



October 15, 2005

1931 N. Meacham Rd.
Suite 100
Schaumburg, IL
60173-4360
phone 847.925.8070
800.248.2882
fax 847.925.1329
www.avma.org

Docket No. 00-071-2
Regulatory Analysis and Development, PPD
APHIS
Station 3C71
4700 River Road, Unit 118
Riverdale, MD 20737-1238

Re: Docket No. 00-071-2; Viruses, Serums, Toxins, and Analogous Products; Records and Reports; Proposed Rule; Withdrawal and Reproposal

Dear Sir or Madam:

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 national voice for the veterinary profession. The association's more than 73,000 members represent approximately 86% 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 congratulates the USDA CVB on proposing to improve post-licensing surveillance of veterinary biologics. The AVMA has great interest in CVB's plans for capture of adverse event report information, analysis of the information, processes for determining regulatory action, and mechanisms for feedback of clinically relevant information to the profession to enhance patient care.

The AVMA is on record supporting vaccinovigilance, which is monitoring of vaccines and other immunobiologicals via a publicly available central reporting system. The system should include reports of adverse reactions or the failure of biologics to protect animals from disease. We recommend that these reports follow a standardized, systematic template. Any compilation or interpretation of these reports should be provided in a form that is useful to biological firms and veterinarians. Such reporting is not currently a function of the USDA-APHIS Center for Veterinary Biologics, but should be. The need for vaccinovigilance is significant and urgent. Animal health, public health, and food safety are protected by credible reporting. Additional funding is required to support adequate vaccinovigilance.

The CVB's reproposal would amend the regulations to include a definition for "adverse event" and "adverse event report" and require licensees and permittees to keep adverse event report records and file reports to the USDA CVB. Specifically, a detailed report would be maintained for every adverse event report received and a summary report of all

adverse event reports received would be compiled and submitted to CVB annually, and six months following original licensing of a product.

Missing Components of Vaccinovigilance System

Vaccinovigilance involves data collection, analysis, and feedback. The USDA proposal describes a plan for collection of adverse event reports from licensees. However, the USDA proposal lacks an identified method of analysis of collected information as well as a plan for further scientific study, regulatory action, and communication of feedback to industry, veterinarians and the public.

Basic vaccinovigilance is safety signal generation from groups of adverse event reports, but once the signal is found there needs to be a prospective way to determine if the safety signal is real. The proposed regulation is silent on how CVB will do safety signal generation or secondary prospective analysis, or how they will staff the increased burden to the USDA.

The nearly absent discussion of these components of an effective post-licensure surveillance system prompts the AVMA to repeat its comments of 2002 for effect:

- Notably absent from the proposed rule is a provision for analysis of submitted reports, transmittal of medically relevant information back to veterinarians, and a process for determination of regulatory action. The USDA should describe the methods of analysis and decision points that it will use.
- The AVMA believes that reporting by veterinarians will be enhanced by a convenient system that returns clinically relevant information. We strongly encourage creation of a standard analysis system to determine when reports of an unusual number or severity have been received. A simple listing of recorded events is insufficient to provide proper guidance to practicing veterinarians and insufficient to evaluate whether regulatory action should be considered. A system for analysis of these reports should include, at minimum, a system to categorize the physiologic or anatomic systems involved, a controlled dictionary to record the clinical signs observed and diagnoses made, and a standardized method of analysis intended to determine when reports of an unusual number or severity have been received.

We suspect the CVB proposal is focused upon information collection in order to mirror the progress of the VICH international harmonization efforts. These harmonization efforts are highly important. But we urge CVB to discuss analysis, action and feedback with U.S. stakeholders so the CVB may lead VICH discussions with the needs of U.S. stakeholders in mind.

Reporting Rate (referred to as Incidence Rate) is Misleading

CVB proposes to use the number of doses of the product distributed or the average number of doses of the product in distribution channels, if available, to calculate the incidence of adverse events associated with a particular product.

