

**USDA (United States Dept of Agriculture) and
CFIA (Canadian Food Inspection Agency)
Regulation of Equine Plasma & Serum Products
for the Equine Practitioner**

American Association of Equine Practitioners White Paper



Introduction

The purpose of this white paper is to provide veterinarians with information regarding equine blood-derived (plasma and serum) products' therapeutic claims, efficacy, safety, and regulatory oversight. The white paper will not take a position on the therapeutic value of these products or attempt to provide overall guidance on clinical application. However, a list of references containing general background information and guidance for clinical application is provided in the [Additional Resources](#) section.

Key Takeaway Points:

United States

- Equine blood-derived products are regulated by the United States Department of Agriculture Center for Veterinary Biologics (USDA CVB) or the U.S. Food & Drug Administration Center for Veterinary Medicine (FDA CVM).
- The USDA CVB issues licenses to manufacturers of plasma and serum veterinary biological products for specific therapeutic claims.
- The best method to determine if a product is licensed by the USDA CVB is to identify the licensee or permittee number and Product Code Number (PCN) on the product label. A list of USDA licensed products is presented in [Appendix A](#).

Canada

- Equine blood-derived products are regulated by the Canadian Centre for Veterinary Biologics (CCVB) of the Canadian Food Inspection Agency (CFIA) or the Veterinary Drugs Directorate (VDD) Health Canada (HC).
- At time of printing, all Canadian licensed plasma products are manufactured in the USA and all but one are licensed by the USDA CVB.
- The best method to determine if a product is licensed by the CFIA-CCVB is to verify the product on the [CFIA website](#). A list of CFIA-CCVB licensed products is presented in [Appendix B](#).

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Overview of Regulation of Plasma and Serum Products in the United States

USDA versus FDA regulation

It is important for the equine veterinarian to understand differences between products regulated and licensed by USDA CVB from those regulated by the FDA CVM to make informed choices on product use. Companies may sell products regulated by both USDA CVB and FDA CVM. The AAEP and AVMA PLIT recommends that veterinarians use licensed products whenever possible, as these products have been tested and shown to be safe and effective for their labeled use(s). ***At the time of publication, there are currently NO FDA licensed equine blood-derived products. Therefore, the remainder of this white paper will focus solely on USDA regulation of equine serum and plasma products.***

Veterinary Biological Products Regulated and Licensed by USDA

A list of USDA licensed equine antibody products is provided in [Appendix A](#).

The Virus-Serum-Toxin Act authorizes the USDA Animal and Plant Health Inspection Service (APHIS) to regulate veterinary biological products. APHIS regulates veterinary biological products where the primary mechanism of action is an immunologic response in the animal. A list of benefits of USDA regulation of serum and plasma products is provided in [Appendix C](#). The CVB, under USDA APHIS, administers the veterinary biologics program to license and oversee products according to title 9, Code of Federal Regulations (CFR), parts 101-124 as well as Veterinary Services Memoranda, CVB Notices, and other guidance found on the CVB website ([APHIS CVB Biologics and Guidance](#)). *The following terms are interchangeable throughout this document: USDA licensed, APHIS licensed, CVB licensed or combinations of USDA, APHIS, and CVB.*

Products may be manufactured in the U.S. by a licensee, or by a permittee if prepared in a foreign country and imported into the U.S. CVB grants a product license to a licensee and a permit to a permittee for each veterinary biological product that is proven to be safe, pure, potent, and efficacious. A specific claim for each product is approved based on pivotal efficacy and safety studies conducted to support licensure and is stated on the product labeling. Each serial of finished product is tested to ensure purity, safety, and potency prior to release onto the market.

