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Department of
Agriculture

Animal and Plant
Health Inspection
Service

Veterinary Services

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PROPOSED REVISIONS FOR COMMENT

VETERINARY SERVICES MEMORANDUM NO. 800.203

Subject: General Licensing Considerations: Compatibility of Components

To: Veterinary Services Management Team
Veterinary Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

This memorandum provides guidance for evaluating the compatibility of components in combination biological products formed by assembling previously licensed products

II. CANCELLATION

This memorandum cancels Veterinary Services Memorandum No. 800.203, dated May 28, 2002.

III. BACKGROUND

The products covered by this memorandum are vaccines and similar prophylactic immunobiologicals, such as bacterins or toxoids, which contain antigens intended to actively stimulate an immune response in the recipient. Antigenic fractions with previously established efficacy in licensed products may be combined to form a new polyvalent product. It must be verified that the efficacy of each fraction has not been compromised in the new product when compared to a product with known efficacy.

IV. DEFINITIONS

A. Component Interference

Component interference is an adverse alteration of the expected immune response to one antigen by the presence of another antigen or component in the same product.

B. Excessive Interference

Interference is excessive when there is reason to believe the product's efficacy against disease has been decreased by the alteration of the immune response due to interference.

C. Fraction

A fraction of a prophylactic immunobiological product refers to an antigen (organism) and the form in which it appears (e.g., modified live, inactivated, subunit, toxoid, vectored, etc.).

D. Reference Product

A reference product is a product for which efficacy in the target species has been directly demonstrated.

E. Test Product

A test product is a new polyvalent product formed by combining fractions from previously licensed product(s) and/or adding new antigens to licensed combinations.

V. GUIDELINES

Material submitted to support a test product must include information verifying the absence of excessive component interference. Support for the absence of excessive interference may be provided by one of the following.

A. Efficacy Study

A satisfactory efficacy study conducted with the test product may be used to verify the absence of excessive interference on the efficacy of the vaccine antigen that was challenged. Efficacy studies may be conducted when licensing any test product and must be conducted for the following:

1. *Avian and Fish Products* – Conduct an efficacy study for each fraction of new polyvalent products intended for use in poultry or fish.

2. *Mammalian Products* – Conduct an efficacy study for each fraction of new polyvalent products intended for use in mammals if the new product differs significantly from the licensed products in composition, production methods, or recommended vaccination regimen.

B. Existing Information

Submit convincing objective data documenting the absence of excessive interference. Such information may include previous studies or documented experience with the fractions comprising the test product.

C. Potency Test

Validated potency tests which accurately reflect a fraction's efficacy may be sufficient support for the absence of excessive interference. Acceptable potency tests have been limited to the *in vivo* tests found in the Standard Requirements for *Leptospira* species, *Clostridium* species, and the equine viral encephalitides (Code of Federal Regulations, Title 9, Part 113).

D. Comparative Serology

Conduct a study in the target species comparing the serological responses between a group vaccinated with the test product and a group vaccinated with a reference product. In many instances, the serologic response of interest will be a serum titer, and the group geometric mean serum titers (GMT) would be compared. The absence of excessive interference would then be supported if the GMTs were equivalent.

1. *Methods*

a. Equivalence. Two values are equivalent if they differ by less than an amount which is considered meaningful in a clinical or practical sense. The range within which two values are considered equivalent is termed the equivalence margin.

b. Formulation. Formulate the test and reference products from the same bulk lot of each antigen common to both products. The volume of each antigen (and therefore the potency) should be the same in both products.

c. Serum titer. Use a validated assay that measures an antibody response that has been shown to be related to efficacy.

2. *Design.* Design the study for statistical analysis and inference by accepted equivalence methodology.

a. Route of administration. Equivalence should be evaluated for each route of administration separately.

b. Serum collection time. Collect serum near the time of peak response to the reference product. If serum is collected on more than one occasion, adjust for multiplicity by estimating simultaneous confidence intervals for all occasions. Important differences at any time point may be an indication of excessive interference. If there is reason to believe the products' antibody response profiles over time are different, design the study so that the profiles may be directly evaluated.

c. Variance components. The objective of a serological interference study

is to draw conclusions about the immunogenicity of the test product based on the average serological response of vaccinated animals. Such studies may benefit from reducing the impact of assay variance on interval estimates. Studies intended to do so should be designed to include multiple titrations on each serum specimen and the variance components estimated from an appropriate statistical model.

3. *Criteria*

a. Noninferiority. The serological noninferiority of the test product must be demonstrated. Serological noninferiority means that the expected GMT of the group vaccinated with the test product is not lower than the expected GMT of the group vaccinated with the reference product by more than the equivalence margin.

b. Lower margin. Protocols proposing serological equivalence studies must explicitly state the criterion determining the noninferiority margin. Use the 70% criterion, which aims to show that the test product GMT is at least 70% of the reference product GMT, unless another criterion is justified. A 70% titer ratio corresponds to a difference of about one half of a twofold dilution in a serial dilution assay. (The 70% criterion does not necessarily apply to applications other than antigen interference studies.)

c. Confidence. For serological noninferiority studies, use a 0.075 level of significance. For example, if comparing a confidence interval to the equivalence margin, use an 85% confidence interval. For noninferiority, compare only the lower end of the confidence interval to the lower end of the equivalence margin. For full equivalence, no part of the confidence interval should lie outside the equivalence margin.

d. Increased serological response. In comparative serology studies, serum titer is used as an indicator of the overall immune response. If the humoral responses to vaccination with the test and reference products are equivalent, then the critical assumption is made that cell-mediated processes and their relative contributions to the overall immune response are unlikely to be materially affected as well. A change in that balance may be signaled by an antibody response that is either increased or reduced. Thus, if the GMT of the new product is dramatically higher than the reference product GMT, further study of the potential impact on the overall protective immune response is warranted.

e. Lack of seroconversion. If more than a trivial number of animals in a group do not seroconvert, it is not appropriate to estimate the group GMT. The presence of many nonresponders may indicate that serology is not a

suitable way to evaluate component interference. If the distribution of serum titers is typical for the antigen, serological comparisons may be considered valid, but statistical modeling based on mixture distributions may be necessary. If a nested model is appropriate, simultaneous evaluation should be done of the fraction seroconverting, and the GMT of animals that have seroconverted.

3. *Field Studies* - The variability of the humoral response in some cases may require that a serological equivalence study include more subjects than available for an experimental study. Serum derived from appropriately designed field studies may be used to study serological equivalence. For example, subjects in a field safety trial may be randomized to new and existing products. While such subjects would not necessarily be seronegative, they would emulate the target population as well as the rest of the field safety study sample.