Executive Order 12988

This rule has been reviewed under Executive Order 12988, Civil Justice Reform. This rule: (1) Preempts all State and local laws and regulations that are inconsistent with this rule; (2) has no retroactive effect; and (3) does not require administrative proceedings before parties may file suit in court challenging this rule.

Paperwork Reduction Act

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

List of Subjects in 9 CFR Part 94

Animal diseases, Imports, Livestock, Meat and meat products, Milk, Poultry and poultry products, Reporting and recordkeeping requirements.

Accordingly, 9 CFR part 94 is amended as follows:

PART 94—RINDERPEST, FOOT–AND–MOUTH DISEASE, FOWL PEST (FOWL PLAGUE), EXOTIC NEWCASTLE DISEASE, AFRICAN SWINE FEVER, HOG CHOLERA, AND BOVINE SPONGIFORM ENCEPHALOPATHY: PROHIBITED AND RESTRICTED IMPORTATION

1. The authority citation for part 94 continues to read as follows:

Authority: 7 U.S.C. 147a, 150ee, 161, 162, and 450; 19 U.S.C. 1306; 21 U.S.C. 111, 114a, 134a, 134b, 134c, 134f, 136, and 136a; 31 U.S.C. 9701; 42 U.S.C. 4331 and 4332; 7 CFR 2.22, 2.80, and 371.2(d).

§ 94.6 [Amended]

2. In § 94.6, paragraph (a)(2) is amended by removing the words ''Northern Ireland, Norway,''.

Done in Washington, DC, this 15th day of April 1997.

Donald W. Luchsinger,

Acting Administrator, Animal and Plant Health Inspection Service.

[FR Doc. 97–10101 Filed 4–17–97; 8:45 am]

BILLING CODE 3410–34–P

DEPARTMENT OF AGRICULTURE

Animal and Plant Health Inspection Service

9 CFR Parts 101 and 113

[Docket No. 94–051–3]

RIN 0579–AA66

Viruses, Serums, Toxins, and Analogous Products; In Vitro Tests for Serial Release

AGENCY: Animal and Plant Health Inspection Service, USDA.

ACTION: Final rule.

SUMMARY: We are amending the regulations to provide for the use of in vitro potency tests when conducting immunoassays to determine the relative antigen content (potency) of a serial of inactivated veterinary biological product once immunogenicity is established using host animal tests. Such tests would be conducted using unexpired immunogenic reference preparations and parallel line assays, or other methods which demonstrate linearity, specificity, and reproducibility at least equivalent to the parallel line assay. Firms currently using immunoassays which do not meet the standard in this amendment will have 2 years from the effective date of this final rule to update their filed Outlines of Production. This amendment also changes the title of the section and adds definitions of ''Master reference,'' ''Working reference,'' ''Qualifying serial,'' and ''Immunogenicity'' to the regulations.

The effect of this action is to standardize requirements for in vitro immunoassay potency tests for inactivated products which cannot be evaluated on the basis of virus titer or bacterial counts.

EFFECTIVE DATE: May 19, 1997.

FOR FURTHER INFORMATION CONTACT: Dr. David A. Espeseth, Director, Center for Veterinary Biologics, Licensing and Policy Development, VS, APHIS, 4700 River Road, Unit 148, Riverdale, MD 20737–1237, (301) 734–8245.

SUPPLEMENTARY INFORMATION:

Background

The regulations pertaining to the testing of biologics provide that no biological product shall be released (for sale) prior to the completion of tests prescribed to establish the product to be pure, safe, potent, and efficacious (9 CFR 113.5). Efficacy refers to the specific ability of the product to effect the result for which it is offered when used as recommended by the manufacturer. Tests to establish efficacy include immunogenicity tests in host animals using product which is manufactured according to specified requirements which include specifications for antigen content and/or animal potency. If a product has been tested for immunogenicity in animals and shown to elicit the desired immune response, it should follow that subsequent serials (batches) of the product manufactured to the same specifications should also have the same effect. Based on this premise, once immunogenicity is established in relation to a specific minimum antigen content, it should no longer be necessary to test every subsequent product serial for potency in animals if an evaluation of the relative antigen content can be made by testing the serial or subserial in an acceptable in vitro test system. Therefore, when properly qualified and validated, in vitro immunoassays that determine relative antigen content of a product can serve as acceptable substitutes for potency tests that otherwise would need to be performed in animals.

The regulations in 9 CFR 113.8 pertain to the use of in vitro tests for determining the potency of serials and/or subserials of veterinary biological products after required animal tests are completed. Prior to this amendment, the in vitro test procedures prescribed in § 113.8 were only applicable to products containing live microorganisms. With these amendments § 113.8 will be applicable to both live and inactivated products.