To ensure pure, safe, potent, and efficacious CVB licensed products, the manufacturer (licensee or permittee) must meet the following standards:

- The manufacturing facility where the product is manufactured must pass inspection
- The product must be shown to be efficacious in a controlled clinical trial with data
- The product must be shown to be safe in host animal field studies
- The product and any materials used to make it must be tested to ensure the product is free of known disease agents
- The product must meet purity, safety, and potency standards
- Data must show the product remains potent throughout the product's shelf life

- The product's labeling must be accurate and appropriate and contain a licensee or permittee number, and a product code number (PCN). Label information may not be false or misleading.
- The product must be stored and transported according to label instructions

The following are general requirements for all labeling according to [9 CFR 112](#):

- Licensee or Permittee number generated by CVB (see explanation below).
- True Name generated by CVB to identify the components of the veterinary biological product. Products may share the same True Name
- Product code number (PCN) generated by CVB and related to the components of the veterinary biological product (p-products may share the same PCN)
- Name, address, and phone number of the producer (licensee or subsidiary) or permittee
- Full instructions for use, age, target species, route and schedule of administration, and any other vital information for the product's use, including caution and warning statements
- Storage temperature range for the product
- Slaughter withholding time unless the product is for use in a neonate or companion animal
- Disclosure of preservatives

At licensure, a pharmacovigilance system for recording adverse events is required for licensees and permittees in accordance with [Veterinary Services Memorandum No. 800.125, Preparation and Submission of Adverse Event Reports for Biological Products by Licensees and Permittees](#).

Following licensure, any allegation of false or misleading product claims or advertising are reviewed by CVB in accordance with [Veterinary Services Memorandum No. 800.98, Advertising and Promotional Materials](#).

An exemption from the CVB licensure requirement exists for licensed veterinarians. According to [9 CFR 107.1](#), a veterinarian under a veterinarian-client-patient relationship may administer animal-derived products prepared at the location where the veterinarian conducts day-to-day activities. Refer to the regulation for additional requirements that must be met for this exemption.

Under [9 CFR 107.2](#), states with their own intrastate veterinary biologics licensing programs may also be exempted from CVB licensure requirements. State-licensed products can only be used in that state. Currently, there are no states with active veterinary biologic licensing programs. California previously had a state program which met these requirements; however, as of 2010, the [California Department of Food and Agriculture, Animal Health Branch](#) no longer has the authority to authorize the production/distribution of biologics in California.

Overview of Regulation of Plasma and Serum Products in Canada

VDD versus CFIA regulation

The Veterinary Drugs Directorate (VDD) of Health Canada is responsible for licensing veterinary drugs. Veterinary drugs are subject to the requirements found under the Canadian *Food and Drugs Act* and *Regulations*. For a drug product to be imported for sale, sold or advertised in Canada, it must have a valid Drug Identification Number (DIN). Health Canada's [Drug Products Database](#) provides up-to-date information on drugs approved and marketed for sale in Canada. ***At the time of publication, there are currently no blood-derived drug products approved in Canada.***

Veterinary Biological Products Regulated and Licensed by CFIA

A list of CFIA-CCVB licensed equine antibody products is provided in [Appendix B](#).

The Canadian Centre for Veterinary Biologics (CCVB) of the Canadian Food Inspection Agency (CFIA) is responsible for licensing veterinary biologics including plasma and serum products used in horses. These products are manufactured and/or distributed in Canada under the legal authority of the [Health of Animals Act and the Health of Animals Regulations, Part XI](#). "Licensing" or "Registration" means regulatory approval from the CCVB to manufacture, distribute and/or sell veterinary biologics (VB) in Canada.

Products may be manufactured in Canada, the USA, or another country, with distribution in Canada. All manufacturing facilities must be approved by the CCVB including a review of the facility, personnel, manufacturing and quality control/quality assurance documents, and a pre-licensing inspection of all premises where manufacturing, testing, preservation, packaging, labeling, storage and distribution of the VB are performed. The CCVB's licensing requirements for veterinary biologics are generally similar to those of the USDA-APHIS-CVB, and data submitted to the CVB is also generally acceptable to meet the CCVB's requirements. In most cases, review by the CCVB is performed after USDA-CVB approval is complete; however, in emergency situations, exceptions can be made for concurrent reviews with the USDA-CVB.

General Criteria for Product Acceptability

- The product must be pure, safe, potent and efficacious.
- Each biologically active component must be relevant to infectious animal disease conditions and animal genetics in Canada.
- The product must be manufactured in a facility acceptable to the CCVB.
- The product must be produced and tested in accordance with generally accepted good manufacturing practices and quality assurance standards.

