

- b. Your cleaning validation acceptance criteria do not reflect cleaning process capability, as actual values observed during validation were well below set acceptance criteria. Please evaluate actual data obtained during cleaning validation studies, and set cleaning validation acceptance criteria that reflect your process capabilities.
 - c. Your use of a family approach to cleaning validation allows for introduction of equipment that has not yet been evaluated for cleanability, in that you do not perform at least one cleaning validation run for each equipment within each family. Please perform at least one cleaning validation run for the following equipment: -----(b)(4)-----
certain miscellaneous equipment (----- (b)(4)-----
-----, etc.) and submit the results of these runs for review.
4. You have not performed a bulk drug product shipping validation study that utilizes actual shipper, containers, and modes of transportation normally employed to transport product. Please perform the study and submit the results for review.

Summary:

Biotest Pharmaceuticals Corporation (Biotest) submitted this CR on October 26, 2012. 16 DMPQ CR questions were responded to in this submission. The scope of this review is limited to 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. *According to Validation Report VP-FR-3530, "Final Report for Performance Qualification of the IGIV ----(b)(4)---- Process," (Section 3.2.S.2.5) bioburden test results exceeded acceptance criteria at the -----(b)(4)----- steps. You refer to an investigation report (INV6001) but no mention was made of the identification of a root cause. Additionally, it appears that the corrective action was to -----
----- (b)(4)----- steps which resulted in acceptable results. This type of corrective action is unacceptable and represents a deviation to your validated process. Please indicate whether this ----(b)(4)---- is a reprocessing step or it represents a permanent change to your validated process. In either case, you should provide necessary protocol and a summary validation report to include justification why the root cause has not been identified and no preventive action has been taken to address the bioburden deviations.*

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

-(b)(4).

-(b)(4)

2. Please provide the following facilities and equipment information for the Biotest manufacturing site:

- a. Validation summaries for shared and dedicated equipment.
- b. Validation summaries including system descriptions and data for HVAC, utility systems, and cleaning systems after facility upgrade.

During the process of implementation of manufacturing of Biotest-IGIV, Biotest implemented some new systems, and extensively revalidated man existing systems. The final outcome of this process is a nearly complete validation/revalidation effort for the facility. Biotest was not inspected as part of the initial review of the BLA; therefore facilities information should have been completely documented in the initial BLA. Since submission of this information did not occur, facilities information will be reviewed in this memorandum. This review will only cover the most recent validation efforts associated with implementation of Biotest-IGIV, or for recent facility upgrades, as follows:

Water for Injection (WFI) Systems:

 (b)(4)- WFI systems are in place at Biotest's Boca Raton facility: WFI Systems -----(b)(4)-----

WFI System --- (b)(4) --- was revalidated in 2011 due to changes made during “Phase II” Facility upgrades. Changes include:

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

Installation, Operational and Performance Qualification (IQ, OQ, and PQ, respectively) testing was performed for the system. Sampling and testing of System ----(b)(4)---- Distribution Loops (POU) was conducted over a --(b)(4)--day period. Each POU valve was tested for --(b)(4)- WFI -
----- (b)(4)-----

of the original protocol sampling requirements. Testing also encompassed the WFI Storage Tank. Results met acceptance criteria

STN 125389/0

6 Pages Determined to be Not Releasable: (b)(4)

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

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

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

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

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

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

3. *With regard to your cleaning, sanitization and sterilization of equipment used at the Biotest facility, please provide the following:*
- a. *Validation protocols, summary reports and routine procedures for all equipment used in the manufacture of Biotest-IGIV. Include in your response clean and dirty hold times and containment procedures to prevent cross contamination of shared equipment.*
 - b. *Regarding the (b)(4)- system at the Biotest facility (Section 3.2.A.1.3.3.); the bioburden specification of ---(b)(4)---- is high. Similarly, the endotoxin specification is high at ----(b)(4)---- Both values exceed the limits of the -(b)(4)- used for final rinsing. Please provide your rationale for these specifications and provide data accumulated from your periodic monitoring program.*

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

1 Page Determined to be Not Releasable: (b)(4)

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

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

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

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

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

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

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

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

Biotest has also submitted microbiological data from the most recent monitoring performed for process equipment. In every instance, actual data is far below the limits they have set (all results were (b)(4) for bioburden, --(b)(4)-- for endotoxin). These results are not supportive of use of Biotest's microbiological acceptance criteria, in that these limits do not reflect the process capability of their cleaning procedures (see **CR Question #2**).

