Proposed Rules

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This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF AGRICULTURE

Animal and Plant Health Inspection Service

9 CFR Part 112

[Docket No. APHIS–2011–0049]

RIN 0579–AD64

Viruses, Serums, Toxins, and Analogous Products; Single Label Claim for Veterinary Biological Products

AGENCY: Animal and Plant Health Inspection Service, USDA.

ACTION: Proposed rule.

SUMMARY: We are proposing to amend the Virus-Serum-Toxin Act regulations to provide for the use of a simpler labeling format that would better communicate product performance to the user. We intend to replace the current label format, which reflects any of four different levels of effectiveness, with a single, uniform label format. We are also proposing to require biologics licensees to provide a standardized summary, with confidential business information removed, of the efficacy and safety data submitted to the Animal and Plant Health Inspection Service in support of the issuance of a full product license or conditional license. A simpler label format along with publicly available safety and efficacy data will help biologics producers to more clearly communicate product performance to their customers.

DATES: We will consider all comments that we receive on or before June 20, 2014.

ADDRESSES: You may submit comments by either of the following methods:

- Federal eRulemaking Portal: Go to *http://www.regulations.gov/#!documentDetail;D=APHIS-2011-0049-0009.*
- Postal Mail/Commercial Delivery: Send your comment to Docket No. APHIS–2011–0049, Regulatory Analysis and Development, PPD, APHIS, Station 3A–03.8, 4700 River Road, Unit 118, Riverdale, MD 20737–1238.

Supporting documents and any comments we receive on this docket may be viewed at *http://www.regulations.gov/#!docketDetail;D=APHIS-2011-0049* or in our reading room, which is located in room 1141 of the USDA South Building, 14th Street and Independence Avenue SW., Washington, DC. Normal reading room hours are 8 a.m. to 4:30 p.m., Monday through Friday, except holidays. To be sure someone is there to help you, please call (202) 799–7039 before coming.

FOR FURTHER INFORMATION CONTACT: Dr. Donna Malloy, Operational Support Section, Center for Veterinary Biologics, Policy, Evaluation, and Licensing, VS, APHIS, 4700 River Road, Unit 148, Riverdale, MD 20737–1231; (301) 851–3426.

SUPPLEMENTARY INFORMATION:

Background

The Animal and Plant Health Inspection Service (APHIS) administers and enforces the Virus-Serum-Toxin Act, as amended (21 U.S.C. 151–159). The regulations issued pursuant to the Act are intended to ensure that veterinary biological products are pure, safe, potent, and efficacious when used according to label instruction. The regulations in 9 CFR part 112, ''Packaging and Labeling,'' (referred to below as the regulations) prescribe requirements for the packaging and labeling of veterinary biologics. The regulations ensure that labeling provides adequate information concerning the proper use and safety of the product, including vaccination schedules, warnings, and cautions.

Current APHIS guidelines provide examples of label claims that may be used to reflect the expected performance of the product provided that appropriate efficacy data has been submitted and approved by APHIS. The guidelines describe performance requirements and allowable indications statements for four different levels (tiers) of effectiveness.

In July 2009, representatives of veterinary biologics manufacturers and the American Veterinary Medical Association (AVMA) met with APHIS to discuss the Agency's current labeling guidance and to explore the possibility of developing a single indications statement that would convey clinically useful information to veterinary practitioners and other consumers of veterinary biologics. At that meeting, the AVMA, which represents the largest group of consumers of veterinary biologics, informed APHIS that its members consider labeling indications statements based on the current guidance to be confusing, and expressed a desire for indications statements to provide insight into the actual performance of the product, including summaries of safety and efficacy data.

On the other hand, representatives of the trade associations representing veterinary biologics manufacturers have remarked that their members expend significant resources on studies to provide data to support labeling that includes indications statements emphasizing the unique properties of their product versus that of a competitor. They expressed concern about any change to the labeling regulations that would de-emphasize product differences or require public disclosure of proprietary information that could compromise a manufacturer's competitive position in the marketplace.

