

Proposed Rules

Federal Register

Vol. 66, No. 137

Tuesday, July 17, 2001

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 113

[Docket No. 98–099–1]

Viruses, Serums, Toxins, and Analogous Products; Erysipelothrix Rhusiopathiae Bacterin

AGENCY: Animal and Plant Health Inspection Service, USDA.

ACTION: Proposed rule.

SUMMARY: We are proposing to amend the regulations regarding the standard requirement for Erysipelothrix Rhusiopathiae Bacterin to specify that those requirements apply only to bacterins recommended for use in swine and turkeys, to require that the immunogenicity of such bacterins be demonstrated in a host animal protection study, to establish “protection to market weight/age” as the minimum duration of immunity requirement, and to replace the current mouse protection potency test used for serial release with an in vitro potency test. We are proposing these changes as a result of our evaluation that showed that some swine vaccinated with Erysipelothrix Rhusiopathiae Bacterins that meet the current standard requirement may be diagnosed with acute erysipelas infection before they reach market age. These actions would update the regulations by standardizing the efficacy and duration of immunity requirements, provide for the use of a validated serial release potency test, and ensure that serials that pass the serial release potency test will also protect swine and turkeys to market weight.

DATES: We invite you to comment on this docket. We will consider all comments that we receive by September 17, 2001.

ADDRESSES: Please send four copies of your comment (an original and three copies) to: Docket No. 98–099–1, Regulatory Analysis and Development,

PPD, APHIS, Suite 3C03, 4700 River Road Unit 118, Riverdale, MD 20737–1238. Please state that your comments refer to Docket No. 98–099–1.

You may read any comments that we receive on this docket in our reading room. The reading room is located in room 1141 of the USDA South Building, 14th Street and Independence Avenue SW., Washington, DC, between 8 a.m. and 4:30 p.m., Monday through Friday, except holidays. To be sure someone is there to help you, please call (202) 690–2817 before coming.

APHIS documents published in the **Federal Register**, and related information, including the names of organizations and individuals who have commented on APHIS dockets, are available on the Internet at <http://www.aphis.usda.gov/ppd/rad/webrepor.html>.

FOR FURTHER INFORMATION CONTACT: Dr. Albert P. Morgan, Chief Staff Officer, Operational Support Section, Center for Veterinary Biologics, Licensing and Policy Development, APHIS, USDA, 4700 River Road Unit 148, Riverdale, MD 20737–1228; (301) 734–8245.

SUPPLEMENTARY INFORMATION:

Background

Standard requirements are prescribed in 9 CFR part 113 for the preparation and testing of certain veterinary biological products. A standard requirement consists of test methods, procedures, and criteria that define the standards of purity, safety, potency, and efficacy for a veterinary biological product. The regulations in 9 CFR 113.119 specify purity, safety, and potency requirements for Erysipelothrix Rhusiopathiae Bacterin.

Although purity, safety, and potency requirements for Erysipelothrix Rhusiopathiae Bacterin are specified in § 113.119 of the standards, they do not prescribe the requirements by which such bacterin must be evaluated for immunogenicity and duration of immunity. Most of the currently available Erysipelothrix Rhusiopathiae Bacterins were licensed on the basis of host animal protection studies performed in either swine or turkeys. In the typical host animal protection study, swine or turkeys were vaccinated with Erysipelothrix Rhusiopathiae Bacterin and challenged with virulent *Erysipelothrix rhusiopathiae* culture 2 to 4 weeks post vaccination. The

elapsed time between the completion of the immunization regimen and the administration of the challenge culture establishes the duration of vaccinal immunity. Therefore, 2 to 4 weeks’ protection would be the demonstrated duration of immunity provided by Erysipelothrix Rhusiopathiae Bacterin licensed in accordance with the requirements currently specified in the regulations in § 113.119.

Currently, the serial release potency test prescribed in § 113.119 is a mouse protection relative potency assay in which an Erysipelothrix Rhusiopathiae Bacterin (Unknown) and an *Erysipelothrix rhusiopathiae* standard reference bacterin (Standard) are compared in their ability to protect mice challenged with a virulent *Erysipelothrix rhusiopathiae* culture. The mouse potency test measures the relative strength of the Unknown as compared to the Standard and provides an indication of the ability of the Unknown to protect swine against erysipelas. The Standard used in the mouse potency test must have been shown to protect swine against erysipelas. The Unknown is considered to be potent enough to protect swine against erysipelas if it passes the mouse protection test.

