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United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

Center for Veterinary Biologics

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CENTER FOR VETERINARY BIOLOGICS NOTICE 08-13

Subject: International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH): Final Guidelines for Backpassage Studies

To: VS Management Team (VSMT)
Directors, Center for Veterinary Biologics
Biologics Licensees, Permittees, and Applicants

I. PURPOSE

The purpose of this notice is to inform interested parties of the disposition of the comments received in response to the *Federal Register* notice of availability and request for comments on a draft guideline titled, "Target Animal Safety: Examination of Live Veterinary Vaccines in Target Animals for Absence of Reversion to Virulence, (VICH GL41)" developed by the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH).

Veterinary Services has included the final guideline for General Licensing Considerations: Backpassage Studies in the revised version of Veterinary Services Memorandum 800.201, which accompanies this notice.

II. BACKGROUND

The guideline was published in the *Federal Register* (Federal Register Vol. 69, No. 246, Docket No. 04-129-1) on December 23, 2004. Since the topic of the draft guideline concerns veterinary biological products, comments on its provisions were requested so that any relevant input could be forwarded to the draft to the VICH for its consideration to support the expertise available to the working group preparing the final guideline.

III. COMMENTS AND DISPOSITION

Comments related to specific revisions of the draft guideline, and corresponding dispositions, are as follows:

Section 2, Study Design, Paragraph 1: It was suggested that the second sentence of the first paragraph be revised to encompass instances in which Master Seed still exists, but not in sufficient quantity to complete testing. The second sentence was revised to reflect the instances in which Master Seed still exists, but not in sufficient quantity to perform the trial.

It was suggested that the sixth line of the first paragraph be revised to include how time intervals between inoculation and harvest are determined. The sixth line of the first paragraph was revised to indicate that the time interval between inoculation and harvest for each passage must be justified based upon the characteristics of the test organism, to address how time intervals between inoculation and harvest are determined, based on the characteristics of the test organism.

It was suggested that the eighth line of the first paragraph be reworded to clarify that repeat test material is used in the next passage and that the repeat test can be included as a passage in the total number required. The eighth line of the first paragraph was revised, and additional wording was added to provide this clarification as follows: "If recovery is successful, passages should continue through five groups of animals. Appropriate methods, preferably *in vitro* propagation, should be used to confirm the presence and to determine the number of the test organisms at each passage. *In vitro* propagation may not be used to expand the passage inoculum."

Section 2, Paragraph 5: It was suggested that instances in which the first route of inoculation may be different from the routes of inoculation used in subsequent passages be included. This paragraph was revised as follows: "The initial administration and subsequent passages shall be carried out using a recommended route of administration or natural route of infection that is most likely to lead to reversion to or increase in virulence and result in recovery of the organism following replication in the animal. The route used must be justified." This wording allows the firm to provide scientific justification for routes of inoculation used.

Section 2, Paragraph 8: A comment was made indicating that repeating the second and performing a sixth passage each in 8 animals would require extra use of animals and may not be needed. A recommendation was made that the trial be set up to include the initial passage, minimum of 8 animals, second, third, and fourth passages, 2 animals and fifth passage, minimum of 8 animals. The paragraph was reworded as follows: "If the fifth group of animals shows no evidence of an increase in virulence indicative of reversion during the observation period, further testing is not required. Otherwise, materials used for the first passage and the final passage should be used in a separate experiment using at least 8 animals per group to directly compare the clinical signs and other relevant parameters. This study should be done by the route of administration that was used for previous passages. An alternative route of administration may be used if scientifically justified."

Section 2, Paragraph 9: Rewording was suggested to emphasize that the tests should be performed only when attenuation is the result of a known marker or genetic change. The paragraph was reworded as follows: "When attenuation of a test organism is known to be the result of a well characterized specific marker or genetic change, additional tests using suitable molecular biological methods for comparison of the initial seed organism and the

organism recovered from the final passage should be performed, thus confirming the genetic stability of the attenuation marker in the vaccine strain."

Section 3, Glossary, definition of minimum release titer: A comment was made that the definition in the glossary should be consistent with the VICH Target Animal Safety document. The definition was worded as follows, "The expected lowest number of viable organisms required per dose in vaccines at the time of release, verified by efficacy and stability data.

/s/ Richard E. Hill, Jr.

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