



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: STN: 125488/0

From: Lilin Zhong, Biologist, CBER/DH/LPD/HFM-345

Through: Michael Kennedy, Ph.D., Biologist (Team Lead), CBER/DH/LPD/HFM-345

CC: Edward Thompson, RPM, HFM-370

Applicant: Instituto Bioclon, S.A. de C.V.

Product: Crotalidae (pit viper) Immune F(ab')₂ (Equine) Injection
Trade name: Anavip[®]

Subject: Final Review of Original BLA – Viral Clearance

Recommendation

Approval

Executive Summary

The manufacturing processes for Anavip include three viral clearance steps: 1) Pepsin Digestion; 2) Heat Inactivation/(NH₄)₂SO₄ precipitation; 3) Nanofiltration with (b) (4) filters. These processes have been validated with four model viruses ((b) (4)) to achieve the following total Log₁₀ viral reduction factors:

(b) (4)

Transmissible spongiform encephalopathy (TSE)-related issues are reviewed by Maria L. Virata-Theimer, Ph.D., Chemist, CBER/OBRR/DH/LPD HFM-345.

Background Summary

This submission by Instituto Bioclon, S.A. de C.V. (Bioclon) for the product of Anavip[®] [Crotalidae (Pit-Viper) Immune F(ab')₂ (Equine) Injection] was received by CBER/FDA on 18-MAR-2013 as an original BLA for the management of patients with North American envenomation to include prevention of late and recurrent coagulopathies.

Anavip[®] is a sterile, nonpyrogenic, lyophilized, and polyvalent preparation of equine immune globulin F(ab')₂ fragments, manufactured from plasma of horses immunized with venom of *Bothrops asper* and *Crotalus durissus*. The product is made by pepsin digestion of horse plasma to remove the F_C portion of immune globulin, followed by fractionation and purification steps. The manufacturing procedure is nearly identical to that of Anascorp[®] (STN 12335/0), which was approved by the FDA in 2011. This submission used Anascorp[®] information as the references.

This review concerns with the evaluation of viral clearance capacity of the manufacturing process. Consult reviewer is Dr. Pei Zhang at CBER/OBRR/DH/LPD HFM-345.

CMC Review Summary

1. Anavip manufacturing process – Venom Production, Plasma Collection, and Plasma Fractionation

1.1 Venom Production

The (b) (4) venoms (*Crotalus Durissus* and *Bothrops Asper*) are purchased from a (b) (4) supplier. The venoms are analyzed for (b) (4)

1.2 Plasma Collection

All horses are required to receive vaccines against rabies, and West Nile virus in addition to the following viruses:

1. Venezuelan Equine Encephalitis (VEE)
2. East Equine Encephalitis (EEE)
3. West Equine Encephalitis (WEE)
4. Influenza
5. Tetanus
6. Rhinopneumonitis

Equine Virus Type	Vaccination	Screening	Status
Equine Infectious Anemia		(b) (4)	Tested (Horses tested by Bioclon)
Venezuelan Equine Encephalitis	+		Vaccination
Eastern Equine Encephalitis	+		Vaccination
Western Equine Encephalitis	+		Vaccination
Equine Influenza	+		(b) (4)
Rabies	+		Vaccination
West Nile Virus	+		Vaccination
Tetanus	+		Vaccination
Rhinopneumonitis	+		Vaccination
(b) (4)			None (does not exist in Mexico)
(b) (4)			None (does not exist in Mexico)

Selection of horses to be bled is based on the results of (b) (4)

1.3 Plasma Fractionation

(b) (4)

Table 1: The manufacturing process for virus clearance includes:

Manufacturing Step	Description
Pepsin Digestion	(b) (4)
Heat Inactivation and (NH ₄) ₂ SO ₄ precipitation	(b) (4)
Nanofiltration (Pall DV20)	(b) (4)

2. Viral Clearance

2.1. Choices of actual/model viruses for clearance studies:

Four model viruses, (b) (4), are used in validation studies (Table 2).

