales data inconsistent with incident counts; and
- Sales data deficiencies, inconsistencies, or ambiguities.

[1] EPA Evaluation of Pet Spot-on Products: Analysis and Plans for Reducing Harmful Effects https://www.epa.gov/pets/epa-evaluation-pet-spot-products-analysis-and-plans-reducing-harmful-effects

III. PILOT

Due to the deficiencies identified in its review of the 2008-2014 data, EPA developed a submission template in order to better standardize submissions of enhanced reporting data on both sales data and adverse event incidents across registrants. Such standardized submission formats will considerably improve the ability of EPA to review the data using state-of-the-science pharmacovigilance methods. EPA decided to first pilot the submission templates and reporting program over the course of a year. A public webinar was held on June 7, 2017, to introduce the proposed pilot program, ask for volunteers, and discuss anticipated statistical analysis.[2] Up to nine spot -on registrants were asked to participate in the pilot program for CY 2016. Five registrants volunteered to participate in the pilot, use the template for one year, and provide feedback. The objective of the pilot was to:

- Test the standard template that will facilitate submission and analysis of enhanced incident reporting;
- Obtain feedback from pilot participants and other interested stakeholders regarding the feasibility and usability of the template to inform meaningful analyses of the data; and
- Use information from the pilot to modify the template based on registrant feedback and EPA experience.

As part of this pilot, the five registrants agreed to submit Spot-on product incidents and sales data for 2016 Q1 and Q2 (January-June 2016) using the Excel-based data submission templates provided by EPA. On August 4, 2016, EPA held a Q and A conference call to get initial feedback from the five participating registrants. Additional feedback was exchanged again in fall 2016 during individual webinars that were held for each of the registrants participating in the pilot. The pilot continued for Q3 and Q4.

The final data were submitted in February 2017 and the pilot results are encouraging, suggesting the collection of this enhanced incident data in an Excel-based spreadsheet is feasible. In addition to working with the registrants during the pilot, EPA has worked with a commercial

[2] Spot-on Incident Reporting Template & Statistical Analysis Plan https://www.epa.gov/sites/production/files/2016-06/documents/rd_hed_combined_spot-on_slides_final_.pdf

Pharmacovigilance (PV) software vendor to ensure that data is compatible with this software and established analytical tools. Furthermore, EPA consulted with FDA's Center for Veterinary Medicine and made efforts to harmonize with FDA's process as much as possible, including use of the VedDRA terminology.[3] Public comment has been encouraged and welcomed since May 2016 when the Pilot was first introduced on the web as an OPP update.

IV. ANALYSIS

EPA has fully reviewed the data to ensure that the submission template and pilot submission program address the deficiencies identified previously. As future data is collected using the reporting template, EPA will perform descriptive analysis to characterize the results and, if appropriate, evaluate potential signals using statistical analysis and detailed review of incident case narratives. EPA will adopt a tiered approach for this analysis, based on the quality, completeness, and strength of pilot data, using the tiered process described below:

Tier	Data Source	Description
Level 0: Aggregate Incident Data System Query	OPP's Incident Data System	Descriptive analysis will be performed using OPP's Incident Data System (IDS). IDS captures data on domestic animal (pet) incidents received under FIFRA 6(a)(2) from registrants and is reported in aggregate form on a quarterly basis. IDS data includes the number of incidents reported for quarter, severity of the incidents, products implicated, but does not include species or any narrative information regarding exposure scenario or symptoms.
Level 1: Reporting Odds Ratio (ROR), by Severity Outcome	Spot-on Enhanced Reporting Data	RORs will be calculated using enhanced reporting data to compare the odds of a given outcome (or event) for one product to odds of (same) outcome to another. This analysis will likely evaluate the ROR of Death (or Death+Major) incidents for each product *vs*. all other products combined, by species.
Level 2: Incident Rate Ratio (IRR), by Severity Outcome	Spot-on Enhanced Reporting Data	IRRs will be calculated using enhanced reporting data to compare the rate of a given outcome (or event) for one product to the rate of (same) outcome to another. This will likely evaluate the IRR of Death (or Death+Major) incidents for each product *vs*. all other products combined, by species. Rates will be estimated using sales data submitted as part of enhanced reporting.
Level 3: Signal-Based Case-by-Case Review & Causality Analysis	Spot-on Enhanced Reporting Data	This signal-based case-by-case review evaluates cases on an individual basis and incorporates information in the submitted narrative. This may involve investigating IRR on a symptom rather than a product basis and may incorporate causality analysis.

[3] VedDRA stands for Veterinary Dictionary for Drug Related Affairs and is an international-accepted standardized (controlled) terminology which includes terms for clinical signs

EPA understands that – for all levels or tiers described above – that signals are signals only, representing simple "disproportionalities" (sometimes referred to as SDR (signals of disproportionate reporting)). Such signals are considered to be hypotheses and do not necessarily imply causal relationships between the exposure and the health effect or outcome. Signal detection does not replace hands-on clinical review of case reports and veterinary medical judgment. Also the limitations and biases associated with reported data may limit utility, will require cautious interpretation. Nevertheless, EPA believes that the methods described above – and the use of the newly-developed standardized incident reporting template – will considerably improve the ability of the Agency to evaluate the data it receives and ensure the continued safety of these products.

V. CONCLUSION

EPA worked with the five spot-on registrants who agreed to participate by submitting spot-on product incident and sales data for 2016 using the Excel-based data submission templates provided by EPA. After considering/incorporating feedback obtained through the pilot, the final sales and incident templates are ready for release and use by spot-on registrants.