On May 17, 1995, we published in the **Federal Register** (60 FR 26381–26384, Docket No. 94–051–1) a proposal to amend the regulations regarding the use of in vitro potency tests in place of animal tests for immunogenicity. The proposed rule provided for the use of a parallel line assay, or other valid method, and an unexpired reference preparation in an in vitro immunoassay for relative antigen content to determine the potency of a serial of inactivated product. In proposing the parallel line assay or equivalent valid method and the use of an unexpired reference as a standard for in vitro immunoassay potency tests for serial release, APHIS did not intend to preclude the validation of existing in vitro immunoassays or the adoption of technological advances in antigen quantitation.

We solicited comments concerning our proposal for 90 days ending August 15, 1995. We extended the comment period an additional 30 days ending September 14, 1995 (60 FR 36743–36744, Docket No. 94–051–2, July 18,

1995). We also announced that we would be having a public hearing on August 1, 1995, in Ames, IA, to have further discussion related to in vitro testing by interested persons. We received comments from four licensed manufacturers, and a national trade association representing U.S. manufacturers of animal health products. Three comments from biologics producers were received at the public hearing on August 1, 1995, in Ames, IA. While generally supportive of in vitro immunoassay tests for determining the relative antigen content and thereby the potency of products, most commenters suggested changes in one or more sections as proposed. Others suggested that the comment period be extended and the proposal be submitted to negotiated rulemaking. We carefully considered all of the comments we received. They are discussed below.

Analysis of Comments and APHIS' Response

Four commenters requested that the comment period be further extended for 10 months beyond September 14, 1995, and that negotiated rulemaking be initiated. In response to this comment, APHIS notes that the history of this rulemaking began with a proposed rule published on May 17, 1995 (60 FR 26381–26384, Docket No. 94–051–1). The comment period of 90 days was extended to 120 days until September 14, 1995, in response to a request for an extension from a national trade association (See 60 FR 36743, July 18, 1995, Docket No. 94–051–2). In addition, a public hearing was held on In Vitro Potency Testing on August 1, 1995, in Ames, IA to obtain further comment on this topic. Contrary to the commenters' request, the comment period cannot be further extended for negotiated rulemaking because the initiation of negotiated rulemaking necessitates the withdrawal of the current proposal and the proposal of another rule after the conclusion of the negotiated rulemaking. APHIS believes that the publication of a final rule with appropriate consideration of responses and comments would be a more efficient way of handling this matter and would allay concerns and clarify issues raised by the commenters. Therefore, the request for further extension of the comment period and initiation of negotiated rulemaking is not granted.

Two commenters expressed concern that by specifying that in vitro immunoassays used to determine relative antigen content be parallel line assays, APHIS would be imposing a requirement which would not allow the industry to take advantage of technological advances that are occurring in the area of antigen quantitation. APHIS proposed the parallel line assay as a standard for immunoassay tests for relative antigen content. Assay formats which are equivalent to or exceed the parallel line assay standard could have been used as provided for in 9 CFR 113.4. In response to these comments, however, APHIS has amended §§ 101.5(q) and 113.8(a) in the final rule to provide specifically for the use of other valid methods for determining relative antigen content which demonstrate linearity, specificity, and reproducibility at least equivalent to the parallel line assay.

Five commenters recommended amending the rule to allow laboratory animal tests and antibody titers that have been correlated to host animal protection to be used to requalify or extend the dating of reference preparations. One of the commenters pointed out that the proposed standard requirement for Escherichia coli (E. coli) bacterins (59 FR 51390–51392, October 11, 1994) which also uses a parallel line immunoassay to test for potency, includes such a provision. In addition, the commenter interpreted the E. coli standard requirement to imply that in vitro assays may be used in place of reference requalification in host animals. In response to the commenter, APHIS agrees that the proposed E. coli standard requirement allows antibody titers and laboratory animal studies, previously correlated to protection, to be used to requalify reference preparations. These same provisions were available under the proposal to amend §§ 101.5 and 113.8 (See proposed terminology in § 101.5(o) which provides for direct or indirect correlation of potency to host animal immunogenicity). However, by specifying in proposed § 101.5(q)(1) that Qualifying Serials used to requalify or extend the dating of a Master Reference shall be ''tested for immunogenicity in host animals,'' APHIS may have inadvertently implied that laboratory animal tests could not be used for reference requalification. This was not the intent of the proposed regulation. In response to the commenter, the final rule has been amended in § 101.5(q)(1) to clarify the definition of Qualifying Serial to provide for the use of procedures acceptable to APHIS which will include antibody titers and laboratory animal testing along with host animal immunogenicity for reference requalification.