During the review process, data must be provided to support the purity, potency, safety and efficacy of the product and to support label claims. Studies supporting efficacy and safety must be conducted with serials equivalent to the final product

General Requirements for Labeling ([Veterinary Biologics Guideline 3.3](#))

- Assigned name
- Manufacturer
- Location of manufacturer
- Serial number
- Establishment License Number- as issued by the regulatory authority of the country where the manufacturer is located (i.e., USDA Licensee or Permittee number)
- Directions for use, or instructions to consult a carton or package insert for full directions
- Expiry date
- All components, including antigens and preservatives
- Quantity of veterinary biologic in the container, expressed in metric units or doses
- Storage temperature expressed in metric units
- Withdrawal period, if applicable

As stipulated by Section 135.1 of the [Health of Animals Regulations](#), any "serious expected" or "serious unexpected" adverse events related to the use of a veterinary biologic, including lack of efficacy, must be reported to CCVB within 15 days of that information becoming known to the permit or license holder from a veterinarian or animal owner.

Under certain special circumstances, Canadian veterinarians may apply to the CCVB for permission to obtain a veterinary biologic that is unlicensed in Canada, for use under their supervision in research or in emergency situations. To obtain a Permit to Release Veterinary Biologics the veterinarian must provide the CCVB with adequate justification for the use of the unlicensed product in Canada and if granted the permit will generally be issued for specific serials (batches) of product

USDA Regulatory Requirements for Antibody Products

The regulatory requirements for equine blood-derived antibody products are found in [9 CFR 113.450](#). *Note: Canada does not have an equivalent guidance document on regulatory requirements for plasma or serum at the time of publication.*

Below is a summary of general requirements for antibody products:

Donor horses

The [9 CFR 113.450](#) regulations specify that animals used for the manufacture of antibody products shall be healthy. This health status is determined by physical examinations by, or under the direct supervision of, a licensed veterinarian and by tests for infectious diseases.

These animals must be maintained at the licensed establishment. Animals are tested for infectious diseases at regular intervals, and all records of testing and examinations must be maintained. The regulations stipulate that an animal that tests positive for an infectious disease shall not be used in the manufacture of antibody products. Before the first use of a horse for production of antibody products, the animal must be tested and found negative for the following per the 9 CFR regulations:

- Equine infectious anemia (EIA) by a laboratory approved by APHIS
- Piroplasmiasis (*Babesia equi* {*Theileria equi*} and *Babesia caballi*) at the NVSL (National Veterinary Services Laboratories)
- Dourine (*Trypanosoma equiperdum*) at the NVSL (National Veterinary Services Laboratories)
- Glanders (*Burkholderia mallei*) at the NVSL (National Veterinary Services Laboratories)
- Brucellosis by a laboratory approved by APHIS
- Equine parvovirus-hepatitis (EqPV-H) by a laboratory approved by APHIS (per [CVB Notice 19-03](#)).

Following initial donor horse testing, all horses are subsequently tested annually for EIA, and if housed with any other species, shall be retested for brucellosis. Horses are also tested annually for equine parvovirus-hepatitis per [CVB Notice 19-03](#). All horses used for production must be kept separate and isolated from any untested or positive animals. Any animal testing positive must be removed from the herd, and the remaining animals must be retested. Production will be suspended until the remaining animals all test negative not less than 28 days after removal of the positive animal.

An [Outline of Production \(OP\)](#), filed with CVB, describes in detail the testing and hyperimmunization/treatment of horses. If any of the antigens (vaccines) used to hyperimmunize donor horses are not a CVB licensed veterinary biological product, the antigens used must meet rigid requirements for purity, identity, and associated requirements as specified in [9 CFR 113.450](#). (This is in reference to antibody products used in donor animals to produce antibody products for a specific disease, e.g. *R. equi*, *E. coli*).