4. Please provide validation reports for the -----(b)(4)----- systems used at the Biotest facility.

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

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

(1) (4)

1 Page Determined to be Not Releasable: (b)(4)

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

All deviations observed in testing were corrected for and the parameters retested. All subsequent testing passed, and Biotest considers this system to be validated. While Biotest's conclusions regarding validation of this system appear well founded, given the information provided, this information should be verified during the next biennial inspection, as the final report does not provide sufficient detail to assure that testing was carried out as specified.

5. *The leachables study performed by -----(b)(4)----- for the ---(b)(4)----- used to -----(b)(4)----- from Biotest to --(b)(4)-- resulted in the detection of leachables in ----(b)(4)----- analysis. You conducted a toxicological risk assessment -----(b)(4)----- and concluded that the ---(b)(4)----- can be used without negative impact on ----(b)(4)----- quality; however, this report was not included in the submission for review. Please submit the report supporting your conclusions.*

Biotest submitted the report, entitled "Toxicology assessment of the -----(b)(4)----- -----." Based on this report, Biotest's conclusions that leachables observed in leachable studies performed in support of use of the ----(b)(4)---- appear appropriate (they contend that that there is negligible risk of adversely affecting the immunoglobulin structure, efficacy, and patient health). However, review of this type of information should be performed by a toxicologist, and this subject will be covered in the scope of a requested toxicology consult review.

The CR questions below relate to -----(b)(4)-----, the contract fill finish facility specifically for the manufacture of Biotest-IGIV. These questions have been addressed by the approval of BL STN 103945/5308 for filling at -----(b)(4)----- . Only differences between the product used to license this facility will be addressed here.

6. *Please provide a copy of --(b)(4)-- product changeover and line clearance procedures.*

Biotest provided a copy of --(b)(4)-- changeover and line clearance procedures: SOP 2-QC-006, "Area, line, and equipment clearance sign-off and Material verification" SOP 30-MFF-021, "Change over, set up, operation and maintenance of the -----(b)(4)-----" SOP 30-MF-030, "Change-Over, Operation and Preventative Maintenance of -----(b)(4)-----." These SOPs are sufficient for their intended purpose.

7. *Please provide Validation Summaries for critical process equipment and utilities at the --(b)(4)-- site (Section 3.2.A.1.1).*

This question was covered under BL STN 103945/5308.

8. *In section 3.2.P.7 you provide the specifications for the container closure system for the final product but did not provide studies conducted to assure the integrity of the container closure system or to ensure that the vial and stopper are non-reactive with the product. Please provide container closure integrity studies as well as extractable and leachable studies in support of the container closure system.*

Biotest container closure integrity test (CCIT) states that a minimum of (b)(4) media filled vials were subjected to CCIT. An additional (b)(4) vials will be used for positive, negative, and growth promotion controls. Testing will consist of -----

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

Results provided for this CCIT test were acceptable, as negative controls were negative, positive controls positive, and all (b)(4) experimental vials exhibited no growth.

----- (b)(4) ----- performed a qualitative extractables evaluation of the container closure system used for Biotest-IGIV. Conclusions of the study indicate that evaluated --- (b)(4) ----- glass vials sealed with a ----- (b)(4) ----- indicate that extractable compounds from the stoppers include the ----- (b)(4) ----- . None of these were detected in the ----- (b)(4) -----, however. --(b)(4)-- is was extractable in --- (b)(4) --- for the stoppers. A number of extractable compounds were present that could not be identified, but again, none of these were present in the ----- (b)(4) ----- subgroup.

9. *The section for aseptic process simulation (Section 3.2.A.1.4) lacks sufficient narrative to allow a complete evaluation of the process. Please provide the media fill protocol for the relevant filling line, including fill volume, type of medium used, incubation parameters, interventions, growth promotion results and summary reports for media fills. Include in your response the identification of what rooms are covered by the media fills and whether any facility isolates were used during growth promotion testing.*

This question was covered under BL STN 103945/5308.