In response to the comment regarding the use of in vitro assays to requalify or extend the dating of a reference in place of performing studies in animals, in vitro tests may not be substituted for animal tests for reference requalification. The proposed E. coli standard requirement stated that an in vitro procedure may be used to monitor the potency of the Master Reference for indication of decline, but specified that the reference must be requalified when a decline in potency is detected. As proposed in the proposed E. coli standard requirement, the immunogenicity of Qualifying Serials used in reference requalification studies may be based on host animal studies (challenge or antibody titer) or laboratory animal studies as provided in protocols acceptable to APHIS. Therefore, to clarify these points and to eliminate the apparent inconsistency between the two proposed rules, APHIS is amending § 113.8(d)(2) pertaining to in vitro testing to include a monitoring provision and to clarify that: (1) The monitoring procedure can only be used to monitor the unexpired reference to detect when a decline in potency has occurred between requalification intervals, and (2) to specify that, if such monitoring procedures indicate the potency of the reference is declining, the reference must be requalified either by testing a Qualifying Serial in host animals or by providing other evidence of reference immunogenicity, e.g., antibody titers or laboratory animal test data previously correlated to host animal protection, or a new reference must be prepared and qualified. In vitro monitoring, however, would not be a substitute for reference requalification at the end of product dating.

One commenter suggested amending § 113.8(c)(5) to include a provision to allow a firm to declare a potency test with valid lines a ''no test'' if the firm does not have confidence in the test result. APHIS does not agree that it would be appropriate to declare such a test a ''no test''. The regulation, as proposed, allows a firm to retest a serial two times when the initial test shows that potency is less than the required minimum potency. The commenter's suggestion, however, would make potency testing subjective and allow a firm to disregard valid results that are not consistent with a desired outcome. Conceivably, a serial with unsatisfactory test results could be retested indefinitely. In response to this comment, APHIS has clarified provisions for the retesting of such serials and permitted up to three retests to be performed. Provisions have also been added to permit the potency test to be repeated under certain specified conditions.

Two commenters requested that firms be allowed more than two years to

convert currently approved in vitro immunoassays that are described in filed Outlines of Production that are not parallel line assays, to parallel line assays or to another method which demonstrates linearity, specificity, and reproducibility at least equivalent to the parallel line assay. They believed that the two-year timetable will have a negative impact on new product development, and therefore result in fewer new products on the market. In response, APHIS realizes that some firms may require more than two years to convert to parallel line assays or other valid methods. However, two years from the effective date of the final rule should be adequate time for most firms to validate their immunoassays and requalify references for existing products, considering that a single reference requalification procedure may be applicable to several different products. Also, those firms experiencing difficulty in meeting the time period may be granted additional time, if justified, by requesting an extension as provided in the regulations. Therefore, no change to the regulations is made in response to these comments.

One commenter requested that the definition of ''Master Reference'' in § 101.5(o) be amended to include options and directions for stabilizing and storing reference preparations. The commenter believed that this will result in more options for treating the references. APHIS does not agree that the rule needs to be amended. The definition of a ''Master Reference'' does not limit the options available to firms when it comes to stabilizing, storing, lyophilizing, or freezing Master References provided that such procedures are described in the filed Outline of Production. Specifying such procedures in the definition, however, would limit the industry to the procedures defined. Since the proposed definition does not limit the available options, no change to the regulations is made in response to this comment.

Another commenter requested clarification of proposed § 101.5(p) of the regulations. The commenter inquired if a purified antigen preparation could serve as the Working Reference. As proposed in § 101.5(p) of the regulations, the Working Reference may be the Master Reference, and since the Master Reference may be a purified preparation of the protective immunogen (antigen), it follows that a purified antigen can serve as the Working Reference. Therefore, no change to the regulations is made in response to this comment.

One commenter recommended amending proposed § 101.5(q)(1) of the rule to require Qualifying Serials for reference requalification to be produced at the minimum antigen level specified in the Outline of Production instead of specifying that the geometric mean relative potency not exceed 1.0 when compared to the Master Reference. The commenter reasoned that, by specifying that the amount of antigen in the Qualifying Serial not exceed the amount of antigen contained in the Master Reference, the antigen level contained in the Master Reference is a more appropriate benchmark (measure of protection) than is the antigen content specified in the Outline of Production. The commenter believed that the amount of antigen specified in the Outline of Production should establish the antigen requirement for the Qualifying Serial. APHIS does not agree with the commenter's recommendation. In measuring relative potency, the antigen level used to demonstrate host animal protection becomes the benchmark by which other serials are measured and is the level of antigen to be contained in a Qualifying Serial that is used to determine if the Master Reference is still protective and therefore eligible for continued use in the potency assay. The commenter's recommendation of using a regular production serial and devising a calculation procedure to show antigen equivalency is an indirect method that was considered by APHIS and determined to be inappropriate and less meaningful than the provision in the APHIS proposal. Therefore, no change to the regulations is made in response to this comment.