Manufacturing and Testing of Final Product

The OP also describes in detail the processing and testing of the blood-derived material used to produce a serial. All antibody products must be subjected to an inactivation procedure (cooling, heating, ionizing radiation, or other procedure acceptable to APHIS) to mitigate potential extraneous agents. All non-frozen liquid antibody products must contain at least one preservative. Purity and safety testing is required on final container samples for each serial and sub-serial of the product. This includes dried and liquid products for parenteral administration as well as dried products for oral use. Appropriate batch records are required to be kept on each serial of product produced, including testing results. Results of the testing for each serial and sub-serial are submitted to the CVB for approval to be sold and distributed.

The following are additional requirements for antibody products intended for treatment of failure of passive transfer in equid patients. In addition to all requirements noted above:

- Products must contain a specified minimum quantity of IgG per dose.
- Product must only be recommended for use in equine neonates.
- Products will contain the term “IgG” in the true name of the product.
 - *Exception: “Normal Serum, Equine Origin” produced by Colorado Serum Company. See explanation below in “Labeling”*
- An IgG Reference Product must be established and used to assess potency of subsequent serials. This potency reference is generally established during an efficacy trial using colostrum-deprived newborn foals, utilizing pre- and post-treatment neonate blood samples. Pre- and post-treatment serum IgG concentrations are determined using a RID (radial immunodiffusion) technique acceptable to CVB. The dosage used for this potency testing will be in accordance with label directions of the product. Any adverse reactions observed during potency testing must be recorded.

Labeling

One potential point of confusion for labeling of equine blood-derived products is the use of the term “Normal” in the True Name. Typically, products with “Normal Equine Plasma” or “Normal Equine Serum” labels are considered non-USDA CVB licensed products. However, there is one product on the market (see [Appendix A](#)) – “Normal Serum, Equine Origin” produced by Colorado Serum Company which **is USDA CVB licensed** and sold under Colorado Serum Company or its subsidiary Professional Biological Company. The reason these labels contain “Normal” in the True Name but are legitimately licensed products reflects when these were first licensed, very early in the genesis of licensed antibody products. Taking into account the aforementioned exceptions, practitioners should recognize that all other products with “Normal Equine Serum” or derivatives on the label are likely non-USDA CVB licensed products.

How may a veterinarian verify a licensed product with a specific therapeutic claim approval?

USA

1. Identify the licensee or permittee number on the label. Each CVB licensed product must bear a CVB generated unique identifier for the manufacturer.
 - a. Licensee number: A U.S. Veterinary Biologics Establishment License Number/Veterinary License Number (VLN or licensee number) on the label as a number of three digits, e.g. 333.
 - b. Permittee number: In the case of a Permittee, the label will have the U.S. Veterinary Biological Product Permit Number/Veterinary Permit Number (VPN or permittee number) as a three-digit number followed by a letter, e.g., 333A.

2. Consult the [USDA Veterinary Biological Product Catalog](#). The catalog is a living document updated quarterly.
3. Contact the product manufacturer. Contact information for USDA licensed equine biologic product manufacturers is provided in [Appendix D](#).

CANADA

1. Consult the [CFIA Veterinary Biologics Licensed Database](#).
2. Consult the product manufacturer.

The AAEP would like to thank Dr. Amy Gill of the USDA, Dr. Sheila Tan of the CFIA's Canadian Centre for Veterinary Biologics, and Drs. Hélène Chagnon and Elise Tatone of Health Canada's Veterinary Drugs Directorate for contributing to this whitepaper.

White paper approved by the AAEP Board of Directors - 2022.

Appendix A: USDA Licensed Equine Antibody Products (as of 2022)

For up-to-date products and manufacturers, consult the [USDA Veterinary Biological Products Catalog](#).

PRODUCT	COMPANY	INDICATION
Normal Equine Serum Normal Serum	Colorado Serum Company	Indicated as an aid in the nonspecific treatment of equine infections and disease conditions
Normal Serum-Equine Normal Serum	Professional Biological Company, a subsidiary of Colorado Serum Company	Indicated as an aid in the nonspecific treatment of equine infections and disease conditions
West Nile Virus Antibody	Colorado Serum Company	Treatment of disease caused by West Nile Virus
ENDOVAC-Equi® <i>Salmonella Typhimurium</i> Antiserum	Endovac Animal Health LLC	Recommended for attenuating the effects of <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> when administered prior to challenge
HiGamm-Equi IgG	Lake Immunogenics, Inc.	Use in the treatment of failure of passive transfer in the neonate
Plasmune IgG	Lake Immunogenics, Inc.	Use in the treatment of failure of passive transfer in the neonate
Pneumomune-Re <i>Rhodococcus Equi</i> Antibody	Lake Immunogenics, Inc.	Use in the prevention or reduction in severity of <i>Rhodococcus equi</i> pneumonia in the neonate
High-Glo Equine IgG	Mg Biologics, Inc.	Treatment of failure of passive transfer for neonatal foals

