

**From:** Thompson, Edward  
**Sent:** Wednesday, October 16, 2013 10:38 AM  
**To:** 'Jennifer Spinella (jspinella@raretx.com)'  
**Cc:** Waites, Nancy; 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')<sub>2</sub> (Equine) Injection. We are providing the following comments and request for additional information to continue our review:

**1. Environmental Monitoring Action Levels for Aseptic Area**

For environmental monitoring, the action levels for the Grade (b) (4) area are acceptable (b) (4) (b) (4) for non-viable particulates, and (b) (4) (b) (4) for viable particles); however the environmental monitoring action levels for the viable particulates of the surrounding areas appear to be incorrect. The non-viable particle action level for a Class (b) (4) area is correct at (b) (4) (b) (4) but the viable monitoring action level is (b) (4) (b) (4) for surrounding areas. This is typically the action level for a Class (b) (4) area. The action level for a Class (b) (4) area is (b) (4) (b) (4). Please confirm this is a typographical error and the surrounding areas meet Class (b) (4) recommendations for both viable and non-viable monitoring.

**2. Vial Defect Allowances**

You state that the Critical defect specification during visual inspection is (b) (4) (b) (4)" and the Major defect specification is (b) (4) (b) (4). Typically, the critical defect allowance is tighter than the major defect allowance. Please provide the rationale for your specifications.

**3. Media Simulation**

The description of the media simulation does not provide a sufficient amount of detail of the simulated lyophilization process. Please provide a description of the simulated lyophilization process. It is unclear if a vacuum was pulled, if there was any kind of temperature control or temperature setting in the lyophilizer, or if the shelves were raised to fully stopper the vials at the completion of the simulated process.

**4. Lyophilization**

- a. Please provide the glass transition temperature of your product and explain how the recipe for Anavip accommodates this temperature.
- b. Please indicate if temperature of the product was monitored during the lyophilizer qualification. Also, please indicate if the temperature of the product is monitored during routine lyophilizer operations.

- c. Please provide the graph printout for the Anavip cycle run during the placebo run during the lyophilizer qualification. In addition, provide the graph printout from all three conformance runs.

**5. Biological Indicators**

Please provide the D-value of the biological indicators used in the autoclave and lyophilizer qualification tests.

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 November 6, 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