PMRA Guidance Document

Revisions to Data Requirements for Pesticide Products used on Companion Animals

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1.0 Purpose

The purpose of this document is to communicate to industry and other interested parties revisions to the toxicology data requirements related to animal safety testing used by Health Canada's Pest Management Regulatory Agency (PMRA) for pesticide products used on companion animals (Use-site Category 24). The revised data requirements will be in effect at the date of publication of this PMRA Guidance Document and will apply to all applications received on or after this date.

2.0 Background

In September 2018, Health Canada's PMRA published the Regulatory Proposal, PRO2018-01, *Consultation on Proposed Regulatory Changes for Pesticide Products Used on Companion Animals*.[1] PRO2018-01 summarized the analysis of 5928 animal incident reports involving spot-on products. At the conclusion of this analysis, Health Canada's PMRA recognized that, despite a high number of incident reports received for spot-on products, these products have value in the marketplace. Health Canada's PMRA took into consideration the severity of the effects observed in the reported incidents (which were predominantly minor to moderate) in relation to the seriousness of the conditions that may result from contact with pests (such as fleas and ticks) that they are designed to control.

Health Canada's PMRA requires data to assess the safety to treated animals as part of its assessment for these types of products. The companion animal safety (CAS) study is the core study used by Health Canada's PMRA to assess animal safety. The analysis of incident reports outlined in PRO2018-01 included a comparison between the effects reported in the incidents and any effects noted in the CAS studies submitted to support the registration of spot-on products. Due to the limitations in the typical design of a CAS study, the effects observed in the CAS studies often lacked consistency with those reported in incident reports. The results of this analysis therefore highlighted the need to strengthen the current data requirements for animal safety testing for pesticide products used on companion animals.

Proposals to amend the data requirements for companion animal products and to include potential side effects on spot-on product labels were presented in PRO2018-01. Six sets of comments were received during the consultation period. Responses to the comments that pertained specifically to the proposed change in data requirements are summarized in Appendix I of this document. These comments were considered by Health Canada's PMRA and did not impact the proposed changes to the data requirements for products used on companion animals.

[1] The purpose of PRO2018-01 was twofold: 1) to obtain input on a proposal requiring registrants and applicants of spot-on products to list potential side effects on the product label, and, 2) to propose that the data requirements for pesticide products for use on companion animals under Use-site Category 24 be amended to include a clinical safety study, in addition to the previously required companion animal safety study (DACO 4.6.9). This PMRA Guidance Document addresses the data requirements for companion animals. A separate PMRA Guidance Document (*Label Improvements for Spot-on Pesticides Used on Companion Animals*) has been published regarding labelling amendments.

3.0 Animal Safety Testing Strategy

The current assessment related to animal safety for products used on companion animals relies primarily on the results of the CAS study,[2] which is designed to determine if there is an adequate margin of safety if the product is misused. In the CAS study, groups of animals representing the target population are treated with the pesticide at the intended label dose as well as at exaggerated doses that are typically threefold and fivefold greater than the intended label dose. The animals are then assessed for potential adverse effects.

As a result of the analysis of incident reports summarized in PRO2018-01, it was determined that the CAS studies available for spot-on pesticide products were of limited value as a predictive tool, particularly in detecting less common findings that may become evident following wide-scale use in many animals. This is due to the fact that these studies provide a limited examination of indicators of toxicity and are performed in a laboratory on healthy animals that represent a fairly homogeneous population. Furthermore, test groups in the CAS study typically consist of only four to six animals per sex, per dose level.

In exploring possible improvements to the animal safety testing strategy for products used on companion animals, Health Canada's PMRA considered the regulatory approach to similar products in other jurisdictions. The current Health Canada PMRA data requirements are in line with those of the United States Environmental Protection Agency (USEPA) for similar products. However, the USEPA also recognized the limited predictive value of the CAS study following a similar analysis of incident reports involving spot-on pesticide products in the United States.[3]

For the evaluation of veterinary drugs, a study similar in design to the CAS study, a margin of safety study, is required.[4] [5] In addition to a margin of safety study, a clinical safety study is also required for veterinary drugs. The clinical safety study provides an evaluation of potential adverse effects at the intended label dose under actual use conditions and is often designed to include an assessment of the efficacy of a proposed drug. When compared to the CAS study or the margin of safety study, the clinical safety study involves a larger group size, thus increasing the chance of detecting adverse reactions, as well as providing a more diverse test group representative of the target population.

A clinical safety study is not currently required by Health Canada's PMRA to assess the safety of a pesticide product used on companion animals. Health Canada's PMRA therefore proposed in PRO2018-01 that the data requirements for products used on companion animals be expanded to require clinical safety studies. Clinical safety studies conducted under actual use conditions will enhance Health Canada's PMRA assessment of the safety of these products. Data obtained from

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2 "Health Effects Test Guidelines: OPPTS 870.7200 Companion Animal Safety [EPA 712–C–98–349]." Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency. August 1998.

