

From: Thompson, Edward
Sent: Thursday, August 22, 2013 10:01 AM
To: 'Jennifer Spinella (jspinella@raretx.com)'
Cc: Kennedy, Michael
Subject: Information Request for BL 125488/0

Contacts: Jennifer Spinella

Dear Ms. Spinella:

We are reviewing your March 16, 2013 biologics license application (BLA) for Crotalidae (pit viper) Immune F(ab')₂ (Equine) Injection. We determined that the following information is necessary to continue our review:

1. Please provide the CoAs for the Snake venom (*Bothrops asper*) Lot: (b) (4) and Snake venom (*Crotalus durissus*) Lot: (b) (4), used in your potency assay validation. Please provide details on the stability program for these 2 snake venom lots and the (b) (4) Lot (b) (4) standard.
2. Please (b) (4) _____). Please provide modified SOPs and validation protocol.
3. Please provide a comparison of the drug substance batch record version used to manufacture the process validation lots of Anavip to the drug substance batch record version used to manufacture the Anascorp comparator lots. This comparison should highlight any changes in procedure between the two batch records.
4. Please indicate the maximum filtration time allowed at each filtration/(b) (4) step used in the manufacture of drug substance, and the procedures followed in the event of a filter clogging event.
5. Please indicate the maximum time allowed for your (b) (4) step.
6. Please provide a batch formula for your drug substance, including minimum and maximum volumes of ingredients including the hyperimmune plasma and concentrates from manufacturing stage (b) (4).
7. The cresol specification for Anavip is set at NMT 0.99 mg/vial, which is significantly higher than for Anascorp®. Given the potential for adverse reactions due to cresol such as generalized myalgias and possible carcinogenicity, please provide the following:
 - a. An appropriate justification for the amount of cresol in Anavip.
 - b. Please clarify (b) (4) _____ in Anavip and what types of changes would be required for which manufacturing steps.

c. Submit a toxicological assessment on the safety of cresol at these doses.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your response to this information request as an amendment to this file by September 5, 2013 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is March 18, 2014.

Please send an email message acknowledging receipt of this request.

If you have any questions, please contact me at (301) 827-9167.

Sincerely,

Edward Thompson
Regulatory Project Manager
FDA/CBER/OBRR/DBA/RPMB

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