



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

Date: August 12, 2011

To: To File (BLA STN 125389/0)

From: Malgorzata G. Mikolajczyk, Biologist
CBER/DH/LPD, HFM-345

Through: Michael Kennedy, Ph.D., Team Leader
CBER/DH/LPD, HFM-345

CC: Lilin Zhong, Biologist, Co-chairperson
CBER/DH/LPD, HFM-345

Applicant: Biotest Pharmaceuticals Corporation (BPC)

Product: Immune Globulin Intravenous, Human 10%
Trade name: Biotest-IGIV

Subject: Final Review: Biotest BLA: Process Validation

Recommendation

A Complete Response (CR) Letter with the items listed below.

CR Letter item

1. The data from two conformance lots was insufficient to show robustness of the process parameters. The robustness studies provided did not assure robustness at the outer limits of the -----(b)(4)-----.

Background Summary

Biotest Pharmaceuticals Corporation is submitting a BLA for a 10% immune globulin intravenous (IGIV) for the treatment of Primary Immune Deficiency Disorders. As per the FDA recommendation in a June 25, 2009 Type C meeting, Biotest is utilizing a “two and two conformance lot approach” due to additional facility modifications at the Boca Raton, FL manufacturing site. Biotest submitted this BLA with 2 conformance lots and was planning on manufacturing 2 additional conformance lots in February 2011. Biotest also submitted comparability data for the clinical and conformance lots. The 2 additional conformance lots were not yet manufactured by the end of the review cycle; therefore, a CR letter will be issued.

Biotest-IGIV (Bivigam) is a liquid 10% (100 g/L) IgG preparation manufactured from Source Plasma according to a modified Cohn-Onclay cold alcohol fractionation process. There are 3 virus inactivation steps in the Biotest process: Precipitation and Removal of Fraction III and Depth Filtration, TNBP/Triton X-100 Treatment, and 35nm Virus Filtration.

The drug substance is stored and shipped to the contract filling site (----- (b)(4) -----) in the -----
--(b)(4)----- . Biotest is requesting -----(b)(4)-----.

The final product is formulated with (b)(4) mM glycine, (b)(4) mM NaCl, and (b)(4) Polysorbate 80. The drug product (final product) will be filled in (b)(4) glass vials in configurations of 5 g in 50 ml or 10g in 100 ml solution for infusion. The stoppers are -----(b)(4)----- rubber. Biotest is requesting a shelf life of 24 months at 2-8°C.

My review will focus on the Process Validation section of this BLA.

Process Validation Review

--(b)(4)--

9 pages redacted (b)(4)

Table 2.3.P.5-1

Specifications of Biotest-IGIV drug product (unlabeled vials)

Test parameters	Specifications	Method	SOP
Appearance	Clear to slightly opalescent liquid; colorless to pale yellow; free of turbidity and visible particles	Visual Inspection	QC2130
pH	4.0 – 4.6	pH	QC2129
Protein	90 – 110 g/L	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4) Purity (Protein Composition)	≥ 96% Gamma Globulin	(b)(4)	(b)(4)
Identity (Human)	Human - Positive	(b)(4)	(b)(4)
Chloride	100 – 140 mM	(b)(4)	(b)(4)
Glycine	200 – 290 mM	(b)(4)	(b)(4)
Polysorbate 80	0.15 – 0.25%	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
Sterility	Meets 21 CFR 610.12 Requirements	(b)(4)	(b)(4)
Pyrogenicity	Meets USP requirements at the 21 CFR 610.13 dose	USP/CFR	16E-02
IGIV Potency (Polio Titer)	(b)(4)	(b)(4)	(b)(4)
IGIV Potency (Measles Titer)	≥ 0.60x CBER Ref Std, Lot 176 or ≥ internal std	(b)(4)	(b)(4)
IGIV Potency (Diphtheria Titer)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
Particulate Matter	(b)(4)	(b)(4)	(b)(4)

*

•

(b)(4)

LETTER-READY COMMENTS (sent 7-8 April 2011; response received 9 May 2011)

1. The validation and characterization of your manufacturing process is not complete in that:

a. -----

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

-----.

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

4 pages redacted (b)(4)

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

2. Please describe how you set the bioburden limits.

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

-----.

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

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

3. Please provide DEV3234 mentioned in report FR-2009-13.

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

-----.

4. Please provide a table of all the deviations, including those that occurred in the QA laboratory. Please also include a brief description and the associated validation report number, if applicable.

Biotest provided the list of deviations.

5. Please provide an explanation for the ----- (b)(4) ----- following nanofiltration ----- (b)(4) -----.

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

6. Please provide the executed batch record for Lot --- (b)(4) ---.

Biotest provided the requested batch record.

I reviewed the batch record and found a couple comments that seem minor, but may not have been listed as deviations. These were not found on the list of deviations that was requested in Question 5. For example:

- i. -----
----- (b)(4) -----

- ii. -----
----- (b)(4) -----

Biotest did not complete their conformance batch production; therefore, the batch records for the future conformance lots will be evaluated to see if similar inconsistencies are seen.

7. Please provide the SOPs for the preparation of buffers used during the -----(b)(4)----- process.

Biotest provided the requested SOPs.

*I reviewed most of the SOPs and noted that the buffers are prepared by -----
---(b)(4)----- is checked and if not correct, the buffer is discarded.*

8. Please provide an SOP and raw test results for the plasmin/plasminogen and albumin tests.

Biotest provided the requested SOPs. The SOP and results appear acceptable.