Two commenters expressed confusion regarding proposed §§ 113.8(a)(4) (i) and (ii) of the rule. The commenters noted that although § 113.8(a)(4) refers to in vitro methods for determining the potency of inactivated products, the cited examples, i.e., determining $\log_{10}$ virus titer and determining the live bacterial count only apply to live products. APHIS agrees that the wording of proposed § 113.8(a)(4) is contradictory and has amended the final rule, eliminating the contradictory sections, by incorporating the provisions of § 113.8(a)(4) into § 113.8(a)(3) as follows:

(3) Establishing a satisfactory potency test for the product in accordance with the following provisions:

(i) Potency of live products may be determined by $\log_{10}$ virus titer or determining the live bacterial count based on the protective dose used in the Master Seed immunogenicity test plus an adequate overage for adverse conditions and test error; and

(ii) Potency for inactivated products may be determined using tests for relative antigen content by comparing the antigen content of the test serial to a reference preparation using a parallel line immunoassay or equivalent method which measures linearity, specificity, and reproducibility in a manner acceptable to APHIS.

One commenter requested that the phrase ''an appropriate difference'' referred to in proposed § 113.8(b)(5) be further defined. Proposed § 113.8(b)(5) pertains to in vitro potency tests for live vaccines in which potency is measured in terms other than $\log_{10}$ virus titer or live bacterial counts, e.g., Marek's Disease vaccines in which potency is measured in terms of plaque forming units (PFU). Generally, an appropriate difference pertains to how a serial is determined to have satisfactory potency when the initial potency test determines that the serial contains less than the number of PFU's specified in the Outline of Production (OP) or standard requirement and the manufacturer elects to retest the serial to rule out test system error as the cause of the unsatisfactory test result. In accordance with § 113.8(b)(5), the manufacturer must specify in the OP the difference between the average PFU count obtained in the retest and the PFU count obtained in the initial test so that the initial test may be considered a result of test system error. The commenter did not suggest what this appropriate difference in PFU or organism count should be. APHIS has noted that the appropriate difference between test results may be different for each product and this is the reason the proposed rule specified that this value should be placed in the product Standard Requirement or filed OP. From data submitted to APHIS, however, it is also noted that an acceptable guideline for determining such appropriate difference would be if the difference between the average PFU count obtained in the retest and the count obtained in the initial test exceeds 20 per cent. However, because no specific value was proposed by the commenter, and there is a need to address specific product differences, no change to the regulation is made in response to this comment.

One commenter proposed that tests for relative antigen content which cannot be termed satisfactory or unsatisfactory should be called ''no tests'' and be eligible for unlimited retesting without prejudice. In response, APHIS points out that § 113.8(c)(1) of the regulation classifies a test that results in no valid lines as a ''no test''. Typically, this designation is used when a deficiency in the test system renders an invalid test result which is

unsuitable for reaching a conclusion regarding the potency of a serial; such serials may be retested. An equivocal test as that test is used in § 113.8(c)(2), is a test that results in valid lines which are not parallel. Therefore, the test is considered inconclusive and the serial cannot be termed satisfactory or unsatisfactory. In order to clarify the proper handling and disposition of serials of product with equivocal test results, APHIS has amended §§ 113.8 (c)(4) and (5) regarding the retest of serials with equivocal test results due to a lack of parallelism by specifying (1) the number of times such serials may be retested and, (2) the disposition of the serial based on the results of the retest.

Four comments were received related to proposed § 113.8(d)(2). The commenters requested that: (1) Stabilized Master References be allowed to serve as Working References; (2) Master References be allowed an initial dating period at least twice as long as that allowed for a regular serial of product; and (3) Frozen references be allowed an initial expiration dating of 5 years, provided that they are monitored by in vitro methods. In response to these comments regarding item (1), APHIS notes that proposed § 101.5(o) of the regulation specifies that the Master Reference may be used as the Working Reference. Regarding item (2), proposed § 113.8(d)(2) specifies that the dating of the reference shall be equal to the dating of the product or as supported by data acceptable to APHIS. Stability can be demonstrated by repeat testing of the reference over time or by demonstrating that the reference has maintained immunogenicity after being stored for a period of time equal to or greater than the dating period requested. Regarding item (3), allowing longer dating for references based on special treatments or storage conditions may be justified if such treatments or storage conditions are better able to maintain the stability of the reference. Section 113.8(d)(2) provides for determining the stability of the reference on the basis of confirming the immunogenicity in a manner acceptable to APHIS. This would include data from a stabilized monitored reference demonstrating stability in a manner acceptable to APHIS. Therefore, a reference may be allowed to have an initial dating longer than that for a regular production serial, provided that the request for the longer initial dating is supported by appropriate preliminary data and provides for monitoring stability to determine when the potency of the reference starts to decline and for taking appropriate steps to requalify or replace such a reference.