“Reporting rates” and not “incidence rates” are obtained when one compares numbers of adverse event reports to number of doses of biologic sold. An incidence rate can only be calculated using number of doses administered to animals. Therefore, CVB should use the term “reporting rate.”

The proposed regulation indicates that CVB will use dose distribution data “if available.” This appears to create an uneven playing field for biologics firms. It would seem prudent that all firms capture and report the number of doses in the distribution channel.

Communication factors, unrelated to product performance, may increase the number of reports received by firms and consequently inflate the reporting rate. These communication factors include manufacturers’ use of toll free reporting phone numbers, adequacy of staff to receive adverse event calls, corporate guarantee and professional support programs, and publicity surrounding a product. Reporting rates have the potential to be misunderstood.

Over reliance on reporting rates could serve as a negative driver for firms and make it more difficult for firms to be good corporate citizens.

Flagging Further Study

Basic vaccinovigilance is signal generation from groups of adverse event reports, but once the signal is found there needs to be a prospective way to determine if the signal is real.

The frequency, seriousness, and/or unexpectedness of reports serve to signal an area for further investigation.

Once a safety or lack of efficacy signal is noted, the AVMA recommends joint exploration (CVB and firm) of the signal.

Individual Reports

Additional types of individual report information would be useful, including concomitant product administration, route and site of any biologic administration, onset of symptoms (time between biologic administration and symptoms), and human exposures. Additionally, opinion regarding causality of the report should be limited to veterinarians because of their medical training.

Summary Reports

The required summary reports are not well defined by the proposed regulation. It appears that the summary reports are proposed to be essentially collations of the adverse event reports for the period, along with product identifying information and number of doses distributed.

The AVMA proposes that summary reports should be true summaries using electronic line listing of data fields that are organized in a thoughtful manner. Efforts should be made to maximize the usefulness of the summary report.

Reports should be universally recorded and reported without censoring/filtering of information.

Identified purity, potency, safety and efficacy problems should appear in summaries.

Workload and Efficiency

The AVMA believes that significantly more adverse event reports than the USDA's anticipated 10% of approximately 2,000 currently licensed products will be received. Consequently, USDA needs to provide adequate resources to handle the workload and implement efficient processes.

Reports should be submitted electronically by industry to USDA to minimize handling of the data. Electronic submissions enhance efficiency and cost-effectiveness for industry and government.

Avoid Identified Shortcomings

The AVMA has identified shortcomings in the federal drug post-approval surveillance program. The AVMA recommends that USDA avoid similar shortcomings in the proposed biologic adverse event reporting system, namely:

- Adverse event scoring systems that present excessive opportunity for reviewer bias that is neither minimized nor monitored.
- Evaluating quantitative adverse event data subjectively for trends and patterns without the use of sound statistical analysis.
- Evaluating quantitative adverse event data without any apparent monitoring for potential surveillance bias.
- Ample and sound exposure data not being captured in the system, the reporting of which is the responsibility of the profession. Critical to a strong surveillance system is sufficient information.

Feedback Plan

What is the plan for feeding back adverse event information to the profession and others? Veterinarians need prompt information on product recalls, crises, or stop sales.

In Closing

A strong, science-based, transparent, systematic post-market surveillance system is critical to our patients, to our clients and to our profession. It provides a critical portion of the information that our profession needs to maximize the benefits and to minimize the risks for the patients under our care. A strong system reduces two general types of errors. First, it has sufficient sensitivity to provide early, clear detection of associations between particular biologics and adverse side effects in particular segments of our patient population. In the long run, this is required to maintain both the profession's confidence in the biologics we use and our clients' confidence in us. Second, it has sufficient

specificity to reduce the problems with spurious false associations between particular biologics and adverse events in animals' lives. Again, this is required to maintain the profession's confidence in and access to these biologics.

The AVMA strongly supports the USDA's general effort to institute an adverse event reporting system and believes constructive dialogue can further improve the proposal.

Thank you for this opportunity to comment.

Cordially,

A handwritten signature in cursive script that reads "Bruce W. Little".

Bruce W. Little, DVM
Executive Vice President

BWL/ECG