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Animal and Plant Health Inspection Service

Washington, DC 20250

VETERINARY SERVICES MEMORANDUM NO. 800.111

TO: VS Management Team
Directors, Center for Veterinary Biologics
Biologics Licensees, Permittees, and Applicants

FROM: John R. Clifford /s/ John R. Clifford
Deputy Administrator

SUBJECT: Viral Strain Changes in Equine Influenza and Swine Influenza Vaccines (Killed Virus)

I. PURPOSE

This memorandum gives guidance to licensees, permittees, and applicants, per Title 9, Code of Federal Regulations (9CFR) 102.5(c)(1), concerning expedited procedures for influenza virus strain changes in licensed or permitted products containing inactivated (killed) equine and swine influenza viruses.

II. BACKGROUND

Equine influenza and swine influenza are highly contagious diseases that can have a significant economic impact to livestock owners. Equine and swine influenza viruses tended to remain stable in the environment for many years. Recently, however, antigenic shift and drift have been increasingly evident in viruses isolated from field cases of influenza. There is evidence from field studies that older influenza vaccines do not adequately protect animals from the currently circulating viruses. Expedited regulatory procedures that do not compromise the demonstrated efficacy and safety of the licensed products are necessary to keep pace with the antigenic changes seen in the field.

III. POLICY

The Center for Veterinary Biologics will, under the conditions described below, consider changes to the Master Seeds in licensed and permitted killed equine influenza and swine influenza vaccines without requiring additional full-scale efficacy and field safety studies, provided that the production methods have not been significantly altered.

A. General guidelines

1. H7N7 (subtype A1) equine influenza strains are no longer considered

relevant to protection against currently circulating field strains. H7N7 equine influenza virus strains may be removed from currently licensed products without prejudice, and firms are encouraged to remove them.

2. Proposals for additions or substitutions of new strains, or deletions of already present strains, must be submitted to CVB for review and approval prior to changing the licensed products.

   Equine influenza strains should be those recommended by the OIE Expert Surveillance Panel on EIV or otherwise justified by peer-reviewed scientific literature. Strains other than those specifically recommended by the OIE Panel may be used, provided that an equivalent relationship to the recommended strain is demonstrated by subtyping, sequencing, and antigenic analysis using hemagglutination inhibition (HI) tests, in a manner acceptable to the CVB.

   Swine influenza strains should be those justified by expert evaluation or peer-reviewed scientific literature and subtyping, sequencing, and antigenic analysis using HI tests, in a manner acceptable to the CVB.

3. A licensed product may not contain more than three strains of a subtype.

B. Substitution of strains within currently licensed products

1. Up to two strain substitutions within each of the subtypes present in the currently licensed product may be made at any one time. The antigen concentration per dose of each substitute must not be less than the minimum concentration specified in the currently approved Outline of Production for the strain being replaced, unless efficacy of the lowered antigen concentration per dose is demonstrated by a host animal challenge study acceptable to the CVB.

2. Firms must demonstrate the immunogenicity of new strains by demonstrating that the revised product formulation generates a similar immune response as the original formulation in host animals or a suitable laboratory animal model.

   a. The newly formulated product should be tested in at least six immunologically naive host animals at the minimum age recommended for vaccination. Animals that demonstrate an anamnestic response are removed from the study, but may be replaced with an equal number of new animals in a secondary study. Following completion of the study, the antibody geometric mean titer (GMT) should not be less than that demonstrated in the original efficacy study when compared at the same

post-vaccination interval using the same validated assay, but with the new strain's antigen and not the original antigen.

b. The newly formulated product may be tested in a laboratory animal model acceptable to the CVB, provided at least 10 animals are vaccinated. The antibody GMT should not be less than that achieved in the original efficacy study when compared at the same post-vaccination interval using the same validated assay.
c. The use of frozen archived serum samples in an assay directly comparing serologic response to old and new strains will require specific approval by the CVB.
d. When substituting new influenza strains in combination products containing other agents, where antigen interference studies have already been completed satisfactorily, it is not necessary to conduct further interference studies.

C. Addition of strains belonging to subtypes already present

1. Based on adequate justification, additional strains of each subtype may be added to a licensed product.

   For swine influenza vaccines, reassortants arising from new combinations of existing hemagglutinin (H) and neurominidase (N) gene segments (e.g., reassortment of H1N1 and H3N2 subtypes into a H1N2 subtype) will not be considered "new" subtypes. The guidelines in this section apply to the addition of such new reassortants.

2. The antigenic content per dose of the original strains must not be decreased upon the addition of additional strains, unless efficacy of the lowered antigen concentration per dose is demonstrated by a host animal challenge study acceptable to the CVB.

3. Testing requirements to support such additions are the same as those described in Section III.B.2.

D. Addition of strains belonging to new subtypes

1. Based on adequate justification, strains of new subtypes may be added to a licensed product.

2. The minimum antigen content per dose of each of the existing strains must not be decreased upon the addition of a new subtype, unless efficacy of the lowered antigen concentration per dose is demonstrated by a host animal challenge study acceptable to the CVB.

3. The immunogenicity of a strain of the new subtype must be demonstrated by host animal vaccination/challenge, using at least 10 vaccinates and 5 controls. The challenge virus must be a field-relevant strain.

   An entirely new equine or swine influenza vaccine manufactured according to a new process will require efficacy and field safety data as for any new product. Where a reasonable expectation of efficacy can be demonstrated, a firm may apply for a conditional license to expedite use of the product in the field, as described in 9 CFR 102.6 and Veterinary Services Memorandum No. 800.75. Until testing for full licensure of this new product is completed, restrictions on the conditionally licensed vaccine will apply.

IV. MASTER SEED VIRUS REQUIREMENTS

All applicable Standard Requirements for Master Seeds, specified in 9CFR section 113.200 apply. Additionally, the Master Seed characterization must include the H and N subtype designations. Sequence data, indicating the immunologically critical regions in the viral genome (e.g. the nucleotide sequence of the H gene), should be submitted on electronic disk.

V. PRODUCTION RECOMMENDATIONS

Firms are encouraged to develop the Single Radial Diffusion (SRD) assay as a measurement of H antigenic content during production.[1, 2] The SRD test is not suitable in the presence of adjuvant but is a reliable method for standardization of vaccine content prior to adding adjuvant. Reagents specific for the OIE recommended EIV vaccine strains are available from the National Institute for Biological Standards and Control, Hertfordshire, United Kingdom.

Equine antisera specific for various EIV vaccine strains are available as European Pharmacopoeia Biological Reference Preparations (EP BRPs) for serologic testing of EIV vaccines. They are available at the European Directorate for the Quality of Medicines, Cedex, France.

Currently, SRD reagents specific for SIV vaccine strains are not available. An alternative antigen quantification test acceptable to the CVB may be used.

VI. LABELING

Subtype and strain designations, specified according to accepted standards of influenza virus nomenclature, are to be included on the labeling for the product.

VII. REFERENCES

1. Williams MS. Single-radial-immunodiffusion as an in vitro potency assay for human inactivated viral vaccines. Vet Microbiol 37:253-262, 1993.

2. Wood JM, Schild GC, Newman RW, Seagroatt V. An improved single-radial-immunodiffusion technique for the assay of influenza haemagglutinin antigen: application for potency determinations of inactivated whole virus and subunit vaccines. J Biol Stand 5:237-247, 1977.