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General Counsel

May 17, 2010

Office of Pesticide Programs (OPP) Regulatory Public Docket (7502P)
Environmental Protection Agency
1200 Pennsylvania Ave., NW.
Washington, DC 20460-0001

**Re: EPA-HQ-OPP-2010-0229; Pet Spot-On Analysis and Mitigation Plan
Available for Public Comment**

The Animal Health Institute (“AHI”) submits these comments to EPA docket EPA-HQ-OPP-2010-0229; Pet Spot-On Analysis and Mitigation Plan Available for Public Comment. AHI is the national trade association representing manufacturers of animal health products – the pharmaceuticals, vaccines and feed additives used in modern food production, and the medicines and pesticides that keep livestock and pets healthy. Our member companies represent the vast majority of this market segment, as well as serving a significant segment of the world market. Several of our member companies are stewards for market leading flea & tick spot-on products. The animal health products industry has a long record of aggressive pharmacovigilance and proactive, responsible interaction with regulatory agencies on a global basis. As such, we have a tremendous interest in regulatory policy impacting pesticides registered with the Environmental Protection Agency and with flea & tick spot-on products specifically.

AHI member companies have been part of the process addressing flea & tick spot-on products by EPA and offer the following comments:

Process

In April 2009, the EPA announced in a public advisory that it was intensifying its evaluation of pet spot-on flea and tick products; this activity was initiated on the basis of an increase in the number of reported incidents associated with the use of these products. In its advisory, the Agency grouped products with mostly minor incidents and very low and essentially unchanged incident rates together with products with significant increases in incidents. Grouping all of the products together gave the public the perception that all spot-on products had

experienced significant changes in their safety profiles, which is not accurate. This approach not only created public anxiety over the use of these products, but also deprived EPA of important information necessary for decision-making. If EPA had instead engaged individual Registrants as soon as any concerns arose and initiated a cooperative dialog to review the incidents, important information available to Registrants not otherwise immediately available to EPA could have been shared. This could have included information such as the rate, distribution and nature of reported adverse events, the results of any investigation and analysis of adverse events by Registrants, and global product experience. This is not just a commercial issue of brand protection. These products play an important public health function in helping to decrease exposure to the pathogens that can be carried by these parasites. Therefore, undue public anxiety over the use of the products should be avoided.

This concern was expressed to EPA after the initial publicity, and a discussion with individual Registrants relative to EPA product specific concerns was requested before EPA generated additional publicity. Our concern was to avoid additional public anxiety over the products as a class, and to rather focus on any products where specific incident issues had been detected. Our intent was to allow the exchange with EPA of information relevant to analysis and evaluation of adverse event concerns. Our experience has been that the evaluation of adverse events that occur at a very low frequency is often complex, and such interaction with varying perspectives is very helpful in attempting to determine the degree of confidence in assessing causal relationships.

Despite our understanding that EPA agreed with the validity of this approach, the next interaction with EPA was at a meeting of Registrants where EPA detailed its compilation of adverse event data. As some of the EPA data compilations are dated months prior to the date of this meeting, EPA had ample opportunity to work with Registrants prior to this and should have done so. EPA again handled all Registrants and products as a group. Although the data clearly indicates that not all were part of the increased number of reported incidents, there was no attempt made to distinguish among them. All Registrants and products were included whether they were a clear contributor or not. This meeting was almost immediately followed by a press release, press conference, a public web briefing and the public availability of meeting materials and EPA's compilation of adverse events. The public was left with the impression that all adverse events, including death, were directly attributable to a product when, in many instances, no attribution could be made by the Agency. Unfortunately, the process raised public anxiety about the use of all flea and tick products when in fact, many have excellent safety records.

This will be addressed more below; however, the EPA analysis of the adverse event data could really be better described as a categorical compilation of reported data, rather than the investigation and analysis of relevant clinical signs, which we believe would have been the better approach. This latter approach would have allowed EPA to focus on and appropriately draw public attention to specific products/issues without unnecessarily causing public anxiety toward the entire class of products. As a further function of the release of the EPA compilation and generic application across all products in the category, EPA created the environment for the inevitable trial lawyer race to the court house, even where some products had no meaningful change in their safety profile.

Publication of Product Experience

EPA provided a number of caveats to the data compilation reports it has made public, including a warning against direct comparisons of the data for a variety of reasons such as the lack of investigation and causality assessments and the lack of a denominator. However, these disclaimers are frequently lost on the public who tend to draw direct cause and effect conclusions. It is important to note that AHI member companies record all reported events, not just those incidents where there may be the suspicion of a potential causal relationship. Where a large number of doses are administered to a general population, spontaneous disease and other concerns will occur at a background rate and must be separated from concerns over product safety. This analysis is often complex where adverse events may be occurring at extremely low rates. Unfounded concerns may cause consumers to stop using products that are beneficial to animal health.

A major shortcoming in the publication of raw data is that, despite the caveats, it encourages direct lay comparisons. At the same time there is no assurance that various Registrants collect, investigate and report product experience in a consistent fashion. For example, those companies active in the animal health products market have very active internal pharmacovigilance programs to assess reported events. In this context, those manufacturers doing the best job of monitoring their products in the field may actually be penalized.

Analysis

As initially indicated above, EPA's compilation of data could be enhanced. However, we should not lose sight of the fact that the adverse event rate found by EPA of 0.00016 incidents/dose is extremely low. This alone indicates that these products are well tolerated.