In response to the concerns expressed by these stakeholders, APHIS developed a draft guideline (concept paper) concerning the effectiveness indications statements used in veterinary biologics labeling. The draft guideline would replace current indications statements that may reflect any of four different levels of effectiveness with a single indications statement (e.g., a label claim stating that the product can be used ''as an aid in the prevention of _____,'' ''as an aid in the control of _____,'' ''for the prevention of infection with _____,'' or ''for the prevention of disease due to _____'' would be replaced with the statement ''This product has been shown to be effective for the vaccination of healthy animals _____weeks of age or older against _____'').

In addition to a standardized indications statement, the draft guideline would also require biologics licensees to provide a summary of their data, with confidential business information removed, of the efficacy and safety data submitted to APHIS in support of the issuance of the product license. These proposed changes would not alter the current efficacy requirements for veterinary biological products and are not intended to

constitute re-licensure of currently licensed products. These changes would not apply to diagnostic products.

On May 24, 2011, we published in the **Federal Register** (76 FR 30093–30094, Docket No. APHIS–2011–0049) a notice of a public meeting to discuss the draft guideline (concept paper) concerning effectiveness indications statements in veterinary biologics labeling. At the meeting, we received comments from national trade associations representing veterinary biologics manufacturers, the AVMA, a veterinary consulting group, private and academic veterinarians, pet owners, and manufacturers. There was general support to change the format in which expectations of product efficacy are communicated on labels. APHIS has carefully considered the comments received on the draft guideline and has taken these comments into account in the drafting of this proposed rule.

Currently licensed products would not need to be re-licensed based on these proposed changes. This proposal is not intended to change the efficacy requirements for currently licensed veterinary biological products. Disease syndromes and primary parameters used in the case definitions would continue to be included in the indications statement where appropriate.

The licensees would be required to provide the same data as is currently required under 9 CFR part 102. Summaries of these data will be made available to the public on the APHIS Center for Veterinary Biologics (CVB) Web site. We believe that providing safety and efficacy data combined with a simpler labeling format will allow the end user to better assess product performance.

For the purposes of marketing, promotion, or advertising, the manufacturers could include a statement on promotional and advertising materials referring the user to the CVB Web site where additional efficacy and safety data may be found. Promotional studies would not be disclosed on the CVB Web site. We believe this is consistent with previous guidelines and regulations and would not confer an advantage to any particular manufacturer.

The CVB Web site would also provide educational information to address the complex nature of efficacy studies as well as explanatory statistical information, where appropriate, related to individual data summaries. In addition, the Web site would include a statement advising users to consult with a licensed veterinarian for further information regarding the use of a veterinary biological product. We believe an educational component is an integral part of disseminating such complex information as efficacy and safety data.

Biologics licensees would be responsible for providing data summaries with confidential business information removed. The licensee would be required to submit a summary of data with the efficacy/safety reports. If after reviewing the summary of data APHIS disagrees with the accompanying conclusions, APHIS would revise the summary and provide the licensee with the opportunity to review and comment on the revised summary prior to it being posted on the CVB Web site.

The original efficacy and safety data for each component antigen in a product would remain on the Web site indefinitely. Post-licensure data supporting additional efficacy/safety claims, or changes in the time immunity is demonstrated (i.e., time interval between vaccination and challenge) would also be posted to the Web site alongside the original data summary. We believe that providing post-licensure efficacy and safety data alongside the original efficacy data would allow the end user to determine whether the manufacturer is maintaining, increasing, or decreasing the standards used to originally license the product.

Several commenters requested information regarding how study design and results would be disclosed on the data summaries. Given the large number of diseases, vaccine types, and efficacy models, it is not possible to standardize the study design for all efficacy studies. Efficacy data summaries would include information regarding study design and associated raw data used to license the product. Parameters associated with study design would include: Minimum and maximum age of the target species; the diversity of target species; number of animals; whether animals were client owned; States where the study was conducted; serologic status of animals (including presence or absence of maternal antibody when appropriate); and dosage, timing, and route of administration. Information regarding the challenge organism would include the name of the organism (not strain) and concentration, time of challenge relative to the last vaccination, and whether the challenge organism is homologous or heterologous to the vaccine. Safety data summaries would include the same study design information as provided in efficacy data summaries and would include all adverse events that were observed throughout the course of the study.