In response to the commenters, APHIS has amended the regulations to allow frozen references an initial dating period of 5 years, provided that the request for such initial dating is supported by preliminary data and a frozen storage protocol, including monitoring procedures, acceptable to APHIS. As amended, § 113.8(d)(2) reads as follows:

(d)(2) * * * The lot of reference used to determine antigenic content shall have an initial dating period equal to the dating of the product or as supported by data acceptable to APHIS, except that frozen references may have an initial dating of up to 5 years, *Provided,* That the request for dating of frozen references beyond the dating of the product is supported by preliminary data acceptable to APHIS and includes provisions for monitoring the stability of the reference to determine when the potency starts to decline and for taking the appropriate steps to requalify a reference with declining potency either by testing a Qualifying Serial in host animals or by providing other evidence of immunogenicity, e.g., antibody titers or laboratory animal test data previously correlated to host animal protection in a manner acceptable to APHIS. Prior to the expiration date, such reference may be granted an extension of dating, *Provided,* That its immunogenicity has been confirmed using a Qualifying Serial of product in a manner acceptable to APHIS. * * *

APHIS received two comments on proposed § 101.5(q)(2) inquiring into the rationale for requiring the qualifying serial used to extend the dating of a Master Reference to be prepared within 6 months of initiating a requalification test. The commenters believed that the 6 month restriction limited their options relating to production schedules and antigen manufacture. APHIS proposed the 6 month restriction as a means of assuring that qualifying serials used to extend the dating of a reference would be representative of the firm's current production method. APHIS agrees with the commenters regarding the potential restrictive aspects of the 6 month requirement and has amended § 101.5(q)(2) in response to the comment to be more consistent with our intent as follows:

(2) Qualifying serials used to requalify or extend the dating period of a Master Reference shall be determined to be immunogenic in accordance with methods deemed appropriate by APHIS as provided in paragraph (a)(1) of this section, and, in addition, shall be within their permitted dating period and have been prepared in accordance with the production method described in the currently filed Outline of Production.

APHIS received one comment requesting clarification of proposed § 113.8(d)(1) concerning confirmation of the protective dose established for live products in the Master Seed immunogenicity test after three years. In response to this comment, confirming the accuracy of the protective dose for live products three years after completion of a satisfactory immunogenicity test is specified in the Standard Requirements for live viral vaccines, and in the filed Outline of Production for products where standards have not been codified. Including a reference to this requirement for live viral vaccines in § 113.8(d)(1) corrects an omission and provides notification of the requirement to those unfamiliar with this provision of the regulations. As specified in the codified requirements for individual live viral vaccines, only one retest is required. No change to the regulations is made in response to this comment.

We received two comments regarding the definition of a ''Qualifying Serial'' in § 101.5(q)(1). The commenter expressed concern that limiting a qualifying serial to a relative potency, when compared to the Master Reference, of not greater than 1.0 is too restrictive. The commenters suggested that the normal tolerance limits of ±15 per cent for parallel line immunoassays could cause a Qualifying Serial set at 1.0 to be as low as 0.85, which means that it may not pass a requalification test in animals. APHIS does not agree that requiring the Qualifying Serial to have a mean relative potency of not greater than 1.0 is too restrictive. As the commenter is probably aware, test assay variation is to be expected. Usually, a manufacturer will optimize the test system to determine how much variation is normal, and adjust the antigen levels so that the risk of failing a requalification test in animals is minimized. The alternative would require APHIS to include tolerance limits in the regulations. APHIS does not agree that such tolerance limits are necessary. The individual manufacturers can optimize antigen levels based on their individual experiences with test assay variation to assure that a Qualifying Serial with a mean relative potency of not greater than 1.0 will pass the requalification test in animals. No change to the regulations is made in response to this comment.

Therefore based on the rationale set forth in the proposed rule and in this document, we are adopting the provisions of the proposal as a final rule, with the changes discussed in this document.

Executive Order 12866 and Regulatory Flexibility Act

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

This amendment allows any valid in vitro immunoassay to be used in determining the relative antigen content of an inactivated veterinary biological product, provided that it satisfies the parallel line criteria or demonstrates linearity, specificity, and reproducibility equivalent to the parallel line assay using an unexpired reference preparation. This amendment affects all licensed manufacturers of veterinary biologicals utilizing in vitro relative potency immunoassays for determining the potency of animal biological products. There are currently approximately 118 veterinary biologics establishments that may be affected by this rule. According to the Small Business Administration regulations, most of them would be classified as small entities. The majority of these establishments currently utilize in vitro relative potency tests to release serials of veterinary biological products. Since potency testing is already required under § 113.5 of the regulations and since this rule does not require the use of in vitro relative potency tests, any additional cost imposed by the validity requirements specified in this rule should be minimal. In the absence of a standard requirement prescribing a specific potency test for inactivated products, the firms develop a potency test suitable for their product, and designate such tests in the outline of production that is filed with APHIS. Currently, firms are using host animal tests, laboratory animal tests, and a variety of in vitro immunoassays as potency tests for products. This rule does not restrict the firm's discretion to choose the most appropriate test for its product. The rule only prescribes validity requirements for in vitro immunoassays for relative potency. The overall effect of this amendment will be to standardize in vitro immunoassays that are used to determine the potency of inactivated veterinary biological products.

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

Executive Order 12372

This program/activity 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 final 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. There are no administrative procedures which must be exhausted prior to a judicial challenge to the provisions of this rule.

Paperwork Reduction Act

In accordance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*), the information collection or recordkeeping requirements included in this rule have been approved by the Office of Management and Budget (OMB), and there are no new requirements. The assigned OMB control number is 0579–0013.