Antidote 3 Rattler Antivenin	Mg Biologics, Inc.	Neutralizes venom from rattlesnakes, copperheads, cottonmouths/water moccasins
ReSolution <i>Rhodococcus equi</i> Antibody	Mg Biologics, Inc.	Use as an aid in the control of foal pneumonia caused by <i>Rhodococcus equi</i> by reducing disease severity
Equiplas IgG	Plasvacc USA, Inc.	Use in neonatal foals for treatment of failure of passive transfer
Equiplas B <i>Clostridium Botulinum</i> type B Antitoxin	Plasvacc USA, Inc.	Prophylactic administration to foals less than 1 month of age and adult horses with probable exposure to <i>Clostridium botulinum</i>
Equiplas Plus IgG	Plasvacc USA, Inc.	Use in neonatal foals for treatment of failure of passive transfer
Equiplas R <i>Rhodococcus equi</i> Antibody, IgG	Plasvacc USA, Inc.	Use in foals for failure of passive transfer and/or as an aid in the management of <i>Rhodococcus equi</i> infections
Equiplas REA <i>Rhodococcus equi</i> Antibody	Plasvacc USA, Inc.	Administration as an aid in the management and control of respiratory disease associated with <i>Rhodococcus equi</i> infections
West Nile Virus Antibody	Plasvacc USA, Inc.	Passive immunity as an aid in the control of disease associated with West Nile Virus in adult horses
Seramune I.V. IgG	Sera, Inc.	Treatment of failure of passive transfer in neonatal foals
Seramune Oral IgG	Sera, Inc.	Treatment for failure of passive transfer in neonatal foals

Appendix B: CFIA Licensed Equine Antibody Products (as of 2022)

For up-to-date products and manufacturers, consult the [CFIA Veterinary Biologics Licensed in Canada Database](#)

PRODUCT	COMPANY	INDICATION
Proplasma Normal Equine Plasma	Mg Biologics, Inc. **Not USDA Licensed**	Treatment of failure of passive transfer for neonatal foals
Equiplas IgG	Plasvacc USA, Inc.	Use in neonatal foals for treatment of failure of passive transfer
Equiplas Plus IgG	Plasvacc USA, Inc.	Use in neonatal foals for treatment of failure of passive transfer
Equiplas R <i>Rhodococcus equi</i> Antibody, IgG	Plasvacc USA, Inc.	Use in foals for failure of passive transfer and/or as an aid in the management of <i>Rhodococcus equi</i> infections
Equiplas REA <i>Rhodococcus equi</i> Antibody	Plasvacc USA, Inc.	Administration as an aid in the management and control of respiratory disease associated with <i>Rhodococcus equi</i> infections

Appendix C: Benefit of USDA Regulation of Plasma and Serum Products

Requirement	Benefit
Donor animals must be healthy	Increases quality of product and reduces potential disease transmission risk
Donor animals maintained at licensed facility	Reduce risk of introduction of disease agents
Regular testing of donor animals for infectious diseases: (EIA) (Dourine) (Piroplasmosis) (Glanders) (Brucellosis) (Equine Parvovirus)	Reduce risk of introduction of disease agents
Regular facility inspections	Assure quality and health standards are maintained
Submitted and approved Outline of Production	Assure quality, safety and uniformity of product
Submission of test results for every serial of product and if satisfactory, released by CVB	Assure product meets all requirements for potency and purity
Demonstration of shelf life of product	Assure potency of product throughout dating
Process in place to record reported adverse events	Monitor safety of product in the field

Retention of all production records	Assure consistency of product and can be audited to assure compliance
Approved labeling	Assure appropriate product claims and accurate product information
Testing and assay methods meet USDA requirements	Assure product quality, purity, and safety
Safety testing of final product	Assure product safety
Efficacy studies approved to support claims on labeling	Assure product effectiveness
Process in place for advertising oversight	Assure honest and accurate advertising claims

Appendix D: Contact Information for USDA Licensed Equine Biologic Product Manufacturers

COLORADO SERUM COMPANY and PROFESSIONAL BIOLOGICAL COMPANY AMERICANA LABORATORIES, INC.