The primary outcome and clinically relevant outcomes of the study used for acceptance of the data by APHIS would have to be provided. The data summary would include neither case definitions nor statistical results of an inferential nature (e.g., confidence intervals and p-values). The data would be sufficient to be reasonably understood by an individual with basic medical and scientific background yet contain sufficient information to allow a veterinarian to make an informed decision regarding the performance of the product(s). If the clinical sign is quantified rather than defined as either present or absent, the summary would provide sufficient information so the distribution of the responses could be understood. For example, in addition to the number of control and vaccinated animals with lung lesions, the summary could include such information as minimum, 25th percentile, median, 75th percentile, and maximum percent lung lesions for each group. We believe that presentation of efficacy and safety information as outlined above would appropriately reflect product performance in a standardized format without disclosing study information that may be confidential business information.

After demonstrating the efficacy for a product that contains a combination of many antigens, the manufacturer often mixes those antigens into smaller combinations. Smaller combinations can then be licensed as fall-out products. With regard to the presentation of data for large combination products with fall-out products, in general, efficacy and safety studies are conducted on the largest combination product and not on fall-out products. Efficacy would have to be established for each component antigen in the largest combination product. Safety data summaries would have to be provided for the largest combination product. Efficacy data summaries would be posted for each component antigen on the large combination (parent) product with a list of all smaller fall-out products. Similarly, each fall-out product from a larger combination product would have to reference the parent product under which the efficacy data summary may be found. An educational component would be included on the efficacy and safety data summaries clarifying that fall-out products have been licensed based on efficacy and safety data of a larger combination product. We believe this would bridge data from larger combination products to their associated fall-out products. In order to provide a manageable workload for both the manufacturers and CVB, we will

provide manufacturers with the opportunity to prioritize the submission of product families.

Products that are not yet licensed but are within 6 months of licensure at the time these proposed regulations may become effective would be expected to be fully compliant no later than 1 year after licensure. Products that are more than 6 months away from licensure at the time these proposed regulations may become effective would be expected to be fully compliant at the time of licensure.

For products that are currently licensed, the standardized summary of efficacy and safety data and the revised labels would have to be submitted to APHIS within 4 years of the time these proposed regulations may become effective. Licensees could request an extension of up to 2 years for submitting these materials. Extension requests, which would have to include the reason for the extension and a proposed implementation schedule, would have to be submitted in writing to the CVB Director. Contact information for the Director can be found on the CVB Web site.

Products whose original efficacy data are not available would require a statement on their data summary stating ''Original efficacy data is not available because the product was licensed ''x'' years ago.'' Regardless of the date of licensure of the product, any additional efficacy claims, including new routes of administration, or reference qualification data involving vaccination-challenge studies would be posted to the Web site. We believe that these timelines are appropriate for implementation of this proposed action and do not unnecessarily pose a hardship on the regulated industry or CVB.

Executive Orders 12866 and 13563 and Regulatory Flexibility Act

This proposed rule has been determined to be significant for the purposes of Executive Order 12866 and, therefore, has been reviewed by the Office of Management and Budget.

We have prepared an economic analysis for this rule. The economic analysis provides a cost-benefit analysis, as required by Executive Orders 12866 and 13563, which direct agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects, and equity). Executive Order 13563 emphasizes the importance of quantifying both costs and benefits, of reducing costs, of harmonizing rules, and of promoting flexibility. The economic analysis also provides an initial regulatory flexibility analysis that examines the potential economic effects of this rule on small entities, as required by the Regulatory Flexibility Act. The economic analysis is summarized below. Copies of the full analysis are available by contacting the person listed under **FOR FURTHER INFORMATION CONTACT** or on the Regulations.gov Web site (see **ADDRESSES** above for instructions for accessing Regulations.gov).

Based on the information we have, there is no reason to conclude that adoption of this proposed rule would result in any significant economic effect on a substantial number of small entities. However, we do not currently have all of the data necessary for a comprehensive analysis of the effects of this proposed rule on small entities. Therefore, we are inviting comments on potential effects. In particular, we are interested in determining the number and kind of small entities that may incur benefits or costs from the implementation of this proposed rule. Further, we are interested in receiving information that could be used to further quantify the benefits of this proposed rule.

