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John R. Clifford, DVM
Deputy Administrator for Veterinary Services
Animal and Plant Health Inspection System
United States Department of Agriculture

RE: Veterinary Services Memorandum Draft No. 336: Electronic Freedom of Information Act Involving Veterinary Biological Products

Dear Dr. Clifford:

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.

AVMA Highly Supportive of Draft No. 336

The AVMA is highly supportive of draft no. 336 to publish electronic summaries for all efficacy and safety studies used to support licenses, permits, and product revisions for public access via the agency's website. 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.

The AVMA supports science-based labels that provide pivotal safety and efficacy data summaries (including documented duration of immunity) as a much-improved means of providing product use guidance. We believe these data summaries derived from USDA-reviewed licensure data are greatly needed.

The AVMA is pleased with the improved disclosure of information generated to support product licensure. The AVMA commends the USDA, APHIS, VS Center for Veterinary Biologics for seeing this important initiative to fruition. The EFOIA initiative is one component of AVMA's larger labeling initiative.

General Comments

The AVMA supports CVB moving forward with the release EFOIAs. There is a history of such summaries for animal drugs approved by the FDA Center for Veterinary Medicine (CVM). The proposal states that CVB will write the EFOIA document, which we understand to be similar wording used in the oversight of drugs. We understand it is common practice; however, for drug sponsors to provide a draft FOIA in the submission

process; thus, CVM does not need to generate the FOIA document from scratch. Given the resource and personnel limitations at the CVB, perhaps companies should be encouraged to provide CVB with a draft EFOIA; thus, saving reviewer time (which is a major concern). Further, such practices should help to facilitate the early generation of mutually reviewed/accepted EFOIA information prior to publication. CVB should ultimately be responsible for all EFOIA verbiage; however, it is less resource intensive for CVB to review/amend/approve company supplied text rather than drafting an EFOIA from scratch.

It appears this EFOIA requirement will not be applied retrospectively unless an existing product is changed or updated. While this should help to minimize CVB resource problems, a potential downside is that newer products might have improved and/or updated information based on current science while historic vaccines with the same (or more expansive) label claims may have less information available. Although this could be potentially misleading to the veterinary practitioner at the onset, CVB's proposal represents a place to start. The AVMA believes the CVB should be open to licensees who wish to voluntarily provide EFOIA efficacy/DOI and safety summaries for historically licensed products that are not the subject of a supplemental submission for added claims. EFOIA summaries of this type should not trigger full product reviews.

We affirm that for products licensed prior the implementation of the policy, a standard statement should be provided that indicates licensing was based on the firm meeting general licensing requirements.

In addition, EFOIA requirements should apply to conditional licensed products as well as fully licensed products.

It is important that these summaries 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. The efficacy summary information should be provided in a manner that discourages marketing tactics that seek to differentiate products by making statistically insignificant differences in numerical information significant in the minds of purchasers. Tiers or thresholds may be useful techniques.

We also recognize it is important that these summaries not divulge proprietary information. Information should be included unless a firm can make a compelling case to CVB that it will be a proprietary disadvantage to provide such information.

A company should appropriately type and identify the challenge organism used to generate study data. This information should appear on the product label and in the EFOI summary.

The outcome definition and primary outcome clarification are particularly important, including the study outcome data and how they were analyzed. Care should be taken with the simple reporting of raw data with respect to widely variable efficacy/safety thresholds--especially for new products without universally established standard requirements. Variations in case definition (based on unique study designs, diversity of

challenge isolates, company-tailored outcome criteria, et cetera) could vary greatly within the biologic industry. Consequently, competitive comparisons based on such figures might be invalid and could be potentially false and/or misleading to veterinarians; especially if used inappropriately in advertising and promotional materials—a real temptation. Thus, "data" or "outcome" within an EFOIA document should be provided in a way that is clearly understood and usable for clinical interpretation by the veterinary practitioner. We believe this is achievable and offer an example within this draft.

EFOIA Efficacy Studies Summary Format

The AVMA encourages the publication of efficacy studies 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.

The criteria for use of the commonly used efficacy phrases are not generally known and not revealed in product labeling. Furthermore, one might happen to be familiar with the meaning of these efficacy phrases, but in the case of "*aids in the prevention of*" one still cannot determine what symptoms might be reduced and to what extent, since this phrase alone is inadequately descriptive. Hence, the AVMA urges for provision of pivotal efficacy information on product labels. The user would greatly benefit from a summary of the study that supported biologic license. Such precedent exists with animal drugs approved by the Food and Drug Administration.

When coupled with potentially aggressive marketing techniques, this historically inadequate system for communicating product efficacy has contributed to the inappropriate shaping of expectations; the expectation that all biologics prevent all symptoms of labeled diseases in all vaccinated animals. This is clearly untrue and misleading. As an alternative, the AVMA recommends the use of a single common label phrase that recognizes that biologics assist in the prevention of disease, coupled with the inclusion of efficacy summaries that describe the type and extent of protection, including the impact on clinical symptoms. This system would provide the user with meaningful efficacy information.

The CVB has listed the proposed content of the EFOIA efficacy/DOI study summary format. In an effort to ensure that CVB's proposal meets our needs, we specify our needs below. The AVMA urges that an EFOIA efficacy summary should identify efficacy results, including what outcomes were monitored and how outcomes were determined. The summary should communicate the following facts:

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).

With respect to CVB's reference to the volume of the dose, the administered biologic should be fully described. It should be made clear if a normal commercial dose or minimum immunizing dose was used in the study.

With respect to CVB's reference to the type of animals, 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).

It is understood that data summaries reflect studies that were randomized and blinded when more than one treatment group is utilized, as this is a requirement of licensure studies.

