



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

To: File for 125488

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Through: Michael Kennedy, Team Lead, CBER/OBRR/DH/LPD, HFM-345

CC: Dorothy Scott, Chief, CBER/OBRR/DH/LPD, HFM-345

Product: Crotalidae (Pit Viper) Immune F(ab')₂ (Equine) Injection; "Anavip"

Subject: Final CMC review for STN 125488/0, Crotalidae (Pit Viper) Immune F(ab')₂ (Equine) Injection; "Anavip"

Recommendation:

Approval.

Executive Summary:

Anavip is a lyophilized equine F(ab')₂ concentrate produced from the plasma of horses immunized with *Crotalus durissus* and *Bothrops asper* venom. Anavip is manufactured using the same manufacturing facility, processes, and controls as Anascorp, an antitoxin produced by Bioclon that was FDA approved in 2011. Data submitted by Bioclon supports the comparability and consistency of the manufacturing process and approval is recommended.

Background:

1. STN 125488/0 is an original BLA submission for *Crotalidae* (Pit Viper) Immune F(ab)₂ (Equine) Injection.
 - a. The drug product is a lyophilized equine F(ab')₂ concentrate produced from the plasma of horses immunized with *Crotalus durissus* and *Bothrops asper* venom.
 - b. Phase II and III studies were performed under IND 11275.
2. Process Validation Review:
 - a. The manufacturing process for Anavip is (b) (4) process for Anascorp (STN 125335/0). Bioclon verified that there had been no changes in the manufacturing process or facility for producing bulk drug substance since 2011 (STN 125488/0.14). Bioclon was requested to provide a comparison of the process parameters used for manufacturing both Anascorp and Anavip and did so in STN 125488/0.21.
 - i. While the manufacturing procedure and equipment (b) (4), the Anavip process combines (b) (4)

(b) (4)

3. Review issues

- a. Per the response to FDA information request of 22 August 2013 (STN 125488/0.21), Bioclon has not established maximum filtration times for their process. The average filtration times for each operation were examined for the process validation lots (b) (4) bulk drug substances; see Table 2, below. Bioclon indicated that the BPR will be modified to include maximum filtration times after at least (b) (4) lots.
 - i. Bioclon stated that filter clogging has not occurred during the manufacture of Anascorp or Anavip. In the event of a clog the event would be documented and investigated, while remaining product would be discarded.
- b. Likewise, a maximum time limit has not been set for the (b) (4) step. The average (b) (4) time for the process validation lots was (b) (4). Bioclon has stated that a maximum time limit will be set after at least (b) (4) lots.
- c. Three venom-related issues were discussed at the late cycle meeting:
 - i. Critical reagents for the potency assay (e.g. reference venoms) were not monitored on a stability program.
 - ii. Specific (b) (4) venoms was not demonstrated.
 - iii. (b) (4) were not set.
 - iv. Bioclon will address these limitations via post marketing commitments (see STN 125488/0.33 and 125488/0.41).

4. The manufacturing process for Anavip is as follows. The batch formula is provided in Table 3, below.

a. Venom Production

- i. (b) (4) venoms from *Crotalus durissus* and *Bothrops asper* are purchased from commercial suppliers and stored (b) (4)
- ii. The venom solution is tested against specified release criteria set for (b) (4)
- iii. Venom is stored at (b) (4).

- b. Plasma Collection (per SOP DM-PR-001, revision E, valid April 2011-2013)
- i. Animal husbandry issues including immunizations and bleeding procedures were reviewed in a consult by Dr. John Dennis, D.V.M.
 1. Animals are housed at a Bioclon facility in (b) (4)
 2. The released venom solution is used to immunize horses (b) (4)
 3. The primary immunization series is with (b) (4)
 - ii. Plasma antivenom titers are determined by the method specified in SOP M-CCP-001; horses with a minimum antibody titer of (b) (4) are entered into plasma collection.
 - iii. Horses in the plasma collection program are bled into (b) (4). Approximately (b) (4) of blood are collected per horse.
 - iv. RBCs are (b) (4)
 - v. The plasma from each horse is traceable through the master batch record.
 - vi. (b) (4) is added to achieve a final concentration of (b) (4) in the collected plasma.
 - vii. RBCs from (b) (4)
 - viii. Plasma is transported and (b) (4) at the Tlalpan facility and (b) (4)
- c. Drug substance manufacturing (Batch Production Record DM-PB-009, revision A)
- i. (b) (4)

