
White Paper:
Information on Equine Plasma & Serum
Products for the Equine Practitioner

Developed by the
Biological and Therapeutic Agents
Committee



Introduction

Historically, questions regarding equine blood product therapeutic claims, efficacy, safety and regulatory oversight have been a source of potential confusion for equine practitioners. Over the past decade, issues surrounding these products have consistently appeared on the agendas of the AAEP's Biologic and Therapeutic Agents Committee as well as the annual Forum.

The purpose of this white paper is to provide equine practitioners with factual information on equine plasma and serum products. The paper will focus on differentiating licensed from non-licensed products to aid veterinarians in making informed therapeutic choices.

The white paper will not take a position on the inherent value of these products or attempt to provide overall guidance on appropriate clinical use. However, references for general background information as well as a literature review of recent refereed publications are contained in the paper for those interested in obtaining current "standard of care" opinions.

Summary of key information contained in this paper:

- Not all plasma, serum and blood products being sold are licensed products that receive active oversight from a U.S. regulatory agency.
- Determining the status of these products can be confusing since some are licensed with regulatory approval for a specific claim but may be marketed and advertised for additional claims for which they are not approved.
- When available, the use of a licensed product is preferred over a non-licensed product. (See Table 1).
- The best way to confirm that a product is licensed is to contact the USDA Center for Veterinary Biologics at: CVB@APHIS.USDA.gov or go to the web site WWW.APHIS.USDA.gov/animal_health/vet_biologics or call (800) 752-6255.

Differences between Licensed and Non-licensed Products

Some veterinarians may not realize that they are administering non-licensed equine plasma and serum products to their patients. The dilemma for the equine practitioner is to understand the differences between licensed and actively regulated products versus those that are not licensed and not regulated by the federal government. The ramifications for both the patient and the practitioner are significant. Unfavorable clinical outcomes and less than optimal patient care considerations emphasize the importance of understanding the relevant information needed to make appropriate product choices.

Regulatory Considerations

Equine plasma products which make specific claims such as "treatment of" or "prevention of" are under the regulatory authority of the United States Department of Agriculture/Animal Plant Health Inspection Service (USDA/APHIS), Center for Veterinary Biologics (CVB), by virtue of the Virus-Serum-Toxin Act. (See biologics in the terminology section below.) The regulatory category for products of this type is

referred to as Antibody Products. The purpose of this regulation and oversight is to provide the market with products which have been demonstrated to be safe, efficacious, and potent. The key objectives of the regulation of equine plasma (antibody) products include the following:

- For sale by licensed veterinarians
- Safe and free of disease agents
- Have demonstrated efficacy in a controlled clinical trial
- Have demonstrated field safety in the host animal
- Meets potency standards
- Has a demonstrated shelf life
- Accurate and appropriate labeling
- Appropriately stored and transported

Terminology as defined by the USDA for these types of products includes the following:

Antibody: An immunoglobulin molecule, having a precise glycoprotein structure, produced by certain cells of the B lymphocyte lineage in response to antigenic stimulation, and functioning to specifically bind and influence the antigens that induced its synthesis.

Bacterium-specific products: The true name of a bacterium-specific product shall include the term “antibody” if the component antibodies are directed against a nontoxin antigen or the term “antitoxin” if the component antibodies are directed against toxin; specify the organism against which the product is intended; and indicate the type of animal that supplied the component antibodies. If the antibodies are monoclonal, the term “monoclonal” shall be used.

Biological products: All viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live micro-organisms, killed micro-organisms, and the antigenic or immunizing components of micro-organisms intended for use in the diagnosis, treatment, or prevention of diseases of animals. 9 CFR (Subchapter E) 101.2(w). (These are the products under the regulatory authority of the USDA.)

Combination products: The true name of a product for treatment of failure of passive transfer as well as for the prevention and/or alleviation of a specific viral or bacterial disease shall be named according to the nomenclature prescribed above for virus-specific or bacterium-specific products.

Conditional license: USDA/APHIS may at their discretion issue conditional license for a product when a product has demonstrated purity, safety and a reasonable expectation of efficacy (but not a “standard” demonstration of efficacy as required for a fully licensed product). A conditional license is granted when there is an emergency condition, limited market, local situation or other special circumstance. The conditional license is granted for a specified time period. To obtain reissuance of product license, the licensee must provide date and information obtained since the license was issued.

Failure of passive transfer products: The true name of a product for treatment of failure of passive transfer shall include the term “IgG” and indicate the type of animal that supplied the component IgG.