APHIS is proposing to amend the Virus-Serum-Toxin Act regulations to require the use of a simpler labeling format. This simpler uniform format would allow biologics licensees and permittees to more clearly communicate product performance to the user. Biologics licensees and permittees would also be required to provide a standardized summary of the efficacy and safety data that are submitted to APHIS in support of the issuance of a full product license or conditional product license. The summary of efficacy and safety data would be made available to the public on the APHIS CVB Web site. We believe that the benefits of this rule justify the costs.

A simpler, uniform format would allow biologics licensees and permittees to more clearly communicate product performance information to the end user. Veterinarians, the largest group of consumers of veterinary biologics, often find labeling indications statements based on the current guidance to be confusing, and have expressed a desire for indications statements to provide insight into the actual performance of the product, including summaries of safety and efficacy data. In addition, the rule would simplify the evaluation of efficacy studies, focusing on a basic claim of effectiveness compared to the more complex, tiered approach historically used by APHIS. The proposed rule would reduce the amount of time required by CVB to evaluate study data. Because complex claims require more complex studies, the rule would likely result in fewer studies being found unacceptable. A study that is determined to be unacceptable by APHIS can lead to significant costs to manufacturers. These costs include those associated with duplication of efforts and materials (facilities and animals) used when a study must be redone, and lost marketing opportunities when initial licensing applications are not approved. A novel veterinary biological product can generate revenue in the neighborhood of $5 to $10 million per year. Therefore, lost opportunities due to delays in bringing a product to market can be significant.

This rule would affect all veterinary biologics licensees and permittees. There are approximately 98 veterinary biological establishments, including permittees. These companies produce about 1,900 different products, and there are about 11,700 active approved labels for veterinary biologics. There were about 3,100 labels submitted for approval in the last 12 months by about two-thirds of the companies.

Costs for licensees and permittees of the proposed rule are not expected to be significant, whether the affected entity is small or large. APHIS anticipates that the only costs associated with the proposed labeling format would be one-time costs incurred by licensees and permittees in having labels for existing licensed products reformatted in accordance with the proposed rule. Most biologics companies, in the course of normal business, use a just-in-time method for producing new labels and readily alter their content. Labels are regularly altered, for example, to enhance marketing through changes in design.

Products that are not yet licensed but are within 6 months of licensure at the time these proposed regulations may become effective would be expected to be fully compliant no later than 1 year after licensure. Products that are more than 6 months away from licensure at the time these proposed regulations may become effective would be expected to be fully compliant at the time of licensure. For products that are currently licensed, the standardized summary of efficacy and safety data and the revised labels would have to be submitted to APHIS within 4 years of the time these proposed regulations may become effective. CVB would consider written requests to extend the time

period for submitting the summaries by an additional 2 years if necessary.

In many instances manufacturers would not have to produce new labeling materials before they would do so in the normal course of business, and would only incur additional administrative costs to track the changes. Costs incurred for minor label changes that are coordinated with planned label changes are estimated to range between $99 and $500 per product with labels needing to be changed. We estimate that there are about 6,200 labels associated with about 1,000 products for which there would be this type of coordinated change. For these label changes, the total cost is estimated to range between $99,000 and $500,000.

We expect that about 5,500 of the active labels, associated with 900 products, would be changed other than in conjunction with a planned change. In these cases, manufacturers would incur costs for prepress, graphic design, and printing in addition to administrative costs. All labels for a specific product would be changed at the same time. Based on these activities, the costs of minor label changes that are not coordinated with planned label changes could range from $465 to $1,613 in administrative and labor costs for each product with labels needing to be changed and from $100 to $275 per new label in materials cost. Because veterinary biologics manufacturers are likely to make changes for groups of products, all cattle products for example, there are likely to be savings in administrative and labor costs for those grouped changes. However, based on the above ranges, the total cost for these uncoordinated label changes is estimated to be between $968,000 and $3 million.

Minor costs may be incurred in producing the standardized summaries of efficacy and safety data for currently licensed products within the 4-year implementation period. We estimate that about 1,700 summaries would need to be completed as a result of this rule because efficacy and safety studies are frequently provided for multiple products. The estimated cost would be about $55 per summary, or about $94,000 in total.

