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United States Department of Agriculture

Re: Center for Veterinary Biologics Notice Draft No. 327: Studies to Support Label Claims of Duration of Immunity

I am writing on behalf of the American Veterinary Medical Association (AVMA), established in 1863 and the largest veterinary medical association in the world. As a not-for-profit association established to advance the science and art of veterinary medicine, AVMA is the recognized voice for the veterinary profession. The association's more than 75,000 members represent approximately 85% of U.S. veterinarians, all of whom are involved in myriad areas of veterinary medical practice including private, corporate, academic, industrial, governmental, military, and public health services.

The AVMA recently reviewed the United States Department of Agriculture's (USDA) Center for Veterinary Biologics (CVB) Draft Notice No. 327, which was developed to provide clarification on studies that should be performed by licensees, permittees, and applicants that seek duration of immunity (DOI) claims on veterinary biologics. As relayed in its correspondence to Dr. John Clifford on April 25, 2008, the AVMA recommends that licensees, permittees, and applicants use a single common label phrase that recognizes that biologics assist in the prevention of disease. Such a label phrase should be coupled with the inclusion of efficacy summaries that describe the type and extent of protection (**including duration of immunity**), and the impact on clinical symptoms. This label information would provide the user with meaningful efficacy information.

The AVMA is pleased with the improved disclosure of information generated to support product licensure. The AVMA commends the CVB for providing its recommendations to the relevant stakeholders, regarding the means by which DOI should be determined, and regarding the way in which label claims showing DOI should be designed. The issue of DOI label claims is one component of AVMA's larger labeling initiative.

The AVMA supports science-based labels that provide pivotal safety and efficacy data summaries (including documented DOI) as a much-improved means of providing product use guidance. As veterinarians recommend and administer biologics to millions of animals, the AVMA has repeatedly articulated the need for biologic labels to communicate an appropriate expectation of product performance to users of the products. We believe these data derived from USDA-reviewed licensure data are greatly needed; therefore, the AVMA urges for provision of pivotal efficacy information on product labels.

Specific DOI information is important to veterinarians because at present, the labels generally bear inadequate efficacy information upon which to make an informed product selection. Many veterinarians, and likely more lay users, have no means to obtain realistic expectations of product efficacy.

Duration of Immunity Recommendations

The AVMA urges that science-based labels should provide a summary of data to explain what is known about the DOI for that product. The data summary should identify the measured time interval, what outcomes were monitored, and how the outcome was determined (e.g., challenge, serology). Specifically, biologic labels should state what is known with respect to the interval at which immunity was demonstrated, i.e., animals were challenged x number of weeks post-vaccination.

The AVMA believes it is preferable to use the label phrase "Immunity was demonstrated at... " rather than "duration of immunity" because the latter fails to distinguish between maximum and minimum duration of immunity; a distinction of great clinical relevance. The phrase "Immunity was demonstrated at... " is consistent with the science-based provision of licensure information and offers the opportunity to demonstrate the onset of immunity when available.

In order to best communicate our needs, we have identified an *example format:*

> *This product was evaluated in healthy dogs sero-negative to canine distemper, canine adenovirus type 1 and 2 viruses and housed to prevent exposure to these agents. These dogs were administered a single dose of this product at 6 and 9 weeks of age. One set of ten vaccinates was challenged oro-nasally with canine distemper virus at 14 weeks of age. Five vaccinates were challenged at 90 weeks of age. Non-vaccinated controls exhibited disease typical of canine distemper including fever, anorexia, cough, and seizures. After challenge the vaccinated dogs demonstrated statistically significant reductions in clinical signs as compared to non-vaccinated controls. The signs with significant reductions included viral shedding, anorexia, cough, seizures, and death. This product demonstrated efficacy that is greater than 85% for this fraction. A set of ten vaccinates was challenged oronasally with canine hepatitis virus at 15 weeks of age. Five vaccinates were challenged at 90 weeks of age. Non-vaccinated controls exhibited disease typical of canine hepatitis including anorexia, fever, jaundice, hepatic failure and death. The vaccinated dogs demonstrated statistically significant reductions in clinical signs as compared to controls. The signs with significant reductions as compared to controls were all signs evaluated included viral shedding, anorexia, hepatic failure and death. This product demonstrated efficacy to prevent infection for this fraction. A set of ten vaccinates was challenged oronasally with canine adenovirus type 2 virus at 17 weeks of age. Five vaccinates where challenged at 90 weeks of age. Non-vaccinated controls exhibited disease typical of canine adenovirus type 2 disease including anorexia, fever, and cough. The vaccinated dogs demonstrated statistically significant reductions in clinical signs as compared to controls. The signs with significant reductions were fever, cough, and viral shedding. This product demonstrated efficacy that is less than 85% for this fraction.*
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> *This product was evaluated in healthy dogs with maternally derived antibodies greater than 1:16 to canine distemper at 6 weeks of age. These dogs were housed to prevent exposure canine distemper virus. These dogs were administered a single dose of this product at 6 and 9 weeks of age. One set of ten vaccinates was challenged oro-nasally with canine distemper virus at 14 weeks of age. Non-vaccinated controls exhibited disease typical of canine distemper including fever, anorexia, cough, and seizures. The vaccinated dogs demonstrated statistically significant reductions in clinical signs as compared to controls. The signs with significant reductions included viral shedding, anorexia, cough, seizures, and death. This product demonstrated efficacy that is greater than 85%.*