Failure of passive transfer: A condition of neonates characterized by an abnormally low concentration of circulating maternal IgG.

IgG (Immunoglobulin G): One of the several recognized classes of structurally related glycoproteins whose representatives included all known antibodies.

Monoclonal: Produced by or derived from the offspring of a single common progenitor cell.

Virus-specific products: The true name of a virus specific product shall include the term “antibody,” specify the disease for which the product is intended, and indicate the type of animal that supplied the component antibodies. If the antibodies are monoclonal, the term “monoclonal” shall be used.

9 CFR: Title 9 Code of Federal Regulations is the regulatory document which outlines all requirements for biological products licensed by the USDA. These documents can be accessed on the Center for Veterinary Biologics Web site at:

http://www.aphis.usda.gov/animal_health/vet_biologics/vb_cfr.shtml

The following are general requirements for all USDA licensed antibody products:

The regulations specify that animals used for 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. The animals are tested for infectious disease at regular intervals and all records of testing and examinations must be maintained. Before the first use of a horse for antibody production, the animal must be tested and found negative for:

- Equine infectious anemia (EIA) by an approved APHIS laboratory
- Piroplasmiasis (*Babesia equi* {*Theileria equi*} and *Babesia caballi*)
- Dourine (*Trypanosoma equiperdum*)
- Glanders (*Burkholderia mallei*) at the NVSL (National Veterinary Services Laboratories).
- Brucellosis by an approved APHIS laboratory

Following initial testing, all horses are then tested annually for EIA and, if housed with any other species, shall be retested for brucellosis. 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 retested. Antibody production will be suspended until the remaining animals all test negative not less than 28 days after removal of the positive animal.

Appropriate batch records are required to be kept on each serial of product produced. All blood derived products which are not frozen after processing must contain a specific preservative within a range of concentration as specified in 9 CFR. Purity 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.

If the antigens (vaccines) used to hyperimmunize donor animals are not a licensed veterinary biological product, the antigens used must meet rigid requirements for purity, identity and associated requirements as specified in 9 CFR. (This is in reference to

vaccine products used in donor animals to produce antibody products for a specific disease, e.g. *R. equi*, *E. coli*).

The following are specific requirements for products for treatment of failure of passive transfer (specifically for horses). All requirements as noted above, plus:

- Contain a specified minimum quantity of IgG per dose.
- Recommended for use only in equine neonates.
- Products will contain the term “IgG” in the true name of the product.
- Qualification of 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 at least 20 colostrum-deprived newborn foals, utilizing pre- and post-treatment neonate blood samples. Pre- and post-treatment serum IgG concentrations will be determined using a RID (radial immunodiffusion) technique acceptable to APHIS. The dosage used for this potency testing will be in accordance with label directions of the product. Any adverse reactions observed during potency testing will be recorded.

Additional requirements of USDA licensed products:

- USDA licensed products will have on their label an establishment “license” number of three digits or in the case of a Permittee, a three-digit number followed by a letter, e.g., 333A.
- A formal review process whereby any allegations of false or misleading product claims or advertising will be reviewed by the CVB.
(Standards for labeling and Advertising Claims--Veterinary Services Memorandum 800.98)

It is important for the practitioner to understand the USDA has oversight only for those products which make any type of “disease prevention or treatment claims” as outlined above. (See definition of biological product in terminology section). For all other veterinary blood/serum products (which do not meet the definition of biologics as noted above), the Center for Veterinary Medicine (CVM) of the Food and Drug Administration (FDA) has regulatory authority/oversight. An example of such a product would be an equine serum or plasma product sold for “antibody supplementation” but with no specific disease prevention or treatment claim. However, from a practical perspective, this type of product is a very low regulatory priority for the CVM and, as a result, there is really no true oversight of these “non-licensed” products. It is also noted the CVM does not currently have/require any type of approval process for these products. The CVM does, however, encourage practitioners to report any adverse events associated with the use of these products directly to their (CVM) offices at www.fda.gov/cvm or call (888) FDA-VETS.

In recent years there has been an ongoing discussion between the USDA and the FDA regarding oversight of these products which are non-licensed and seem to “fall through the regulatory cracks.” Consequently equine plasma and serum products which make no disease or treatment claims are manufactured and sold with no regulatory oversight.

The practitioner needs to understand that if he or she is using such products:

- 1) They may not be providing optimal care for their equine patients.
- 2) The AAEP and AVMA PLIT recommends that veterinarians use a licensed product when one is available that achieves the clinician's desired results, because it has been tested and proven safe and effective for the labeled use(s).

