

MEETING SUMMARY

Meeting with Registrants: EPA Evaluation of Pet Spot-on Products Analysis and Mitigation Plan

March 17, 2010, 9:30 am to 11:00 am
Room N-4830, One Potomac Yard
2777 S. Crystal Drive
Arlington, VA 22202

Meeting Attendees (see also attached sign- in sheet):

- Summit Vet Pharm, LLC
- Central Life Sciences
- Consumer Specialty Products Association
- The Hartz Mountain Corporation
- Technology Sciences Group Inc.
- Exponent, Inc.
- Bayer Healthcare LLC, Animal Health Division
- Sergeant's Pet Care Products, Inc.
- SafetyCall International
- Merial Limited
- Animal Health Institute
- Pillsbury Winthrom Shaw Pittman LLP
- Pfizer Inc.
- The Accord Group

Via Telephone

- Canada's Pest Management Regulatory Agency

Representatives from EPA:

Office of Pesticide Programs

- Julie Chao, RD
- Venus Eagle, RD
- Kit Farwell, HED
- Claire Geselman, FEAD
- Samantha Hulkower, RD
- Meredith Laws, RD
- Rosanna Louie, RD
- Mary Manibusan, HED
- Autumn Metzger, RD
- Kimberly Nesci, RD
- Lois Rossi, RD
- Kevin Sweeney, RD

Office of General Counsel

- Michele Knorr
- Erin Koch

Meeting Summary

The above-listed representatives from industry, EPA, and Canada's Pest Management Regulatory Authority (PMRA) met on March 17, 2010, to discuss the Agency's analysis of the enhanced adverse incident pet reports, the Agency's conclusions, and a mitigation action plan needed to minimize adverse effects to pets.

The Agency presented background information about the increase in the number of reported adverse incidents seen between 2007 and 2008 associated with the use of spot-on dog and cat products to control fleas and ticks. As part of that summary, the Agency described the information received from the registrants of pet spot-on pet products after holding a meeting on May 5, 2009. EPA explained that that information was analyzed by EPA's expert internal veterinarian team and the resulting Technical Review Document was peer reviewed by the Food and Drug Administration's (USFDA) Center for Veterinary Medicine (CVM) and Canada's Pest Management Regulatory Authority (PMRA).

The Agency shared the following regarding the analysis of the enhanced incident reporting:

- The Agency explained that its objective in its analysis was to describe the nature of the incidents, and to identify susceptible subpopulations or other trends associated with the use of the spot-on products;
- The Agency described the types of detailed information received in the enhanced incident reports;
- The Agency described additional sources of data and methods to analyze and corroborate the received enhanced incident reports, including toxicological studies and literature by expert veterinarians;
- The Agency described its review process, including the methods used to standardize the incident data in order to compare and evaluate the data; and,
- The Agency shared its key findings from the analysis, as follows:
 - o Most incidents were minor, but unfortunately there were some pet deaths and "major incidents" reported. The Agency learned that the most commonly affected organ systems were dermal, gastrointestinal, and nervous.
 - o Dog Findings
 - small breed dogs were affected more than larger breeds for some products
 - the amount of product in a single dose needed to vary more for small to large dogs – that is, how much the dog weighs matters a lot in deciding how much of a product should be used.
 - o Cat Findings
 - misuse or accidental exposure of cats to dog products was an important problem; cats can be harmed by dog products; and
 - label warnings against use of dog products on other animals, especially cats, are not working well enough and this appears to be a global concern.
 - o Safety Testing: The team also found that the data we now require to determine the safety of these products for pets do not accurately predict the toxicity seen in the incidents that took place.

The Agency concluded that, based on its peer-reviewed analysis, mitigation is necessary to prevent adverse effects to pets. The Agency then presented a regulatory action plan that is being

pursued that will include immediate further restrictions on products, tighter regulations, and a public outreach campaign. Specifically, the Agency is pursuing the following actions:

- **Further Restrictions on Products**

- **Dosing.** To address concerns about dosing, the Agency is pursuing requiring label and/or packaging changes that would result in more narrow pet weight ranges per vial size. This means there will be more categories for the weights of pets so that small, medium, and large dogs get the right amount of product. Pet owners should always be aware of the weight of their pet and purchase and use the correct product for their pet's weight.
- **Improve labeling to avoid confusion between dog and cat products.** Because there were problems reported with cats exposed to dog products, the Agency needs to address this problem and is pursuing the following actions:
 - Label changes that prohibit the use of the same brand names on cat and dog products; and
 - Requiring appropriate, clear label statements to address concerns with cat exposure to dog products as a result of direct application or interactions between cats and dogs in multi-pet households after the application of dog products.
- **Make labels more understandable.** To improve label clarity, EPA will pursue changes such as larger fonts and pictograms.
- **Make other label changes as needed.** EPA will meet with companies individually to review their products and discuss additional changes to labels or ingredients that the Agency feels are needed. These actions may include anything from adding a more complete list of potential side effects to product labels to canceling products.
- **Inert Ingredients.** To address uncertainties about the “inert” (non-active) ingredients in these products and how they might contribute to toxicity, EPA will be pursuing the following actions:
 - No longer allow the interchangeable use of inert ingredients in these formulations;
 - Determine whether additional information is needed and, if so, require that information to evaluate certain inert ingredients; and
 - Disallow inerts that have suspected toxic effects when and if these are identified.

- **Tighter Regulation**

- **Standardized reporting.** To be able to monitor these products better, EPA is pursuing more standardized reporting on adverse effects and sales. This will allow the Agency to more effectively review incidents, and if concerns are raised, give EPA information to act.
- **Pre-market clinical trials and post-market surveillance.** The Agency is taking steps to bring data requirements in line with FDA's requirements for similar products. This will allow EPA to be more consistent with how FDA regulates similar animal drugs, which includes pre-market clinical trials and a formal post-market surveillance program, and will allow the Agency to more thoroughly assess the safety of the products.

- **Grant conditional registrations for new products.** Future pet spot-on registrations and amendments to new registrations will be restricted by appropriate conditions and time-limitations to allow EPA to continue to ensure the safety of these products after they are available to the public.

After the Agency presented their findings and the regulatory action plan, there was a question and answer session.

Questions and Answers:

Registrants asked many questions about the process by which the Agency is releasing the information, the analysis conducted, and the mitigation plan being pursued. The summary below describes the types of questions asked and the Agency's responses, but is not a transcript. The meeting was not recorded therefore a transcript is not available.

1. *The registrants had logistical questions about the schedule for the release of the findings and the rationale for the rigorous schedule. The registrant had questions about the timing for making the Agency's reviews and decisions available to the public.*

The Agency described the following process: the data evaluation records (DERs) are being made available for each registrant immediately after the 9:30 am briefing and that the total set of DERs is being posted for public access at 2:00 pm along with the Technical Review Document and the Agency's mitigation plan. The Agency explained that it was criticized for the May 2009 meeting with the registrants and, as such, it is releasing to the public as soon as possible after the registrant meeting the same information provided to the registrants to help eliminate doubts that the public may have about the impartiality of the Agency decisions.

2. *Registrants asked questions about how the information from the enhanced incident reporting was analyzed.*

The Agency stated that its analysis, which includes a description of the methods, will be available at the end of this meeting and will be made available to the public at about 2:00 pm. The Agency noted that the Technical Review Document was peer reviewed by PMRA and US FDA's CVM. The Agency stated that the data evaluation records (DERs) for each individual product describe/summarize the enhanced incident data after the Agency standardized the format of the information to more appropriately compare similar incidents. With the standardized incident information, the team was able to determine for each product the relative ratios of the number and severity of each type of incident.

3. *Registrants asked questions about the factors EPA considered in its decision to impose additional restrictions on products.*

The Agency responded that the Agency's expert veterinary team concluded from its intensive analyses of the enhanced reporting information that mitigation measures are necessary to avoid preventable adverse effects to pets. The Agency explained that the factors considered are described in detail in the DERs and the Technical Review

Document. The Agency stated that there are a number of mitigation measures that the Agency is pursuing in order to minimize future adverse incidents to pets. The Agency stated that it feels these incidents are avoidable.

4. *Registrants had questions about the mitigation measures the Agency seeks to implement immediately, including what are the additional reporting requirements and new labeling requirements for the spot-on products.*

The Agency responded that further, product-specific discussions will need to take place in order to finalize details of the mitigation measures. Some of the immediate requirements can include disallowing alternate formulations, requiring the submission of additional information for inert ingredients if there are suspected potential toxic effects, time-limited conditional registrations of new products, and product labeling clarity improvements.