Regulatory Reform

This action is part of the President's Regulatory Reform Initiative, which, among other things, directs agencies to remove obsolete and unnecessary regulations and to find less burdensome ways to achieve regulatory goals.

List of Subjects

9 CFR Part 101

Animal biologics.

9 CFR Part 113

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

Accordingly, 9 CFR parts 101 and 113 are amended as follows:

PART 101—DEFINITIONS

1. The authority citation for part 101 continues to read as follows:

Authority: 21 U.S.C. 151–159; 7 CFR 2.22, 2.80, and 371.2(d).

2. Section 101.5 is amended by adding new paragraphs (o), (p), (q), and (r) to read as follows:

§ 101.5 Testing terminology.

* * * * *

(o) *Master reference.* A Master Reference is a reference whose potency is correlated, directly or indirectly, to host animal immunogenicity. The Master Reference may be used as the working reference in in vitro tests for relative potency. The Master Reference may also be used to establish the relative potency of a serial of product used in requalification studies and to establish the relative potency of working references. The preparation of a Master Reference as described in a filed Outline of Production may be:

(1) A completed serial of vaccine or bacterin prepared in accordance with a filed Outline of Production;

(2) A purified preparation of a protective immunogen or antigen; or

(3) A nonadjuvanted harvested culture of microorganisms.

(p) *Working reference.* A Working Reference is the reference preparation that is used in the in vitro test for the release of serials of product. Working References may be:

(1) Master References; or

(2) Serials of product that have been prepared and qualified, in a manner acceptable to Animal and Plant Health Inspection Service for use as reference preparations.

(q) *Qualifying serial.* (1) A serial of biological product used to test for immunogenicity when the Master or Working Reference is a purified antigen or nonadjuvanted harvest material. Qualifying serials shall be produced in accordance with the filed Outline of Production, tested for immunogenicity in accordance with methods deemed appropriate by the Animal and Plant Health Inspection Service, and have a geometric mean relative potency, when compared to the Master Reference, of not greater than 1.0 as established by: independent parallel line assays with five or more replicates; or other valid assay methods for determining relative antigen content which demonstrate linearity, specificity, and reproducibility at least equivalent to the parallel line assay and are acceptable to the Animal and Plant Health Inspection Service.

(2) Qualifying serials used to requalify or extend the dating period of a Master Reference shall be determined to be immunogenic in accordance with methods deemed appropriate by the Animal and Plant Health Inspection Service as provided in paragraph (a)(1) of this section, and, in addition, shall be within their permitted dating period and have been prepared in accordance with the production method described in the currently filed Outline of Production.

(r) *Immunogenicity.* The ability of a biological product to elicit an immune response in animals as determined by test methods or procedures acceptable

to the Animal and Plant Health Inspection Service.

PART 113—STANDARD REQUIREMENTS

3. The authority citation for part 113 continues to read as follows:

Authority: 21 U.S.C. 151–159; 7 CFR 2.22, 2.80, and 371.2(d).

4. Section 113.8 is amended as follows:

a. The section heading is revised to read as set forth below.

b. Paragraph (a) is revised to read as set forth below.

c. Paragraph (b) introductory text is revised to read as set forth below.

d. Paragraph (b)(5) is revised to read as set forth below.

e. Paragraph (c) is redesignated as paragraph (e) and new paragraphs (c) and (d) are added to read as set forth below.

f. In redesignated paragraph (e), in the introductory text, the reference to ''paragraph (b)'' is removed and ''paragraphs (b) and (c)'' are added in its place. In redesignated paragraph (e)(4), the reference to ''paragraphs (c)(1),'' is removed and ''paragraphs (e)(1),'' is added in its place.

§ 113.8 In vitro tests for serial release.

(a) Master Seed which has been established as pure, safe, and immunogenic shall be used for preparing seed for production as specified in the Standard Requirements or in the filed Outline of Production. The Administrator may exempt a product from a required animal potency test for release when an evaluation can, with reasonable certainty, be made by:

(1) Subjecting the master seed to the applicable requirements prescribed in §§ 113.64, 113.100, 113.200, and 113.300;

(2) Testing the Master Seed for immunogenicity in a manner acceptable to the Animal and Plant Health Inspection Service (APHIS);

(3) Establishing satisfactory potency for the product in accordance with the following provisions:

(i) Potency for live products may be determined by $\log_{10}$ virus titer or determining the live bacterial count based on the protective dose used in the Master Seed immunogenicity test plus an adequate overage for adverse conditions and test error; and

(ii) Potency for inactivated products may be determined using tests for relative antigen content by comparing the antigen content of the test serial to a reference preparation using a parallel line immunoassay or equivalent method which measures linearity, specificity, and reproducibility in a manner acceptable to APHIS.

