



Animal and Plant
Health Inspection
Service

Veterinary Services

Center for Veterinary
Biologics

1920 Dayton Avenue
PO Box 844
Ames, IA 50010

(515) 337-6100

CENTER FOR VETERINARY BIOLOGICS NOTICE NO. 19-03

TO: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics
Veterinary Services Leadership Team
American Veterinary Medical Association

FROM: Byron Rippke
Director

SUBJECT: New Extraneous Agent Testing Requirement for Equine-Origin
Antibody, Antitoxin, Serum, and Plasma Products Regulated by
APHIS

I. PURPOSE

This Notice informs interested parties of a new testing requirement for donor horses and completed APHIS-regulated antibody, antitoxin, serum, and plasma products of equine origin for freedom from equine parvovirus-hepatitis.

II. BACKGROUND

Recently published research describes equine parvovirus-hepatitis as a probable cause of equine serum hepatitis.^{1, 2, 3} The research indicates that the virus is present in, and can be spread by, administration of equine serum and/or plasma.

Title 9, *Code of Federal Regulations*, part 113.450(c)(2) states: “An animal that tests positive for an infectious disease shall not be used in the manufacture of antibody products.” The presence of equine parvovirus-hepatitis in licensed veterinary biologics poses a newly identified and unacceptable risk, requiring regulatory action.

III. ACTION

A. Donor Horses

All horses used as donor animals for the manufacture of APHIS-regulated antibody, antitoxin, serum, and plasma products must test negative for the presence of equine parvovirus-hepatitis in blood samples, by test methods acceptable to APHIS. Donor herds must be tested annually, and all additions to the donor herd must test negative prior to sharing physical space or being allowed contact to donor animals. If a negative animal in the herd subsequently tests positive, contact the Center for Veterinary Biologics (CVB) for guidance on additional requirements.

B. Serial Release Testing

In addition, each completed serial of APHIS-regulated antitoxin, antibody, serum, or plasma product labeled for use in equines must test negative for equine parvovirus-hepatitis by test methods acceptable to APHIS, as listed in the respective Outline of Production. Test results must be reported on APHIS Form 2008 in accordance with the Outline of Production. Exemptions to the serial testing requirements may be considered if data acceptable to APHIS demonstrate that production methods prohibit the presence of the infectious virus in the completed product.

C. Product Labeling

1. Labeling of products licensed for use in equines must bear a caution statement indicating that use of equine serum and plasma products has been associated with hepatitis (Theiler's Disease).
2. Labeling of products of equine origin licensed for use in species other than equine must bear a caution statement stating "Do not use in equine species." This statement may be removed once donor herd testing described in Section III.A is fully implemented.
3. Once in compliance with Sections III.A and B, equine product labeling may bear a statement affirming the product has tested free of equine parvovirus. Additional statements indicating freedom from other specific viruses with less definitive associations to equine hepatic disease⁴ may be considered by the CVB with submission of an acceptable test and test validation data. The caution statement for Theiler's Disease must remain.

IV. IMPLEMENTATION/ APPLICABILITY

The policy applies to prelicense and licensed equine-origin antibody, antitoxin, serum, and plasma products, regardless of animal species for administration. Policy regarding the use of equine-origin serum in the production of other biologicals such as vaccines is currently being reviewed and will be addressed separately.

Products must be in compliance with Sections III.A and B within 18 months of the publication date of this notice. Labels must be in compliance with Parts 1 and 2 of Section III.C within 6 months of the publication date of this notice. Outlines of Production must be updated with applicable testing and labeling changes as they are implemented.

V. REFERENCES

1. Divers TJ, Tennant BC, Kumar A, McDonough S, Cullen J, Bhuva N, Jain K, Chauhan LS, Scheel TKH, Lipkin WI, Laverack M, Trivedi S, Srinivasa S, Beard L, Rice CM, Burbelo PD, Renshaw RW, Dubovi E, Kapoor A. New Parvovirus Associated with Serum Hepatitis in Horses after Inoculation of Common Biological Product. *Emerg Infect Dis.* 2018; 24(2):303-310.
2. Tomlinson JE, Tennant BC, Struzyna A, Mrad D, Browne N, Welchel D, Johnson PJ, Jamieson C, Löhr CV, Bildfell R, McKenzie EC, Laverack M, Renshaw RW, Dubovi E, Kapoor A, Meirs RS, Belgrave R, Engiles J, Van de Walle GR, Divers TJ. Viral testing of 10 cases of Theiler's disease and 37 in-contact horses in the absence of equine biologic product administration: A prospective study (2014-2018). *J Vet Intern Med.* 2019: Jan; 33(1) 258-265.
3. Tomlinson JE, Kapoor A, Kumar A, Tennant BC, Laverack MA, Beard L, Delph K, Davis E, Schott II H, Lascola K, Holbrook TC, Johnson P, Taylor SD, McKenzie E, Carter-Arnold J, Setlakwe E, Fultz L, Brakenhoff J, Ruby R, Trivedi S, Van de Walle GR, Renshaw RW, Dubovi EJ, Divers TJ. Viral testing of 18 consecutive cases of equine serum hepatitis: A prospective study (2014-2018). *J Vet Intern Med.* 2019: Jan;33(1) 251-257.
4. Chandriani S, Skewes-Cox P, Zhong W, Ganem DE, Divers TJ, Van Blaricum AJ, Kistler AL. (2013). Identification of a previously undescribed divergent virus from the Flaviviridae family in an outbreak of equine serum hepatitis. *Proceedings of the National Academy of Sciences of the United States of America*, 110(15), E1407–E1415.