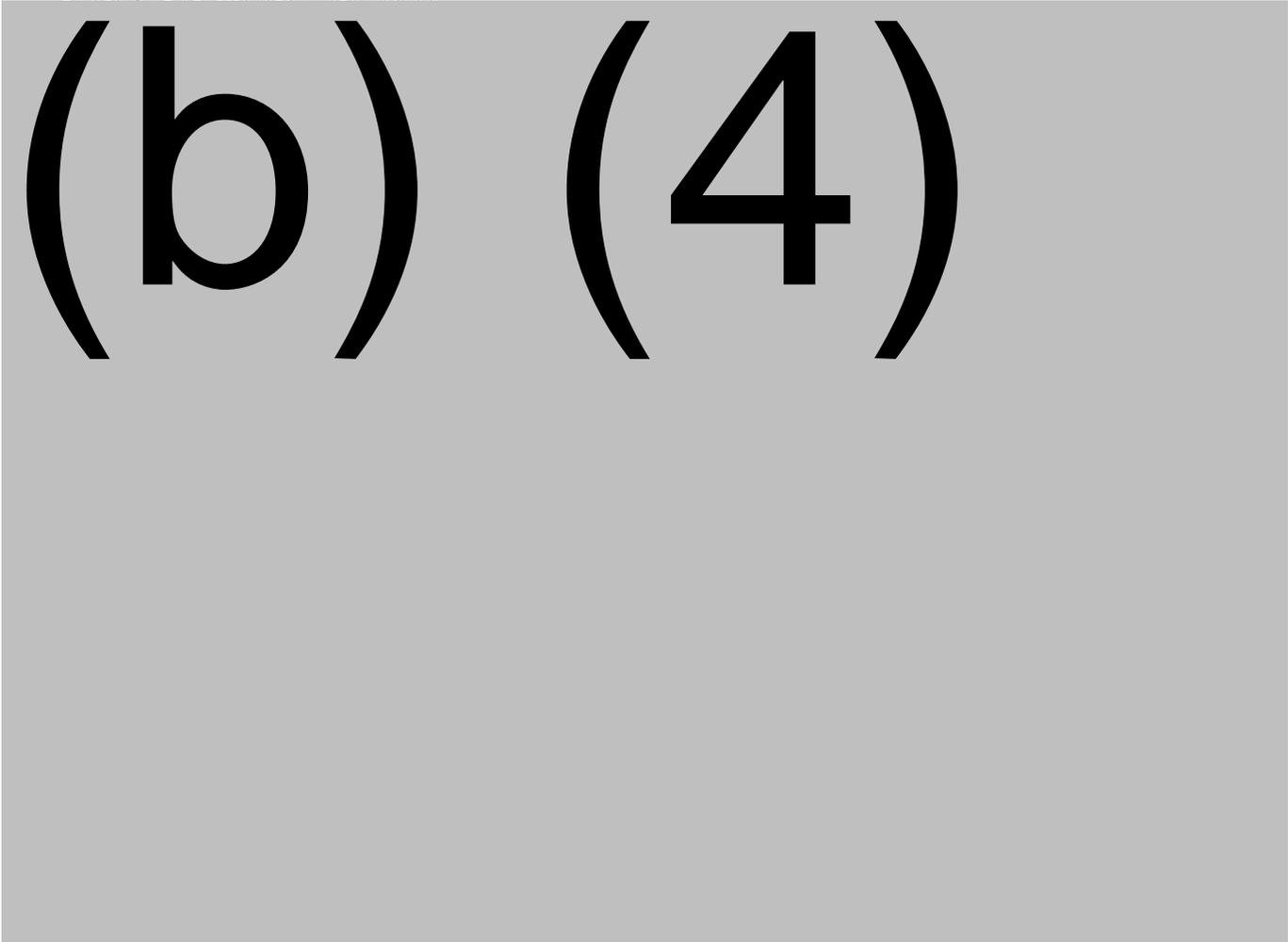
(b) (4)

- B. Additional information on the test article used for your viral clearance studies, including the date of manufacturing, the specific steps the test articles were taken.

Sponsor responded on September 5, 2013:

- A. All the critical parameters used at the commercial production of Anavip were tested during the viral clearance test. During the ^{(b) (4)} precipitation, a (b) (4) ammonium sulfate was used to test viral removal/inactivation under the worst-case condition (Table 3).

Table 3: Parameters were tested



(b) (4)