(b) In the case of live products, each serial and subserial of desiccated product derived from an approved Master Seed and bulk or final container samples of each serial of completed liquid product derived from an approved Master Seed shall be evaluated by a test procedure acceptable to APHIS. On the basis of the results of the test, as compared with the required minimum potency, each serial and subserial shall either be released to the firm for marketing or withheld from the market. The evaluation of such products shall be made in accordance with the following criteria:

* * * * *

(5) *Exceptions.* When a product is evaluated in terms other than $\log_{10}$ virus titer or organism count, an appropriate difference between the average potency value obtained in the retests and the potency value obtained in the initial test shall be established for use in paragraphs (b)(3) and (b)(4) of this section to evaluate such products and shall be specified in the product Standard Requirement or filed Outline of Production.

(c) In the case of inactivated products, bulk or final container samples of completed product from each serial derived from an approved Master Seed, shall be evaluated for relative antigen content (potency) as compared with an unexpired reference by a parallel line immunoassay or other procedure acceptable to APHIS.[1] Firms currently using immunoassays which do not satisfy this requirement shall have 2 years from the effective date of the final rule to update their filed Outlines of Production to be in compliance with this requirement unless granted an extension by the Administrator based on a showing by the firm seeking the extension that they have made a good faith effort with due diligence to achieve compliance. On the basis of the results of such test procedures, each serial that meets the required minimum potency shall be released to the firm for marketing; each serial not meeting the required minimum potency shall be withheld from the market. The evaluation of such products shall be made in accordance with the following criteria:

(1) A test that results in no valid lines is considered a ''no test'' and may be repeated.

(2) An initial test (test 1) that results in valid lines that are not parallel is considered a valid equivocal test. Release of the serial may not be based on such test since the result cannot be termed ''satisfactory'' or ''unsatisfactory.''

(3) If the initial test (test 1) shows that potency equals or exceeds the required minimum potency, the serial is satisfactory without additional testing.

(4) If the initial test (test 1) is an equivocal test due to lack of parallelism, the serial may be retested up to three times (tests 2, 3, and 4) with disposition to be as specified in paragraphs (c)(4)(i) and (ii) of this section; *Provided,* That, if the serial is not retested or the other provisions of this section are not satisfied, the serial shall be deemed unsatisfactory.

(i) If: The first retest (test 2) following an initial equivocal test; the second retest (test 3) following two consecutive equivocal tests (tests 1 and 2); or the third retest (test 4) following three consecutive equivocal tests (tests 1, 2, and 3) shows that the potency equals or exceeds the required minimum potency, the serial is satisfactory.

(ii) If the first retest (test 2) following an initial equivocal test shows that potency is less than the required minimum potency, disposition of the serial will be based on the outcome of retests 2 and 3 (tests 3 and 4) as follows: if either retest (test 3 or 4) shows that potency is less than the required minimum potency, the serial is unsatisfactory. If either retest 2 or retest 3 (tests 3 or 4) is an equivocal test, or in the event that each retest (tests 2, 3, and 4) following an initial equivocal test is also an equivocal test, the accumulated test results shall be considered indicative of a lack of potency and release of the serial withheld. In which case, the licensee may submit data confirming the continued validity of the test system to APHIS for review and approval. If the data are acceptable to APHIS, the potency test may be repeated by the firm, subject to the provisions specified in paragraphs (i) and (ii) and confirmatory testing by APHIS.

(5) If the initial test (test 1) shows that potency is less than the required minimum potency, the serial may be retested a minimum of two times (tests 2 and 3) but not more than three times (tests 2, 3, and 4) with disposition as specified in paragraphs (c)(5) (i) and (ii) of this section; *Provided,* That, if the

[1] A method for evaluating relative antigen content, Supplemental Assay Method 318, and relative potency calculation software are available from the United States Department of Agriculture, Animal and Plant Health Inspection Service, Veterinary Services, National Veterinary Services Laboratories, Center for Veterinary Biologics—Laboratory, 1800 Dayton Road, P. O. Box 844, Ames, Iowa 50010.

serial is not retested or the other provisions of this section are not satisfied, the serial shall be deemed unsatisfactory.

(i) If two consecutive retests (tests 2 and 3) show that potency of the serial equals or exceeds the required minimum potency, the serial is satisfactory. If one of the two retests (test 2 or 3) shows that the potency is less than the required minimum potency, the serial is unsatisfactory.

(ii) If one of the retests (tests 2 or 3) shows that the potency equals or exceeds the required minimum potency and the other retest (test 2 or 3) is an equivocal test, a third retest (test 4) may be performed. If the third retest (test 4) shows that the potency of the serial equals or exceeds the required minimum potency, the serial is deemed satisfactory. If both retests (tests 2 and 3) or if the third retest (test 4) is an equivocal test, the accumulated test results shall be considered indicative of a lack of potency and release of the serial withheld, in which case the licensee may submit data confirming the continued validity of the test system to APHIS for review and approval. If the data are acceptable to APHIS, the potency test may be repeated by the firm, subject to the provisions specified in paragraphs (c)(4) (i) and (ii) and (c)(5) (i) and (ii) of this section, and confirmatory testing by APHIS.