Based on the current standards, it was expected that a serial of Erysipelothrix Rhusiopathiae Bacterin would protect swine or turkeys until they reached market weight/age if it passed the mouse protection test. However, we have received complaints that swine vaccinated with Erysipelothrix Rhusiopathiae Bacterin at an early age were being diagnosed with erysipelas before reaching market weight/age. In response to these complaints, we evaluated four representative Erysipelothrix Rhusiopathiae Bacterins recommended for use in swine and found that three of the four failed to protect swine at 22 weeks of age, which is the age at which most swine are marketed. We did not evaluate Erysipelothrix Rhusiopathiae Bacterin recommended for use in turkeys for duration of immunity.

On the basis of our evaluation of Erysipelothrix Rhusiopathiae Bacterins, we concluded that the mouse protection serial release potency test using the *Erysipelothrix rhusiopathiae* standard reference bacterin should be discontinued. This is because all of the

serials that failed to protect swine to market weight had passed the mouse protection relative potency test required for serial release. Western blot analyses performed on *Erysipelothrix rhusiopathiae* cultures used in our studies provided evidence that mice and swine recognize different immunogens. This may account for the failure in our analysis.

As a result of our findings, we are proposing to amend the regulations in § 113.119 to require that *Erysipelothrix Rhusiopathiae* Bacterin be tested for immunogenicity and duration of immunity in swine and/or turkeys. As a serial release potency test, we are proposing to require each serial of *Erysipelothrix Rhusiopathiae* Bacterin to be: (1) Tested for relative antigen content (potency) as compared with an unexpired *Erysipelothrix rhusiopathiae* reference bacterin by an in vitro parallel line immunoassay or other procedure acceptable to APHIS, or (2) evaluated in animals using antibody titers or other animal test data previously correlated to host animal protection as evidence of immunogenicity.

We are also proposing to specify that the requirements prescribed in § 113.119 pertain to *Erysipelothrix Rhusiopathiae* Bacterins for use in swine and turkeys. The basis for this proposed amendment is a host animal vaccination challenge study conducted by APHIS in which 6-week old pigs vaccinated with *Erysipelothrix Rhusiopathiae* Bacterin were protected against challenge with a virulent *Erysipelothrix rhusiopathiae* culture at 22 weeks of age.

Immunogenicity

We are further proposing that *Erysipelothrix Rhusiopathiae* Bacterins be evaluated for immunogenicity in swine and/or turkeys as appropriate. Thirty *Erysipelothrix rhusiopathiae*-susceptible swine and/or turkeys (20 vaccinates and 10 controls) of the youngest age recommended on the label would be vaccinated with an *Erysipelothrix Rhusiopathiae* Bacterin (master reference bacterin or qualifying serial, as defined in the regulations in § 101.5) by each route of administration recommended on the label.

Protection to Market Weight/Age (Duration of Immunity)

The proposed changes to the regulations in § 113.119 would also require *Erysipelothrix Rhusiopathiae* Bacterin to protect vaccinates against the characteristic signs of erysipelas until they reach market weight, which occurs at approximately 22 weeks of age for swine and 14 weeks of age for

turkeys. To demonstrate protection and duration of immunity, swine used in the immunogenicity study would be challenged with a virulent culture of *Erysipelothrix rhusiopathiae* at 22 weeks of age or older, while turkeys would be challenged with a virulent culture of *Erysipelothrix rhusiopathiae* at 14 weeks of age or older.

Potency

Under this proposed rule, each serial would have to be evaluated for relative antigen content by a direct or indirect in vitro parallel line immunoassay using a monospecific antibody that has been shown to provide passive protection in animals after challenge with virulent *Erysipelothrix rhusiopathiae*. Alternatively, potency could also be determined by measuring serologic response in animals, provided that such response had been correlated to protection in a host animal immunogenicity study using a protective protein.

Reagents

In order to facilitate the development of *Erysipelothrix Rhusiopathiae* Bacterin that provides the host animal protection and duration of immunity specified in this proposed rule, APHIS will supply reagent (monospecific antibody) produced by the hybridoma cell line ERHU1-B60-91, which is the same cell line that produced the antisera used to demonstrate passive protection and to purify the protein used to demonstrate active protection in the host animal vaccination-challenge study conducted by APHIS that serves as the basis for this proposed rule. If they prefer, firms could develop their own reagents for use in satisfying the requirements specified in this proposed rule. However, we believe that the use of APHIS-supplied reagent would greatly reduce the expenditure of time and resources needed to develop a potency test that would ensure that the product provides the duration of immunity that would be required by this proposed rule.