3 USEPA Pet Spot-On Analysis and Mitigation Plan, March 2010; Docket EPA-HQ-OPP-2010-0229.

4 "Guidance for Industry Preparation of Veterinary New Drug submissions. Health Canada Veterinary Drugs Directorate." March 2007.

5 "Target Animal Safety for Pharmaceuticals VICH GL43." Veterinary International Co-operation on Harmonization (of Technical Requirements for Registration of Veterinary Medicinal products – EU). July, 2008.

a clinical safety study will provide Health Canada's PMRA with more extensive information with which to assess the safety of these products, and subsequently communicate key information on the product label relating to possible adverse effects, if detected. Moreover, this amendment to the data requirements allows Health Canada's PMRA to be more closely aligned with the approach of Health Canada's Veterinary Drugs Directorate (VDD) for regulating similar products.

4.0 Amendment to Data Requirements for Products used on Companion Animals

In order to enhance the testing strategy for products used on companion animals, Health Canada's PMRA is amending the data requirements for any pesticide products used on companion animals (regardless of product type) to include a clinical safety study, in addition to the previously required CAS study (DACO 4.6.9 in Use-site Category 24).

Health Canada's PMRA recommends that applicants consult the guidelines and guidance issued by Health Canada's VDD[6] and the Veterinary International Cooperation on Harmonisation (of Technical Requirements for Registration of Veterinary Medicinal Products)[7] when designing clinical safety studies.

Applicants are also encouraged to undertake a pre-submission consultation with Health Canada's PMRA for specific recommendations on proposed study protocols prior to study conduct. These studies can be designed to assess, concomitantly, the efficacy of the proposed product under actual conditions of use.

5.0 Implementation Strategy

This new data requirement will apply to applications to register pest control products used on companion animals (Use-site Category 24), regardless of product type, that are received by Health Canada's PMRA on or after the date of publication of this PMRA Guidance Document.

6 "Guidance for Industry Preparation of Veterinary New Drug submissions. Health Canada Veterinary Drugs Directorate." March 2007.

7 "Target Animal Safety for Pharmaceuticals VICH GL43." Veterinary International Co-operation on Harmonization (of Technical Requirements for Registration of Veterinary Medicinal products – EU). July, 2008.

Appendix I Comments and Responses

Six sets of comments were received during the consultation period for the PRO2018-01. Commenters included the pesticide industry, non-governmental association groups representing the interests of public and animal health, as well as a member of the public. There was varied support for the proposed clinical safety study data requirement for companion animal products, including two comments which did not agree with the proposed data requirement. These comments have been summarized and where relevant, grouped by theme. The summarized comments and responses to these comments by Health Canada's PMRA are outlined below.

1. Comments related to aligning data requirements with those of Health Canada's Veterinary Drugs Directorate (VDD)

Comments were received from a registrant regarding the proposal to align testing strategies for spot-on products with those of Health Canada's VDD. This commenter was of the opinion that veterinarians have a vested interest in making products more difficult to register as it drives business to them. The commenter also stated that veterinarians prescribing veterinary drugs are not required to report incidents to Health Canada, in contrast with products registered under the *Pest Control Products Act* that have a mandatory incident reporting requirement for manufacturers. The commenter concluded that, other than an opinion provided by the Canadian Veterinary Medical Association (CVMA), no evidence was presented to support the alignment of requirements between Health Canada's PMRA and VDD.

Health Canada's PMRA Response:

The proposed regulatory changes for pesticide products used on companion animals do not include the requirement that these products be sold exclusively by veterinary health professionals. In addition, the requirements to submit incident reports, or adverse reactions, are similar for pesticide products and veterinary drugs. Reporting of both adverse reactions to Health Canada's VDD and incident reports related to pesticide products to Health Canada's PMRA is mandatory for manufacturers, as per Canada's Food and Drug Regulations and the Pest Control Products Incident Reporting Regulations, respectively. While they are encouraged to do so, veterinarians and other health care professionals are not required to report such incidents/adverse reactions to Health Canada. The evidence to support the alignment of data requirements between Health Canada's PMRA and VDD is not based on the results of the CVMA survey, but on the in-depth analysis of incident reports and available data related to assessing safety to treated animals for spot-on pesticides that pointed to limitations in the current testing paradigm for these products.

