

4.8 ANTIBODY PRODUCTS

Regulations and Policy

- Regulations are in 9CFR 113.450-499
- Where 113.450(h)(2)(ii) applies, see also 9CFR 113.30.
- [REDACTED]
- CVB Notice 99-26, alternative safety tests for oral products
- VS Memorandum 800.100 makes provision, **under specified conditions**, for considering exemption from using heat or ionizing radiation to treat equine plasma products for oral or parenteral administration to horses under 113.450(e)(1) and exemption from the mouse safety test under 9CFR 113.450.

- [REDACTED]
- [REDACTED]

Categories that Affect Requirements

- Antibodies to specific antigens (for diagnostics), including Monoclonal Antibodies: This is not in the scope of this chapter; see test kit requirements.
- Antibodies to specific antigens (disease claim): See the 9CFR (some specific antibodies are covered in the 9CFR); otherwise, as determined for the proposed claim
- Failure of Passive Transfer (FPT) products: See 9CFR 113.499.
- “Normal” serum: The CVB does not regulate normal plasma or colostrum. Although normal serum has been licensed in the past, normal serum is not considered for licensure (at this time.)
- Oral products (FPT and specific antibody against disease)
- Parenteral products (FPT and specific antibody against disease)
- Dried products (e.g., dried lacteal secretions)

True Names

- **FPT:** <animal species> IgG
 - Example: Bovine IgG
- **Specific antibodies:**
 - Bacterial: <Name of bacterium> <Antibody or Monoclonal Antibody>, <animal species> Origin
 - Example: Escherichia Coli Antibody, Bovine Origin
 - Example: Escherichia Coli Monoclonal Antibody, Murine Origin
 - Viral: <Name of virus or viral disease> Antibody, <animal species> Origin
 - Example: Duck Virus Hepatitis Antibody, Chicken Origin

- Note that no distinction is made in the True Name whether the specific antibody is derived from serum, plasma, or colostrum. “Chicken Origin” applies to egg yolk-derived antibodies as well.
- **Mixed claim products:** If the product has a claim for FPT and a specific Ab, this is reflected in the true name (e.g., Bovine IgG – Escherichia Coli Antibody, Bovine Origin).

Product Codes

All antibody products are in the 3XXX.XX series.

Source of antibody

- **Blood donors:** Must be from a closed herd on licensed premises. Random-sourced slaughter blood is not currently allowed.
- **Milk/colostrum donors:** Must be from a closed herd OR part of a Grade A dairy.
- **Egg yolk donors:** Must be from a closed flock OR part of a flock approved for table egg production for human consumption

Testing of Source Animals: See 9CFR 113.450(c)(2)

- **Horses:** As per the 9CFR (EIA, piroplasmosis, dourine, glanders, brucellosis) and also for EVA in untreated products. Firms may voluntarily do additional testing (e.g., WNV, equine parvovirus)
- **Cattle:** As per the 9CFR. If the cattle are in a Grade A Dairy supplying only lacteal secretions, they are exempted from brucellosis testing.
- **Sheep:** Brucellosis. Firms may voluntarily do additional testing.
- **Other species:** As specified in the Outline.
- Additional testing may be required, based on published scientific literature, if deemed necessary

Product Treatment

- 9 CFR 113.450(e) describes the required procedures for inactivation of potential contaminating organisms, including heat treatment or ionizing radiation: See 9CFR 113.450(e)(1-3) for acceptable protocols.
- Acceptable preservatives and concentrations are in 9CFR 113.450(f). See 9CFR 113.30 regarding testing for salmonella when preservatives are added.
- If not treated, a label warning is required.

Hyperimmunization antigens

- Must be a USDA-licensed product OR an antigen described in the Outline. Generally, hyperimmunization antigens are subject to Master Seed testing and approval (see 9CFR 113.450). If indicated, the reviewer may grant exemptions to some of the requirements for Master Seed testing and/or to the assay required by the regulations (e.g., the sterility assay procedure).

- Some antigens have been obtained from commercial sources and used with a satisfactory Certificate of Analysis.

In regard to species IgG, label wording or advertising that discloses that donor animals are immunized against antigens that are not part of a normal vaccination program for that species, under normal conditions of husbandry for use (i.e., milk production) and a particular geographic region may constitute misleading information and may not be allowed. Hyperimmunization of donor animals, when it is not associated with the label claim and is not disclosed, may not be allowed, as it may constitute a safety issue: i.e., safety studies are generally required for the licensure of IgG products from hyperimmunized animals, particularly when the antigen is not a licensed biological.

