



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality

**To:** Administrative File, STN 125389/0, IGIV (Human)  
**From:** Destry Sullivan, Acting Branch Chief, CBER, DMPQ, MRB II, HFM-676  
**Through:** Laurie Norwood, Deputy Division Director, CBER, DMPQ, HFM-676  
**Subject:** Review of the third Complete Response submitted by Biotest Pharmaceuticals Corporation to provide for manufacture of IGIV at their Boca Raton, Florida facility.

Final action due date: December 26, 2012

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**Recommended Action:**

Approval

**Summary:**

Biotest Pharmaceuticals Corporation (Biotest) submitted this CR on October 26, 2012. Two DMPQ CR questions were responded to in this submission. The scope of this review is limited to those DMPQ CR questions.

**Review Narrative:**

This narrative consists of a repeat of the original DMPQ CR questions in italics, followed by Biotest's response and subsequent analysis.

*1. Your reported bioburden results in your cleaning validation report exceeded the revised acceptance limit -----(b)(4)-----.  
Please provide additional validation studies for the (b)(4) to support that your cleaning procedures are capable of reducing bioburden to meet the acceptance limit.*

Biotest responded as follows:

Biotest performed three CV runs on their worst case ----(b)(4)----, and -(b)(4)- for each of the additional -(b)(4)--. These were all full CV runs. All acceptance criteria were met.

*2. We noted that the ----(b)(4)---- solution interferes with your -----(b)(4)-----  
----- testing performed for the -----(b)(4)----- cleaning validation, and prevent you from demonstrating the ability of your cleaning process to remove product residual. Please perform residual protein analysis on -----(b)(4)----- post-cleaning --(b)(4)--- samples with appropriate acceptance criteria, and submit the data for review.*



Biotest responded as follows:

Biotest executed three additional cleaning validation runs for the ----(b)(4)----  
----- (b)(4)----- . Acceptance criteria were as follows:

- ----(b)(4)-----
- ----(b)(4)-----  
-----  
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- ----(b)(4)-----
- ----(b)(4)-----  
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- ----(b)(4)-----
- ----(b)(4)-----
- ----(b)(4)-----

Testing met acceptance criteria with two exceptions. Two (b)(4) did not meet the acceptance criteria for ----(b)(4)----) on Run 1 and Run 2. Biotest performed an additional run (Run 4) in which all acceptance criteria were met. While this is not ideal (Biotest should have performed one more run to meet the criteria outlined in its protocol), this is acceptable here for the following reasons:

The origin of the CR question was to have the firm obtain a more product specific metric than (b)(4), as the firm was having issue in meeting low (b)(4) specifications due to the nature of the manufacturing step. Therefore, they could have only evaluated cleaning by using the residual protein assay and satisfied the requirements of the CR question.

The firm exceeded (b)(4) acceptance criteria for the two out of specification -----(b)(4)-----  
-----, respectively. Given the point in manufacturing that the ----(b)(4)-----  
occupies, I feel their acceptance criterion is too restrictive ((b)(4) specifications). Therefore, the ability of Biotest to clean this column sufficiently has been demonstrated.