2. Comments related to the ability to detect adverse effects in a clinical safety study

Comments were received from a registrant and a non-governmental association expressing concern that a clinical safety study would not produce the type and/or frequency of adverse effects that would be useful to Health Canada's PMRA assessment of safety to treated animals. These commenters made reference to Health Canada's PMRA use of a rate of one incident per 10,000 units sold in the analysis of incident reports, and noted that a very large sample size would be required in the clinical safety study to produce informative results.

Health Canada's PMRA Response:

As stated in the PRO2018-01, the rate of one incident per 10,000 units sold is used in veterinary pharmacovigilance as a general guide in the analysis of post-market surveillance and incident reporting data as a prompt for further evaluation. This rate does not apply to clinical safety studies.

Health Canada's PMRA acknowledges that a clinical safety study may not result in the detection of all potential adverse effects. However, regulatory authorities responsible for the evaluation of veterinary drugs have been using these clinical safety studies for many years as part of their overall evaluation of a drug prior to approval, and consider these studies valuable in predicting the most common adverse effects that may result from product use. In turn, it is Health Canada's PMRA position that the results from such clinical safety studies, which require supervision from a veterinarian, along with the other manufacturer-supplied data and publicly available information, will enable Health Canada's PMRA to make a more informed decision on the acceptability of these products for the Canadian market.

3. Comments related to extending the requirement for a clinical safety study to other product types

Comments were received from a registrant and a non-governmental association stating that the analysis does not support extending the new requirement for a clinical safety study to companion animal products that are not spot-on liquids, such as shampoos, collars, powders, and sprays. The argument was based on the observation that the analysis conducted by Health Canada's PMRA was limited to incident reports for spot-on products.

Health Canada's PMRA Response:

While the analysis focused on spot-on products, the other product types fall under the same use pattern and Use-site Category (USC 24; Companion Animals) as spot-on liquids. Furthermore, the same limitations identified in the assessment of the safety to treated animals (that is, limitations in predicting the most common adverse effects) for the spot-on products extend to the other product types. Therefore, the requirement for a clinical safety study will apply to all products proposed for use on companion animals, in order to enhance the assessment of the safety of these products.

Health Canada's PMRA encourages applicants and registrants of companion animal products to engage in pre-submission consultations to discuss data requirements pertaining to the safety of treated animals. During these consultations, applicants and registrants have the option to propose alternative testing strategies in order to satisfy Health Canada's PMRA's data requirements for addressing the safety to treated animals.

Alternatively, as with any data requirement, applicants and registrants may provide a scientifically sound justification in support of a data waiver request, or submit an alternative study and/or scientific information to address the data requirement. In both cases, this submitted information will be subject to review by Health Canada's PMRA, which includes confirming the adequacy of this information to support the underlying risk assessment.

4. Comments related to alternative options to the clinical safety study

Comments were received from a registrant regarding the fact that Health Canada's PMRA did not propose alternative options to the new requirement for a clinical safety study.

Health Canada's PMRA Response:

Health Canada's PMRA is adding the requirement for a clinical safety study for products used on companion animals to enhance the assessment of these products. This study is a standard data requirement for closely related veterinary products. Nevertheless, Health Canada's PMRA encourages applicant and registrants of companion animal products to engage in pre-submission consultations to discuss data requirements pertaining to the safety to treated animals. During these consultations, applicants and registrants have the option of proposing alternative testing strategies in order to satisfy Health Canada's PMRA data requirements for addressing the safety to treated animals.

Alternatively, as with any data requirement, applicants and registrants may provide a scientifically sound justification in support of a data waiver request or submit an alternative study and/or scientific information to address the data requirement. In both cases, this submitted information will be subject to review by Health Canada's PMRA, which includes confirming the adequacy of this information to support the underlying risk assessment.

5. Comments related to aligning data requirements with the USEPA

Comments were received from a registrant regarding the fact that a clinical safety study is not a current requirement of the USEPA and they were of the opinion that the requirement will limit products developed for the Canadian market.

Health Canada's PMRA Response:

Similar to Health Canada's PMRA, the USEPA conducted an in-depth analysis of spot-on incident data. As part of the proposed mitigation strategy, the USEPA indicated that it was considering measures to bring data requirements in line with those of the United States Food and Drug Administration (FDA) for similar products.[8] Although a final decision regarding this proposed alignment has not yet been published by the USEPA, it was noted that this alignment would allow for increased consistency with how FDA regulates similar animal drugs, which includes clinical trials, and would allow the USEPA to more thoroughly assess the safety of these products.

[8] USEPA Pet Spot-On Analysis and Mitigation Plan, March 2010; Docket EPA-HQ-OPP-2010-0229.

Furthermore, the proposed data requirements are aligned with data, either required, or recommended for similar products regulated by Health Canada's VDD, the Australian Pesticides and Veterinary Medicines Authority, and the European Medicines Agency's Committee for Medicinal Products for Veterinary Use.