5. *Registrants had questions about the effectiveness of label changes, considering that current warnings are being disregarded by consumers.*

As stated above, the Agency responded that that further, product-specific discussions will need to take place in order to finalize details of the mitigation measures. The Agency wishes to continue discussions about the incident report findings that indicate that, in some cases, current warnings are not working. A possibility that registrants may wish to consider is the availability of market-research information on consumer products. Companies with that data may have information to better inform labeling decisions. EPA also believes that consumer education about both proper use and potential side effects is crucial.

6. *Registrants asked about additional requirements that the Agency anticipates needing from the registrants in the future that would require long-term collaboration.*

The Agency responded that as part of the move to become more similar with FDA requirements for similar topical animal drugs, EPA is looking into additional detailed reporting requirements; clinical trials similar to FDA's clinical trials; and a formalized post-market surveillance process. The interim, the Agency will pursue enhanced adverse event reporting to allow EPA to efficiently continue post-market surveillance and analysis of any incidents associated with the use of these products.

7. *Registrant had questions about how the Agency's plan compares to the FDA's current regulatory processes. Registrants also asked questions about how EPA intends to streamline regulations between the two Agencies and whether changes to guidelines will be subject to rulemaking.*

With regards to the questions about how the Agency's plan compares to FDA requirements, the Agency stated that it is looking into streamlining current regulations and requirements with those of FDA in order to address the information gaps in the information we currently obtain. The Agency explained that it will follow usual, public procedures in order to revise its guidelines.

8. *Registrants had questions on the Agency's plans for public outreach and publicity of the issue to consumers.*

The Agency responded that to maintain transparency to all stakeholders, including the public, EPA has taken steps to keep all interested parties informed as the information and reviews become available. The Agency stated that it recognizes the importance of these flea and tick products and the importance of their availability to a wide range of consumers, but also the importance for consumers to have full understanding of the proper use and potential impacts of these products. In addition to the press announcements and the release of the Agency's Technical Review Document and Data Evaluation Records, part of the public outreach campaign is to inform the public of steps they can take to ensure safe use of pet flea and tick products. The Agency stated that although specific details have not been finalized, some examples could include label clarity improvements, information bulletins and videos, and additional product information made available at the stores where these products are purchased. Based on the current product labeling and the Agency's analysis of the incident reporting, it appears that consumers are not aware of the full spectrum of potential toxicity to pets, such as the possible different effects seen between a dog and cat.

9. *The registrants had logistical questions about the timing of implementing these mitigation measures, to ensure a level-playing field for all companies.*

The Agency acknowledged that the implementation of these mitigation measures will begin as soon as possible, and will be addressed on a case-by-case basis depending on the characteristics of the product in question. In addition, the Agency acknowledged that a proposed (new) product application may be handled differently than an amendment to an existing product and that individual company meetings are needed. The Agency also acknowledged that there are other influencing factors that may need to be considered as part of these decisions, such as how a specific product is market to targeted consumer groups.

10. *The registrants had logistical question about clinical trials for pesticide products; e.g., how unregistered product can be distributed and whether EPA will accept clinical trials conducted for submission to the European Union.*

The Agency responded that there are many questions to address and consider when changing any regulation and that additional discussions and public comment will be needed in the future to address these questions. The extensive collaboration with FDA and the resulting mitigation proposals are unprecedented. By taking the time and effort to make these changes and consider public input as well as input from external experts, the overall credibility and safety of these products will be enhanced.

With regards to clinical trials conducted for the EU, the Agency is open to the possibility of considering these trials and willing to discuss this further.

11. *The registrants had questions about the Agency's plan to better distinguish between cat and dog products (including changes in brand names or other means); specifically, whether we were going to require that distinction in cases where a formulated dog product could be safely used on cats.*

The Agency explained that the rationale behind distinguishing between cat and dog products is because the average consumer may not know the differences between active ingredients and the Agency would like the message that consumers should never use dog products on cats to be more universal. Consumers are typically not aware of the full spectrum of potential toxicity to a pet and current label warnings do not appear to be adequate. In addition, part of the issue is dosing in that, even if an active ingredient could be safely used on cats, generally the dose for cats would be very different than the dose for dogs. The Agency also reiterated that this would be addressed on a case-by-case basis.