EPA has provided very little transparency in the criteria used for their “cleaning” of the data. The process followed by EPA, or lack thereof, is very important to understanding the data. There is ample evidence in the medical literature that cleaning data without consistency or transparency may lead to erroneous conclusions. EPA has provided no transparency to the data omitted from the analysis, and some of the qualifiers for exclusion have the potential to greatly impact the analysis. Clinical signs were lumped together and the System Organ Classes were not aligned with accepted terminology (VEDDRA), both of which can lead to erroneous conclusions. There was no consideration, allowance or accounting for spontaneous background rates of disease, conditions, or deaths, which are extremely important considerations in the evaluation of potential adverse events that occur with an extremely low frequency. Causality assessments are inadequately addressed and appear not to have been considered. The incidence of product misuse is low and has been overly promoted as a problem for all products.

All of these issues would have been very appropriate subjects for discussion with Registrants and would have led to meaningful data analysis.

Branding Restrictions

EPA has expressed a desire to ensure the clear demarcation of product intended for use in dogs from that intended for use in cats. Certainly, we agree that product labeling should clearly indicate the intended species for use. However, we strongly disagree with EPA that placing restrictions upon trade names or branding is an appropriate mechanism. Labeling discussions should be conducted on a case-by-case basis at the individual Registrant level.

We are concerned about potential restrictions EPA is considering on commercial free speech (e.g. branding and trade names) as an early risk management option. Restrictions on commercial speech must be the government’s last resort, not a first choice based on convenience. Advertising and branding of medical products is commercial speech and courts analyze the labeling, advertising, promotion regulations and/or disclosure requirements under the doctrine of commercial speech. See *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 61 (D.D.C. 1998), reversed by, *vacated by, in part Washington Legal Foundation v. Henney*, 340 F.3d 331 (D.C. Cir. 2000). The Supreme Court has specifically delineated the test (the *Central Hudson* test) to be used to analyze government restrictions on commercial speech relative to medical products in *Thompson v. Western States*, 535 U.S. 357 (2002).

One of the *Central Hudson* factors requires that any speech restrictions be no more extensive than necessary. If clear alternatives exist that can advance the government’s asserted interest in a less intrusive manner, the government’s restrictions are invalid. The Supreme Court has stated:

“In previous cases addressing the final prong of the *Central Hudson* test, we have made clear that if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so.” *Thompson v. Western States Medical Center*, 535 U.S. 357, 371 (2002). Indeed, in *Thompson v. Western States*, the Supreme Court chided the government for failing to consider alternatives to advertising restrictions stating: “Indeed, there is no hint that the Government even considered these or any other alternatives. Nowhere ... is there any explanation of why the Government believed forbidding advertising was a necessary as opposed to merely convenient means of achieving its interests. Yet “it is well established that the ‘party seeking to uphold a restriction on commercial speech carries the burden of justifying it.’” ... If the First Amendment means anything, it means that regulating speech must be a last – not first – resort. Yet here it seems to have been the first strategy the Government thought to try.” *Id.* at 373 (citations omitted).

Registrants make substantial investment in their brands, which have earned substantial trust on the part of veterinarians and pet owners. We have seen no actual evidence to suggest that product branding is an issue. Changing well-established products/brands will in our view likely increase confusion rather than ameliorate any that may exist and cause considerable and unwarranted damage to Registrants’ commercial interests.

Public Outreach Campaign

EPA has discussed a public outreach campaign. Since EPA attributes incidents to product misuse and consumer failure to follow label instructions, what type of specific messaging will overcome the obstacle of consumers’ lack of reading labels? Will there be outreach to veterinarians?

Changes in Regulatory Testing

EPA has broadly discussed the potential for changes to pre- and post marketing studies as well as adverse event reporting. It is imperative that any implemented changes comport with the international harmonization efforts for veterinary medicinal products (VICH, <http://www.vichsec.org/>) in which the US government currently participates through the FDA and USDA. As these products are marketed globally, this will greatly decrease the potential for duplicative testing and will take advantage of much work on the part of global regulatory agencies and the global animal health products industry. Additionally, any changes should be made via notice and comment rule-making. If there are to be any interim changes in policy, EPA should clearly communicate them as well as their basis.

Conditional Time-Limited Registrations

The EPA has a mechanism in place to approve products on a conditional, case-by-case basis as well as a mechanism to suggest label updates when appropriate. These mechanisms can be used to satisfy EPA's needs to mitigate any risk it has identified either pre- or post-approval. We contend that there is no need for a mandatory, non-discriminating requirement for conditional approvals. The public interest is neither served nor advanced with this measure, especially for a class of products to which EPA attributes the extremely low incident rate of 0.00016 incidents /dose. EPA should work with individual Registrants to address issues and take precise (as opposed to categorical) action as necessary with respect to individual products. No information has been provided as to the types of conditions and time limitations, or why EPA believes this an appropriate risk management action.

Labeling Changes

EPA should address any label changes on a product and active ingredient specific basis. We do not believe a one-size fits all risk management approach works well in addressing low frequency risk associated with the use of this category of medical products. EPA must ensure consistency in applying any new language that may be required: warning, precaution, contraindication, etc. Moreover, EPA must be able to articulate the criteria and threshold utilized to determine whether or not to include an event under one of those categories on the label. Registrants will need adequate time to implement any label changes and a sell-through period should be provided in order to allow an orderly transition in the marketplace.

Conclusion

As responsible stewards for animal health products, AHI member companies are committed to working with EPA to evaluate and address any concern about the use of these important animal health products.

Sincerely,

A handwritten signature in black ink, appearing to read 'Kent D. McClure', with a long horizontal flourish extending to the right.

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