Purity Tests

- Parenteral products must be tested by 9CFR 113.26.
- Oral Products: Purity requirements are described in 9CFR 113.450(h)(2). This allows a total bacterial count that is specified in the Outline, but coliforms, Salmonella, and fungi may not be present.

Safety Tests

- May use mice in accordance with 9 CFR 113.33(b).
- If mice are not satisfactory, host animals may be used (CVB Notice 99-26).

Potency Tests

- Minimum antibody content for FPT products is described in 9CFR 113.499.
- Nonspecific IgG is determined by RID, by kit or by firm assay. The RID kit or assay is considered to be validated (i.e., validation data are not required).
- Specific antibody products: The potency test must be specific for the antibody(ies) produced by the immunizing antigen OR the antibody presumed to be the one normally present in the product that protects against challenge (e.g., antibody against E. coli K99 in colostrum from cattle not immunized with an E. coli antigen). The assay can be any possessing the appropriate performance parameters (e.g., sensitivity, specificity, dose response, ability to distinguish potent from subpotent serials, analytical range) and appropriate design for the analyte, sample material, and range of interest: For example, it could be an ELISA comparing the serial sample to the Reference and/or internal standards, an agglutination titer, a virus neutralization titer, or an approved Relative Potency (RP) ELISA. As for vaccines, an RP ELISA must be validated using the Reference and sample serials, with critical parameters determined as for a vaccine RP ELISA.

- CVB-PEL laboratory confirmatory testing: FPT products have IgG quantitation conducted by the Bacteriology Section. Products with specific antibody claims are tested by the Section that handles the antigen for which the antibody is specific.

Efficacy

- FPT products: The firm establishes a Reference Serial in a titer comparison study (9CFR 113.499). In 90% of animals, the increase in IgG concentration (pre-treatment vs. 24 hr post-treatment) must be at least equal to concentration of the IgG Species Standard approved by APHIS. Presently the CVB has an approved bovine and equine Species Standard. Serial release is done by comparison of the Serial up for release with the Reference Serial. That is, the Species Standard is used in the efficacy study, but the Reference Serial is used in potency testing as it is of the minimum potency. For other species, the firm may propose, with justification and/or data, the Species Standard to be used in the efficacy study.

Antibody functionality, 9CFR 113.499(b), is not required unless there is an indication that it be done (e.g., production differences between the Reference and finished product that could adversely affect efficacy).

- Specific antibody claims: A host animal challenge efficacy study is generally required. However, a reviewer may consider a host animal titer study, if an effective titer in the animal can be tied to a particular administration protocol of a product of a specified minimum titer. For example, if a particular animal titer is known to be effective in the literature, the firm may attempt to demonstrate the ability of their product to create that titer, upon administration, in the animal.
- Oral colostrum products can be labeled as supplements if study conducted at 50 gram level and replacer if conducted at 100 gram level.

Field Safety

- May be conducted with the efficacy study when very young animals are used. This is therefore in a small number of animals (ie oral products in newborn calves, etc.)

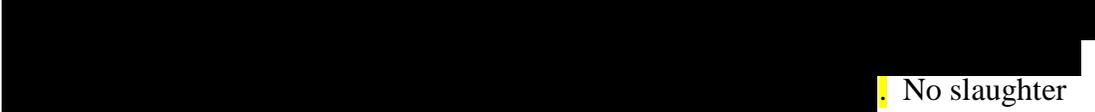
Labels

- Oral products are not recommended for use in animals older than 24 hours
- Parenteral products are not recommended for use in neonatal animals.
- Oral colostrum products can be labeled as supplements or replacers.

Cross-species recommendations are not allowed for FPT products, although these claims may be considered for minor use or minor species, if appropriate efficacy and safety data are accepted by the CVB.

- [REDACTED] Firms may claim a certain IgG level, but to do so they must be able to support presence of that level of IgG in each serial of product with a release

test. If they want to claim a level of antibody against a specific agent, they must similarly support the level of that specific antibody.

-  No slaughter withdrawal statement is needed for a non-injectable (i.e. oral, intranasal, immersion, etc.) product clearly labeled solely for neonatal animals because they do not enter the food chain (see VSM 800.51).