Label Information Recommendations

It is also important that labels provide information that assists clinical decision-making. The user should be able to evaluate the relevancy of the information to the clinical case under management. Specifically, a company should appropriately type and identify the challenge organism used to generate study data, and this information should appear on the product label. The outcome definition and primary outcome

clarification are also particularly important, including the study outcome data and how they were analyzed. Recently, the CVB listed its proposed content of the EFOIA efficacy/DOI study summary format. In an effort to ensure that CVB's proposal meets our needs, we specified our needs below in our April 25, 2008 correspondence. Provided again here are the AVMA's recommended facts that should be communicated in the label information:

minimum and maximum age of target species studied,
diversity of species studied (e.g. all beagles),
number of animals (vaccinates and controls),
route of product administration (e.g., parenteral, oral),
description of the challenge model, including
how animals were challenged,
interval of time to challenge,
how results were measured,
description of mortality and morbidity,
description of alteration of biologically relevant parameters (i.e. clinical signs),
description of scoring system,
description of performance impact (e.g. rate of gain),
identification of whether infection was prevented or extent of disease symptoms prevented,
degree of efficacy achieved,
different results obtained on an antigen by antigen basis for combination products (e.g. distinguish a fraction that provided sterile immunity [i.e. prevention from infection] from a lesser immune response).

We recommend that the dose of the administered biologic should be fully described and that it should be made clear if a normal commercial dose or minimum immunizing dose was used in the study. Regarding the target species, the animals should be described to include the breeds of animal, whether the animals were littermates, and the inclusion criteria for the study (e.g., Specific Pathogen Free, no titer or low titer to the organism in question, presence/absence of maternal derived antibodies).

Finally, we assert that the CVB should include a summary of both the data that was collected from the animals and how that information was evaluated to determine product performance.

Additional Recommendations

The AVMA urges that the annual revaccination recommendation should be removed from all biologic labels where the statement lacks a scientific basis. We support statements indicating that a specific revaccination schedule has not been established for a product and consultation with a veterinarian is recommended.

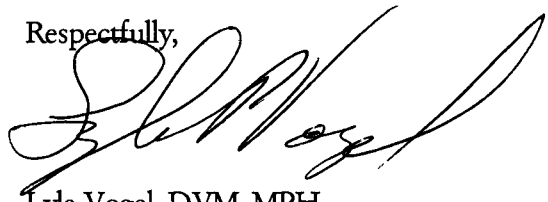
For example, when a firm has demonstrated immunity at one year or another timeframe, the label should NOT bear a revaccination interval driven by that data point. That data point likely represents a minimum duration of immunity. Instead, the label should factually state that immunity was demonstrated based on challenge at a specific interval of time post-vaccination.

Conclusion

The AVMA remains committed to the concept of providing veterinarians with clinically relevant information derived from biologic licensure studies that has the power to influence their medical recommendations and positively impact the health of animals under their care. The AVMA urges that science-based labels should provide a summary of data to explain what is known about the DOI for that product. We commend the CVB for its recognition of the need for specific study protocols to be utilized, in order to procure adequate scientific support for DOI claims.

We offer our thoughtful comments for consideration by the CVB and re-extend our offer to be of assistance should that be beneficial to the Center. Kindly contact Dr. Elizabeth Curry-Galvin, Director, Scientific Activities, 847-925-8070 or egalvin@avma.org for further discussion.

Respectfully,



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