Executive Order 12372

This program is listed in the category of Federal Domestic Assistance under No 10.025 and is subject to Executive Order 12372, which requires intergovernmental consultation with State and local officials. (See 7 CFR part 3015, subpart V.)

Executive Order 12988

This rule has been reviewed under Executive Order 12988, Civil Justice Reform. It is not intended to have retroactive effect. This rule would not preempt any State or local laws, regulations, or policies unless they present an irreconcilable conflict with this rule. The Virus-Serum-Toxin Act does not provide administrative procedures which must be exhausted prior to a judicial challenge to the provisions of this rule.

Paperwork Reduction Act

This proposed rule contains no new information or recordkeeping requirements under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*).

List of Subjects in 9 CFR Part 112

Animal biologics, Exports, Imports, Labeling, Packaging and containers, Reporting and recordkeeping requirements.

Accordingly, we propose to amend 9 CFR part 112 as follows:

PART 112—PACKAGING AND LABELING

■ 1. The authority citation for part 112 continues to read as follows:

Authority: 21 U.S.C. 151–159; 7 CFR 2.22, 2.80, and 371.4.

■ 2. Section 112.2 is amended as follows:

■ a. In paragraph (a)(5), by adding a new first sentence.

■ b. By adding a new paragraph (a)(9)(v).

The additions read as follows:

§ 112.2 Final container label, carton label, and enclosure.

(a) * * *

(5) An indications statement to read ''This product has been shown to be effective for the vaccination of healthy animals _____ weeks of age or older against _____.'' * * *

* * * * * *

(9) * * *

(v) A statement similar to ''For more information regarding efficacy and safety data, go to *http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/animalhealth?1dmy&urile=wcm%3apath%3a%2FAPHIS_Content_Library%2FSA_Our_Focus%2FSA_Animal_Health%2FSA_Vet_Biologics.*''

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■ 3. Section 112.5 is amended as follows:

■ a. In the introductory text, by removing the words ''paragraph (c) of this section and under the master label system provided in paragraph (d)'' and adding the words ''paragraph (d) of this section and under the master label system provided in paragraph (e)'' in their place.

■ b. By redesignating paragraphs (b) through (g) as paragraphs (c) through (h).

■ c. By adding a new paragraph (b).

■ d. In newly redesignated paragraph (d)(1), by removing the citation ''§ 112.5(d)'' and adding the citation ''§ 112.5(e)'' in its place.

■ e. In newly redesignated paragraph (e)(1)(ii), by removing the citation ''§ 112.5(d)(1)(iii)'' and adding the citation ''§ 112.5(e)(1)(iii)'' in its place.

■ f. In newly redesignated paragraph (e)(1)(iii), by removing the citation ''§ 112.5(d)(1)(i)'' and adding the citation ''§ 112.5(e)(1)(i)'' in its place.

■ g. In newly redesignated paragraph (e)(1)(iv), by removing the citation ''§ 112.5(d)(1)(ii)'' and adding the citation ''§ 112.5(e)(1)(ii)'' in its place.

■ h. In newly redesignated paragraph (h), by removing the citation ''§ 112.5(c)'' and adding the citation ''112.5(d)'' in its place.

The addition reads as follows:

§ 112.5 Review and approval of labeling.

* * * * * *

(b) A data summary, available on the Internet at *http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/animalhealth?1dmy&urile=wcm%3apath%3a%2FAPHIS_Content_Library%2FSA_Our_Focus%2FSA_Animal_Health%2FSA_Vet_Biologics,* shall be used with each submission of efficacy and safety data in support of a label claim. Manufacturers will submit the efficacy and safety data information with either the efficacy and safety studies or at the time of label submission. This information will be posted at *http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/animalhealth?1dmy&urile=wcm%3apath%3a%2FAPHIS_Content_Library%2FSA_Our_Focus%2FSA_Animal_Health%2FSA_Vet_Biologics* to allow public disclosure of product performance.

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Done in Washington, DC, this 21st day of March 2014.

Gary Woodward,

Deputy Under Secretary for Marketing and Regulatory Programs.

[FR Doc. 2014–08995 Filed 4–18–14; 8:45 am]

BILLING CODE 3410–34–P