(d) *Repeat immunogenicity tests.* (1) The accuracy of the protective dose established for live products in the Master Seed immunogenicity test and defined as live virus titer or live bacterial count shall be confirmed in 3 years in a manner acceptable to APHIS, unless use of the lot of Master Seed previously tested is discontinued.

(2) All determinations of relative antigen content using parallel line immunoassays or equivalent methods shall be conducted with an unexpired reference. The lot of reference used to determine antigenic content shall have an initial dating period equal to the dating of the product or as supported by data acceptable to APHIS, except that frozen references may have an initial dating of up to 5 years, *Provided,* That the request for dating of the frozen references beyond the dating of the product is supported by preliminary data acceptable to APHIS and includes provisions for monitoring the stability of the reference to determine when the potency starts to decline and for taking the appropriate steps to requalify a reference with declining potency either by testing a Qualifying Serial in host animals or by providing other evidence of immunogenicity, e.g., antibody titers or laboratory animal test data previously correlated to host animal protection in a manner acceptable to APHIS. Prior to the expiration date, such reference may be granted an extension of dating, *Provided,* That its immunogenicity has been confirmed using a Qualifying Serial of product in a manner acceptable to APHIS. The dating period of the Master Reference and Working Reference may be extended by data acceptable to APHIS if the minimum potency of the Master Reference is determined to be adequately above the minimum level needed to provide protection in the host animal. If a new Master Reference is established, it shall be allowed an initial dating period equal to the dating of the product or as supported by data acceptable to APHIS, except that frozen references may have an initial dating period of 5 years, or as supported by data acceptable to APHIS. Prior to the expiration date, such reference may be granted an extension of dating by confirming its immunogenicity using a Qualifying Serial of product.

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Done in Washington, DC, this 15th day of April 1997.

Donald W. Luchsinger,

Acting Administrator, Animal and Plant Health Inspection Service.

[FR Doc. 97–10100 Filed 4–17–97; 8:45 am]

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DEPARTMENT OF AGRICULTURE

Animal and Plant Health Inspection Service

9 CFR Part 156

[Docket No. 93–168–2]

Export Certification of Animal Products

AGENCY: Animal and Plant Health Inspection Service, USDA.

ACTION: Final rule.

SUMMARY: We are amending the regulations concerning inspection and certification of animal byproducts by removing references to ''inedible animal byproducts'' and replacing them with references to ''animal products,'' and by providing for the issuance of export certificates for animal products which do not require inspection. These amendments will facilitate trade in U.S. animal products.

EFFECTIVE DATE: May 19, 1997.

FOR FURTHER INFORMATION CONTACT: Dr. Marolo Garcia, Senior Staff Veterinarian, Products Staff, National Center for Import and Export, VS, APHIS, Suite 3B05, 4700 River Road, Unit 40, Riverdale, MD 20737–1231. Telephone: (301) 734–4401; or E-mail: mgarcia@aphis.usda.gov.

SUPPLEMENTARY INFORMATION:

Background

The regulations in 9 CFR part 156 (referred to as the regulations) govern the inspection and certification of animal byproducts. These regulations were promulgated under authority contained in sections 203 and 205 of The Agricultural Marketing Act of 1946, as amended (7 U.S.C. 1622 and 1624) (the Act). The Act authorizes the Secretary of Agriculture, among other things, to ''inspect, certify, and identify the class, quality, quantity, and condition of agricultural products when shipped or received in interstate commerce, under such rules and regulations as the Secretary of Agriculture may prescribe* * *.'' The Act further states that the intended effect of this authority is that agricultural products may be ''marketed to the best advantage'' and ''that trading may be facilitated.'' The Act also authorizes the Secretary ''to perform such other activities as will facilitate the marketing [and] distribution of agricultural products through commercial channels.'' In addition, the Act states that no person shall be required to use the service.

Animal Byproducts/Animal Products

Until recently, the Animal and Plant Health Inspection Service (APHIS) under the Act was granted authority with respect to voluntary inspection and certification of only inedible animal byproducts. Our regulations have therefore only provided for APHIS to issue export certificates for inedible animal byproducts.

However, effective November 8, 1995, APHIS was granted broader authority under revised delegations of authority from the Secretary of Agriculture and general officers of the Department (see 60 FR 56392, *et seq.*). Among other changes, the Administrator, APHIS, was granted authority to administer the Act ''with respect to voluntary inspection and certification of animal products'' (see 60 FR 56457, 7 CFR 2.80(a)(28)). The effect of this amendment was to give APHIS authority to issue export certificates for all animal products, edible and inedible.

To reflect this change, we published a proposed rule in the **Federal Register** on September 19, 1996, (61 FR 49278–49279, Docket 93–168–2), to amend the regulations to remove the term ''animal byproduct'' wherever it appears, and replace it with the term ''animal