When purchasing an equine plasma product, a veterinarian should ask if the specific product in question is a USDA licensed product. It is important to note that a specific company may sell both licensed and non-licensed equine antibody products.

One additional exception (and potential point of confusion): In general, products with "Normal Equine Plasma" or "Normal Equine Serum" labels are considered non-licensed products. However, there are two products on the market (see Table 2) – "Normal Equine Serum" and "Normal Serum-Equine" – which are USDA licensed. These are identical products, produced by Colorado Serum, but sold under two different labels—one by Colorado Serum and one by Professional Biological Company. The reason the labels of these products contain "Normal Equine Serum" verbiage but are legitimately licensed products goes back to the time the products 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" on the label are non-licensed products.

The major differences between licensed and non-licensed products are summarized in Table 1.

A third category of products that further complicates this issue are those products that may be licensed for a specific claim (such as treatment of the failure of passive transfer) but are sold for additional non-approved uses. For example, product X may be labeled for treatment of failure of passive transfer but could possibly be advertised, either in writing or verbally, containing anti-venom for snake bite or additional botulinum-type antitoxins. The practitioner must differentiate between a licensed and approved label claim written on the product label versus unapproved marketing claims which are not overseen by a regulatory agency. In some cases a licensed product may be promoted by a manufacturer as providing additional non-licensed claims. Product X described here would therefore have no regulatory substantiation that it contained anti-venom or additional botulinum-type antitoxins.

There is one other exception and that has to do with products licensed for intrastate use only. Within the Code of Federal Regulations (9 CFR 107.2), there is an exemption from the USDA licensure requirement if a specific state has its own program to license products. These products can only be used in that state. Currently, California is the only state that has a program which meets these USDA requirements.

How can product licensure and specific therapeutic claim approval be verified?

- When questions arise, the USDA can be contacted by going to CVB@APHIS.USDA.gov. The practitioner can leave a message at this site and a representative from the CVB will contact them.
- For a list of all products currently licensed by the USDA, a practitioner can also go to WWW.APHIS.USDA.gov/animal_health/vet_biologics.

Summary

Not all plasma and serum products currently being sold are licensed or actively regulated. Distinguishing between licensed and unlicensed products can sometimes be confusing but it is important for equine practitioners to understand these differences to be able to make appropriate therapeutic choices. When in doubt, the best way to confirm product licensing status is to contact the USDA. Some non-licensed products or licensed products making unapproved claims may provide a therapeutic benefit. However, without regulatory oversight, equine practitioners or clients have no way of knowing if product efficacy, safety and potency have been substantiated. Whenever possible, it is recommended and in the best interest of our equine patients to use licensed plasma and serum products for their approved label indications.

Table 1: Comparison of licensed versus non-licensed products

Table 2: Listing of current antibody products licensed for use in horses by the USDA (list may not be all inclusive)

³Contact information for licensed manufacturers

⁴General Information Reference and Related Articles

*The AAEP would like to thank Dr. Mary Beth Evans of the USDA and Dr. Chris Melluso of the FDA for their input and expertise in composing this whitepaper.

White paper approved by the AAEP Board of Directors – February 2009.

Table 1: Comparison of Licensed Versus Non-Licensed Products

Requirement	Benefit	USDA Licensed	Non-licensed
Donor animals must be healthy	Increases quality of product and reduces potential disease transmission risk	Yes	No
Donor animals maintained at licensed facility	Reduce risk of introduction of disease agents	Yes	No
Regular testing of donor animals for infectious diseases: (EIA) (Dourine) (Prioplasmosis) (Glanders) (Brucellosis)	Reduce risk of introduction of disease agents	Yes	No
Regular facility audits	Assure quality and health standards are maintained	Yes	No
Submitted and approved Outlines of Production	Assure quality, safety and uniformity of product	Yes	No
Submission of test results for every serial of product and if satisfactory, released by CVB	Assure product meets all requirements for potency and purity	Yes	No
Demonstration of shelf life of product	Assure potency of product throughout dating	Yes	No
Process in place to record reported adverse events	Monitor safety of product in the field	Yes	No
Retention of all production records	Assure consistency of product and can be audited to assure compliance	Yes	No
Approved labeling	Assure appropriate product claims and accurate product information	Yes	No
Testing and assay methods meet USDA requirements	Assure product quality, purity and safety	Yes	No
Safety testing	Assure product safety	Yes	No
Efficacy testing	Assure product effectiveness	Yes	No
Process in place for advertising oversight	Assure honest and accurate advertising claims	Yes	No