The CVB's reference to outcome/results is unclear and should include a summary of both the data that was collected from the animals and how that information was evaluated to determine product performance.

Duration of Immunity is a Component of Efficacy

The AVMA urges that science-based labels provide a summary of data to explain what is known about the duration of immunity 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). We recognize that little may be known about the duration of immunity for some products. The AVMA recommends that what is known by way of the USDA licensure process should appear in the EFOIA efficacy summary.

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 demonstrate 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 for the EFOIA "Efficacy / DOI studies" section:*

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 oro-nasally 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 oro-nasally with canine adenovirus type 2 virus at 17 weeks of age. Five vaccinates when 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.

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%.

Additional Efficacy Recommendations

We believe product users have a very limited understanding of the present label claim classifications for product efficacy. The tiers can be confusing if one is not familiar with the definitions. The EFOIA product efficacy summaries should complement these claims and help clarify expected product performance.

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.

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.

EFOIA Safety Studies Summary Format

The AVMA greatly appreciates CVB's commitment to providing a summary of the pivotal safety information used to support biologic licensing. Biologic users would greatly benefit from enhanced safety information. The historical system did not require the inclusion on labels of basic and useful safety information which was in the possession of the biologic licensee and the CVB.

The AVMA believes an E-FOIA summary of pivotal safety studies will enhance users' product knowledge, allowing veterinarians to customize vaccine recommendations for patients within a veterinarian-client-patient relationship as well as helping veterinarians respond to potential animal adverse reactions to biologics. Provision of such information allows the user to learn of any clinically relevant, unique outcomes of the product's safety evaluation.

The AVMA believes labels should indicate that products are intended for use in healthy animals. The labels should clarify that safety studies were conducted in client-owned animals (which represent field conditions rather than laboratory settings). Labels should identify the minimum and maximum ages of the animals in which safety studies were conducted, including relative animal numbers at each end of the cited range in age of administration. Pregnancy status of animals should be included. Labels should identify any clinically relevant outcomes of the product's safety evaluation, including unique outcomes. We believe label withdrawal times should be based upon scientific data.

In order to fully communicate the beneficial types of information to be included in a safety study summary, the AVMA furnishes the following *example format for the EFOIA "Safety Studies" section*:

This product was evaluated in 345 healthy dogs at five veterinary clinics in four states. Dogs were administered this vaccine as a portion of other routine veterinary services. The age of dogs in this study ranged from 2 weeks to 14 years. Dogs were vaccinated and observed for 30 minutes before discharge. Owners were instructed to observe their animals for responses that might be considered adverse and to report these observations to the veterinarian. All dogs were to be returned in 3 weeks for a single booster dose. 325 dogs were returned for a second dose of vaccine within 2-6 weeks of the original dose. The responses that were determined to be adverse are described below:

Adverse Observation
Transitory Fever

Number of Animals Affected
14

<i>Transitory Site Pain</i>	<i>10</i>
<i>Transitory Site Swelling</i>	<i>3</i>
<i>Death</i>	<i>1</i>

The events fever, site pain, and swelling were considered likely to be vaccine related. All adverse responses determined to be vaccine related were considered to be transitory and did not require treatment intervention. The single report of death could not be investigated due to delayed reporting to the participating veterinarian. This death occurred 20 days post vaccination and is not considered to be related to vaccine use.

Dogs in this study were also administered a variety of other routine medications including heartworm preventive, flea control products, anti-seizure medications, routine vaccines, and thyroid supplements. No drug interactions were identified.

Additional Safety Recommendations

The AVMA believes this is an excellent opportunity to underscore other safety-related labeling recommendations which we believe are highly valuable, though we recognize are beyond the specific scope of Draft 336 which is focused upon EFOIA efficacy/DOI and safety studies:

Once a rigorous adverse event reporting structure is organized, clinically relevant post-marketing product experiences should be periodically added to product EFOIA safety study summaries in a way that fosters a level playing field for competing manufacturers of similar products.

Standardizing pregnant animal label language is a natural next step. The present lack of uniformity in label language makes it difficult to differentiate products that carry real safety risks if used in pregnant animals from those for which safety in pregnant animals is unknown. Veterinarians are faced with unique cases every day in which they must balance benefit and risk. Veterinarians need to have accurate information in order to make the best recommendations for their patients. We suggest use of the following science-based statements, based on the existence or absence of safety data in pregnant animals:

- Safe for use in pregnant animals
- Safety in pregnant animals has not been demonstrated
- Not safe for use in pregnant animals

A common adverse event warning should appear on all biologics indicating that fever, lethargy, inappetence, injection site lesions, allergic reactions, and even death may accompany the use of biologics. It is possible that only some of these reactions may be noted in a particular product's pre-licensure safety studies. However, these potential reactions in animals receiving biological products are so well documented by years of field use of billions of doses that it is inappropriate not to communicate these risks, particularly for the benefit of animals vaccinated by lay users. This information would complement the safety study summary.

Encouragement and Appreciation

In closing, the AVMA has devoted a great deal of resources to the subject of improving biologic product labels over the course of many years because it is a topic of great importance to veterinarians and the clients and patients in their care. 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. We append a Check List of Biologic Labeling Recommendations to share our full vision of potential labeling improvements.

The AVMA is greatly appreciative that the CVB has made such progress on the EFOIA efficacy/DOI and safety summary draft. The AVMA strongly supports the publication of safety and efficacy summaries as a means to communicate an appropriate, science-based expectation of product performance to biologic users. We are well aware of the resource limitations and the many important obligations of the Center. We are also very well aware of the variety of reviews and clearances such proposals require. Thank you for demonstrating leadership and persistence on this important initiative.

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.

Sincerely,

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Elizabeth Curry Galvin, DVM
Director, Scientific Activities

ECG