4950 YORK STREET, P.O. BOX 16428, DENVER, CO, 80216-0428
303-295-7527
Email: colorado-serum@colorado-serum.com
<https://colorado-serum-com.3dcartstores.com/>

ENDOVAC ANIMAL HEALTH LLC (A subsidiary of IMMVAC, INC.)

6080 BASS LANE, COLUMBIA, MO, 65201
800-944-7563
573-874-7108 fax
<https://endovacanimalhealth.com/>

LAKE IMMUNOGENICS, INC.

348 BERG ROAD, ONTARIO, NY, 14519
800-648-9990
585-265-2306 fax
<http://www.lakeimmunogenics.com/>

MG BIOLOGICS

2366 270th ST., AMES, IA, 50014
877-769-2340
Email: plasma@mgbiologics.com
<https://www.mgbiologics.com/>

PLASVACC USA INC.

1535 TEMPLETON ROAD, TEMPLETON, CA, 93465
800-654-9743
805-434-0321
805-434-2720 fax
Email: usmail@plasvaccusa.com
<http://plasvaccusa.com/>

SERA, INC.

P.O. BOX 15866, SHAWNEE MISSION, KS, 66285-5866
913-541-1307
913-541-1712 fax
Email: info@seramune.com
<http://seramune.com/>

Additional Resources:

Arroyo, Luis G et al. *Plasma transfusions in horses with typhlocolitis/colitis*. The Canadian veterinary journal vol. 60,2 (2019): 193-196.

Divers TJ, et al. *New Parvovirus Associated With Serum Hepatitis in Horses After Inoculation of Common Biological Products*. *Emerg Infect Dis* 2018;24 (2) 303-310.

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Kahn S, Blodgett G, et al. *Transfusion With 2 L of Hyperimmune Plasma is Superior to Transfusion of 1 L or Less for Protecting Foals Against Subclinical Pneumonia Attributed to *Rhodococcus equi**. *Journal of Equine Veterinary Science*, Volume 79, 2019. Pages 54-58.

Kopper J.J, et al., *Outcome of horses with enterocolitis receiving oncotic fluid support with either plasma or hetastarch*. *Can Vet J*, 2019. 60(11):p1207-1212.

McClure, J.T., et al., *Evaluation of IgG concentration and IgG subisotypes in foals with complete or partial failure of passive transfer after administration of intravenous serum or plasma*. *Equine Vet J*, 2001. 33(7): p. 681-6.

DeLuca, Jeannine L. DVM; J. T. McClure, DVM, MS, Diplomate ACVIM; D. Paul Lunn, BVSc, MS, PhD, MRCVS, Diplomate ACVIM; and Justin Miller, BSc, *Evaluation of IgG Concentration in Foals with Failure of Passive Transfer after Administration of Intravenous Serum or Plasma* in *Proceedings. 47th Annual Conv Am Assoc Equine Practnr*, 2001:350.

McTaggart, C., J. Penhale, and S.L. Raidala, *Effect of plasma transfusion on neutrophil function in healthy and septic foals*. *Aust Vet J*, 2005. 83(8): p. 499-505.

Peek, S.F., et al., *Prognostic value of clinicopathologic variables obtained at admission and effect of antiendotoxin plasma on survival in septic and critically ill foals*. *J Vet Intern Med*, 2006. 20(3): p. 569-74.

Tomlinson JE, Van de Walle GR, Divers TJ. *What Do We Know About Hepatitis Viruses in Horses?* *Vet Clin North Am Equine Pract* 2019;35(2) 351-362.