Table 2: USDA Current Licensed Equine Antibody Products

PRODUCT	COMPANY	INDICATION
Equiplas IgG	Plasvacc	Use in neonatal foals for treatment of failure of passive transfer.
Equiplas B <i>Clostridium</i> <i>Botulinum</i> type B Antitoxin	Plasvacc	Prophylactic administration to foals less than 1 month of age and adult horses with probable exposure to <i>Clostridium botulinum</i> .
Equiplas J <i>Escherichia coli</i> Plasma	Plasvacc	Administration to modulate the immune response to endotoxic shock associated with Gram-negative infections.
Equiplas Plus IgG	Plasvacc	Use in neonatal foals for treatment of failure of passive transfer.
Equiplas R <i>Rhodococcus equi</i> Antibody, IgG	Plasvacc	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	Administration as an aid in the management of <i>Rhodococcus equi</i> infections.
Foalimmune IgG	Lake Immunogenics	Use in the treatment of failure of passive transfer in the neonate.
Higamm- Equi IgG	Lake Immunogenics	Use in the treatment of failure of passive transfer in the neonate.
Pneumomune- Re <i>Rhodococcus</i> <i>Equi</i> Antibody	Lake Immunogenics	Use in foals as an aid in the control of disease caused by <i>Rhodococcus equi</i> infection.
Seramune I.V. IgG	Sera	Treatment of complete or partial failure of passive transfer in foals.
Seramune Oral IgG	Sera	Treatment for failure of passive transfer in foals.
Normal Equine Serum Normal Serum	Colorado Serum	Indicated as an aid in the nonspecific treatment of equine infections and disease conditions.
Normal Serum- Equine Normal Serum	Professional Biological	Indicated as an aid in the nonspecific treatment of equine infections and disease conditions.
Endoserum <i>Salmonella</i> <i>Typhimurium</i> Antiserum	Immvac	Recommended for attenuating the effects of <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> when administered prior to challenge.
Equine Coli Endotox <i>Escherichia coli</i> Antibody	Novartis	Use in newborn foals as an aid in the prevention of colibacillosis and septicemia caused by K99 pilliated <i>Escherichia coli</i> .
High-Glo Equine IgG	Mg Biologics	Treatment for failure of passive transfer for neonatal foals.

Streptococcus Equi Antibody	Mg Biologics	Use in horses as an aid in the control of disease associated with <i>Streptococcus equi</i> infection. (Conditional license by USDA)
Equine IgG	American Veterinary Reference Labs	Treatment for failure of passive transfer for neonatal foals.

(Note: There are equine plasma products licensed in the state of California {not included in this list} for intrastate use only and which are not licensed by the USDA.)

3Contact Information for Licensed Manufacturers:

COLORADO SERUM COMPANY

4950 YORK STREET, P.O. BOX 16428, DENVER, CO, 80216-0428
 {PROFESSIONAL BIOLOGICAL COMPANY
 4950 YORK STREET, P.O. BOX 16428, DENVER, CO, 80216}
 303-295-7527
 800-525-2065
 303-295-1923 fax
www.colorado-serum.com
edlehigh@colorado-serum.com
www.professionalbiological.com

IMMVAC, INC.

6080 BASS LANE, COLUMBIA, MO, 65201
 573-443-5363
 800-944-7563
 800-944-7563
 573-874-7108 fax
www.immvac.com
immvac@immvac.com

LAKE IMMUNOGENICS, INC.

348 BERG ROAD, ONTARIO, NY, 14519
 585 265 1973
 800 648 9990
 585 265 2306 fax
www.lakeimmunogenics.com

MG BIOLOGICS

2366 270th ST., AMES, IA, 50014
 515-769-2340
 515-769-2390 fax
www.mgbiologics.com
mg@equineplasma.com

NOVARTIS ANIMAL HEALTH US, INC.
Farm Animal Business
1447 140TH ST., LARCHWOOD, IA, 51241
712-477-2811
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712-477-2686 fax
800-843-3386
www.livestock.novartis.com
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PLASVACC USA INC.
1535 TEMPLETON ROAD, TEMPLETON, CA, 93465
805 434 0321
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SERA, INC.
P.O. BOX 15866, SHAWNEE MISSION, KS, 66285-5866
913-541-1307
800-552-3984
913-541-1712 fax
www.seramune.com
sera@everestkc.net

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