Safety

Currently, the regulations require each serial of biological product containing *Erysipelothrix rhusiopathiae* to be tested for safety in guinea pigs in accordance with § 113.38. However, for consistency with the regulations for other bacterins, we are proposing that each serial of biological product containing *Erysipelothrix rhusiopathiae* immunogen be tested for safety in mice in accordance with § 113.33.

Currently Licensed Bacterins

Veterinary biologics manufacturers that produce *Erysipelothrix Rhusiopathiae* Bacterin under the present standards would be allowed 1 year after the effective date of the final rule to come into compliance. In the interim, we would allow such manufacturers to continue to release serials of *Erysipelothrix Rhusiopathiae* Bacterins using the current standards, provided that such serials of product are shown to be effective and the labels for such products specify the demonstrated duration of immunity.

Executive Order 12866 and Regulatory Flexibility Act

This proposed rule has been reviewed under Executive Order 12866. The rule has been determined to be not significant for the purposes of Executive Order 12866 and, therefore, has not been reviewed by the Office of Management and Budget.

We are proposing to amend the regulations regarding the standard requirement for *Erysipelothrix Rhusiopathiae* Bacterins to require that such bacterins be shown to protect vaccinated swine and/or turkeys at least to market weight based on vaccination-challenge studies conducted in host animals. We are also proposing to replace the mouse protection (potency) test used for serial release with an in vitro parallel line immunoassay because we have data that demonstrate that some *Erysipelothrix Rhusiopathiae* Bacterins that pass the mouse potency test do not protect animals to market weight (normally reached at 22 weeks of age for swine and 14 weeks of age for turkeys) when used as directed. The effect of these actions would be to standardize the duration of immunity and potency test requirements for *Erysipelothrix Rhusiopathiae* Bacterins and ensure that serials that pass the potency test also protect animals to market weight.

This proposed rule would affect all licensed manufacturers of veterinary biologics that produce *Erysipelothrix Rhusiopathiae* Bacterins. Currently, there are approximately 135 veterinary biologics establishments, and approximately 45 of these establishments produce *Erysipelothrix Rhusiopathiae* Bacterins. According to the standards of the Small Business Administration, most veterinary biologics establishments would be classified as small entities.

This proposed rule would require each manufacturer of *Erysipelothrix Rhusiopathiae* Bacterins to incur the expense of developing an *Erysipelothrix*

Rhusiopathiae Bacterin that provides the duration of immunity specified in this proposed rule. However, the cost of developing such a bacterin would be greatly reduced if manufacturers use the reagents developed and provided by APHIS. In addition, the in vitro potency test specified in this proposed rule would result in a reduction in the number of animals used for serial release testing and would also reduce the time and personnel costs associated with animal care and housing.

Veterinary biologics manufacturers that produce *Erysipelothrix Rhusiopathiae* Bacterin under the present standards would be allowed 1 year after the effective date of the final rule to come into compliance. In the interim, we would allow such manufacturers to continue to release serials of *Erysipelothrix Rhusiopathiae* Bacterins using the current standards, provided that such serials of product are shown to be effective and the labels for such products specify the demonstrated duration of immunity.

We do not have an alternative option to this proposed rule because swine and turkey producers need a vaccine that offers protection until the animals reach market weight. However, we believe that, in the long term, expended developmental costs would be recovered and manufacturers would actually realize a savings, as the cost of purchasing, feeding, and housing the animals needed to test *Erysipelothrix Rhusiopathiae* Bacterins, as currently required, would be reduced and/or eliminated by utilizing nonanimal (in vitro) potency tests for serial release as proposed in this document.

This proposed rule would not require manufacturers to use the same monospecific antibodies that APHIS used in the host animal protection study. However, manufacturers may use the reagents developed by APHIS to facilitate their ability to comply with the requirements specified in this proposed rule or develop their own.

Under these circumstances, the Administrator of the Animal and Plant Health Inspection Service has determined that this action would not have a significant economic impact on a substantial number of small entities.

Executive Order 12372

This program is listed in the Catalog 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 proposed 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 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 113

Animal biologics, Exports, Imports, Reporting and recordkeeping requirements.

Accordingly, we propose to amend 9 CFR part 113 as follows:

1. The authority citation for part 113 would continue to read as follows:

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

2. Section 113.119 would be revised to read as follows:

§ 113.119 *Erysipelothrix Rhusiopathiae* Bacterin.

Erysipelothrix Rhusiopathiae Bacterin must be produced from a culture of *Erysipelothrix rhusiopathiae* or a culture expressing protective proteins from *Erysipelothrix rhusiopathiae* that are inactivated and nontoxic. Each serial of biological product containing *Erysipelothrix rhusiopathiae* immunogen must meet the applicable requirements of § 113.100 and must be tested for purity, safety, potency, and immunogenicity as prescribed in this section. A serial found unsatisfactory by any prescribed test may not be released. The requirements in this section apply to bacterins used in swine and turkeys. Firms currently producing *Erysipelothrix rhusiopathiae* bacterin that does not satisfy the immunogenicity and/or duration of immunity requirement will have 1 year from the effective date of this rule to be in compliance with this requirement unless granted an extension by the Administrator based on a showing by the firm that it has made a good faith effort with due diligence to achieve compliance.

(a) *Erysipelothrix Rhusiopathiae* Bacterins must be tested for immunogenicity as follows:

(1) For *Erysipelothrix Rhusiopathiae* Bacterins recommended for use in

swine or turkeys, 30 *Erysipelothrix rhusiopathiae*-susceptible animals (20 vaccinates and 10 controls) of the youngest age recommended on the label must be used as test animals for each route of administration.

(2) A master reference (as defined in § 101.5 of this chapter) must be established before the immunogenicity test is conducted. The method of production and conditions of storage of the master reference must be described in the outline of production filed with the Animal and Plant Health Inspection Service (APHIS). The 20 animals used as vaccinates must be injected as recommended on the label with either the master reference or a qualifying serial (as defined in § 101.5 of this chapter). The vaccinates and controls must be examined and their body temperature determined daily for 3 days prior to challenge. At 22 weeks of age or older for swine or 14 weeks of age or older for turkeys, the vaccinates and controls must be challenged with a virulent *Erysipelothrix rhusiopathiae* culture and observed for 7 days. The challenge culture and instructions for preparation and use must be obtained from APHIS.

(3) A satisfactory challenge in swine will be evidenced in the controls by a high body temperature or clinical signs, including, but not limited to, acute illness with hyperemia of the abdomen and/or ears, possibly terminating in sudden death; moribundity, with or without skin lesions; depression with anorexia, stiffness, and/or joint involvement; or any combination of these symptoms and lesions. If at least 8 of the 10 controls do not show characteristic signs of erysipelas during the observation period, including, but not limited to, a body temperature of at least 105.6 °F on at least 2 consecutive days, the test will be considered inconclusive. However, control swine that meet the requirements for susceptibility, except for high body temperature, will be considered susceptible if *Erysipelothrix rhusiopathiae* organisms are isolated from the blood, spleen, or other organs.

(4) A satisfactory challenge in turkeys will be evidenced in the controls by a generalized septicemia accompanied by the isolation of *Erysipelothrix rhusiopathiae* organisms from the joints or organs. If at least 8 of the 10 controls do not show characteristic signs or demonstrate other evidence of infection during the observation period, the test will be considered inconclusive.

(5) To demonstrate immunity after challenge, at least 80 percent of the vaccinates must remain free of clinical signs, and the body temperature of 80

percent of the swine must not exceed 104.6 °F on 2 or more consecutive days.

(6) The allowable dating of the master reference previously qualified as specified in paragraph (a)(2) of this section is the same as the dating of a serial of product or as approved by APHIS. The expiration date and the lot number of the master reference must be specified in the filed outline of production. The dating of the master reference may be extended by confirming its stability in accordance with § 113.8 prior to the expiration date specified in the filed outline of production.

(7) The master reference may be requalified by one of the following methods:

(i) Performing an immunogenicity test as specified in paragraph (a)(1) through (a)(5) of this section, except that the number of test animals may be reduced to 10 vaccinates and 5 controls, provided that 8 of 10 vaccinates and 4 of 5 controls meet the criteria specified in paragraphs (a)(3), (a)(4), and (a)(5) of this section.

(ii) Immunologic methods not requiring vaccination and challenge (e.g., serology) may be used to demonstrate the stability of a reference if the immunologic response was initially correlated to protection during the immunogenicity test. For a satisfactory test, 5 of 5 controls must remain seronegative at a 1:2 dilution, and 80 percent of the vaccinates must demonstrate bioequivalent serologic titers when compared to the protective titers established during the immunogenicity test. The length of the serologic study need not be the same as the immunogenicity test if adequate data acceptable to APHIS exist to correlate the serologic response earlier after vaccination than the immunogenicity test with protection at market weight.

(iii) A purified protein from *Erysipelothrix rhusiopathiae* that has been shown to elicit a protective response to challenge with virulent *Erysipelothrix rhusiopathiae* in swine may be used to requalify a working reference or qualify a new working reference. Such protein must be prepared by immunoaffinity purification methods using monospecific antisera or by other purification methods acceptable to APHIS. The purity and potency of a purified protein master reference must be well-characterized by in vitro methods such as high-performance liquid chromatography, protein quantification methods, immunoblot analyses, and/or other methods acceptable to APHIS. The

immunogenicity of a purified protein master reference must be directly established or indirectly established using a qualifying serial of product as provided in § 113.8 and paragraphs (a)(3), (a)(4), and (a)(5) of this section.

(8) An outline of production and data acceptable to APHIS must be approved for filing before authorization for the use of a new lot of master reference, a new lot of working reference, or a requalified master reference is granted.

(b) *Test requirements for release.* Each serial of *Erysipelothrix Rhusiopathiae* Bacterin must meet the applicable requirements of § 113.100 and must be tested for purity, safety, and potency as prescribed in this section. A serial found unsatisfactory by any prescribed test is not eligible for release.

(1) *Purity test.* Final container samples of completed product from each serial must be tested for viable bacteria and fungi as prescribed in § 113.26.

(2) *Safety test.* Bulk or final container samples of completed product from each serial must be tested for safety as provided in § 113.33(b).

(3) *Potency test.* In accordance with § 113.8(c), bulk or final container samples of completed product from each serial derived from an approved master seed must be evaluated for relative antigen content (potency) by the procedure specified in the filed outline of production as compared with an unexpired reference (which has been shown directly or indirectly to elicit acceptable duration of immunity) by a direct or indirect parallel line immunoassay. Potency may also be evaluated by measuring serologic response in animals that has been correlated to protection provided by a protective protein or other procedure acceptable to APHIS. The immunoassay must use a monoclonal antibody or monospecific antibody that has been shown to impart passive protection in animals following challenge with virulent *Erysipelothrix rhusiopathiae*.

(i) For a valid potency assay, at least two replications of at least six dilutions of the reference must be compared to at least two replications of at least six dilutions of each test serial on the same microtitration plate.

(ii) When comparing the test serial to the master reference by a relative potency method, a satisfactory test must have a minimum relative potency greater than or equal to 1.0. A relative potency of 1.0 is based on the antigen concentration of the master reference or qualifying serial of vaccine used in the host animal duration of immunity efficacy trial specified in paragraphs (a)(3), (a)(4), and (a)(5) of this section or

on the serologic response to a protective immunogen elicited by the master reference or qualifying serial.

(iii) On the basis of the results of such tests, each serial that meets the required minimum relative potency of greater than or equal to 1.0 will be released for marketing. Each serial that does not meet the required minimum potency must be withheld from the market.

(c) *Products without the required duration of immunity.* This section's requirement that an *Erysipelothrix Rhusiopathiae* Bacterin provide 22 weeks' duration of immunity in swine and 14 weeks' duration of immunity in turkeys will become effective 1 year after the publication of the final rule. Producers of *Erysipelothrix Rhusiopathiae* Bacterin may use the 1-year interval between the date of publication of the final rule and its effective date to update their products to provide the required duration of immunity. During this 1-year period, *Erysipelothrix Rhusiopathiae* Bacterins that do not protect vaccinates to market age (22 weeks for swine and 14 weeks for turkeys) may continue to be marketed if the labels for such products specify the duration of immunity demonstrated in the host animal protection study required for licensing. At the end of this 1-year period, *Erysipelothrix Rhusiopathiae* Bacterins that do not provide the minimum specified protection must be withheld from the market until they comply with the requirements of this section.

Done in Washington D.C., this 11th day of July 2001.

Bobby R. Acord,

Acting Administrator, Animal and Plant Health Inspection Service.

[FR Doc. 01-17802 Filed 7-16-01; 8:45 am]

BILLING CODE 3410-34-U

DEPARTMENT OF TRANSPORTATION

Federal Aviation Administration

14 CFR Part 39

[Docket No. 2000-NM-27-AD]

RIN 2120-AA64

Airworthiness Directives; Boeing Model 727-100 Series Airplanes

AGENCY: Federal Aviation Administration, DOT.

ACTION: Proposed rule; withdrawal.

SUMMARY: This action withdraws a notice of proposed rulemaking (NPRM) that proposed a new airworthiness directive (AD), applicable to certain Boeing Model 727-100 series airplanes.