10. Please provide validation summaries for -----(b)(4)----- filter validation.

11. Please indicate the method and procedures used to conduct 100% visual inspection of the final product at the --(b)(4)-- site.

Biotest stated that 100% visual inspection of the Biotest-IGIV final drug product is performed in accordance with --(b)(4)--SOP 2-FF-030 “Visual Inspection of Final Dosage.” The visual inspection is a manual process utilizing qualified operators. Line clearance is performed in accordance with SOP 2-QC-006 Area, Line and Equipment Clearance Sign-Off and Material Verification prior to and following 100% visual inspection. Inspections are performed using a ---

This answers only part of what is required to evaluate visual inspection of Biotest IGIV. Biotest should submit a complete description of the defect set used to evaluate --(b)(4)-- inspectors ability to detect defects in Biotest IGIV (see **CR Question #2**).

12. The reports submitted to support shipping validation conditions (Section 2.3.R with link to 3.2.R.4) do not provide enough information for review. Please provide the following:

a. Additional information regarding how this testing was conducted and on what material; BDS and/or final product.

Biotest responded that the testing was conducted as part of the routine qualification program for one of -----(b)(4)----- temperature controlled trucks. The data were collected on neither BDS nor final product. They were collected from the cargo hold of a loaded truck during a temperature controlled shipment. The truck was loaded with -----(b)(4)----- (see Pankaj Amin follow up questions, February 13, 2012. Further portions of this question will be address in the response to the February 13, 2012 information request, as Biotest’s has not answered the other portions of this question in detail).

b. The contents of the cargo hold during PQ testing. Include how the shipment will be monitored while en route and include an identification of temperature recording devices within a shipment load.

(for b. – d., please refer to Amin IR #18 and the review)

- c. *The rationale for monitoring temperature for only ---(b)(4)----- when transport of the BDS and final filled product would require a much longer cross-country trip.*
 - d. *Data to show the BDS and product temperature range during the ----(b)(4)-----
-----*
 - e. *The PQ summary shows a “Cargo Hold High Temperature During Test Period” time of (b)(4). Although not stated in the report, it is assumed that the temperature range of the study would mimic the storage requirements of the -----(b)(4) ----- °C. Please explain why the High Temperature reading did not result in a deviation.*
13. *Please provide validation summaries of the ----(b)(4)----- of materials used in the Biotest-IGIV filtration and filling process. Include a description of the (b)(4), a description of the ---
--(b)(4)----- process, -----(b)(4)-----, biological challenge and routine monitoring procedures.*

This question was covered under BL STN 103945/5308.

14. *Please provide validation summaries for the autoclaves used in the Biotest-IGIV ---(b)(4)----
----- . Include a description of the autoclaves, a description of the sterilization process, loading patterns, and routine monitoring procedures.*

This question was covered under BL STN 103945/5308.

Information requests pertaining to the CR:

Destry Sullivan April 5, 2012 information request:

- 1) *Please submit the investigation associated with ALR 11-WF-005, observed during qualification of your WFI system.*

Alert Level Report (ALR) 11-WF-005 was initiated in response to the isolation of *Stenotrophomonas maltophilia* from a microbial count test result. *Stenotrophomonas maltophilia* is characterized as an objectionable organism by the firm, and this organism is pathogenic, and frequently colonizes breathing tubes such as endotracheal or tracheostomy tubes, the respiratory tract, and indwelling urinary catheters.

Biotest submitted the deviation report, as requested. The report simply states what was found, and provides the results of three follow up samples that met acceptance criteria. No corrective action appears to have been implemented, nor is there mention of any procedures in place regarding what occurs when an organism such as this is detected.

Due to the time, with respect to the review clock, that this is being reviewed, and the fact that there was no pre-approval inspection associated with this BLA, -----

----- (b)(7)(e), (b)(5) -----
-----.

2) *For major process equipment, as outlined in the Appendices of Module 3, submitted in response to the CR letter, please specify the exact use of each piece of equipment. For example, you provide a general description of the use of --- (b)(4) -----, but you should be explicit in describing the equipments' function. If this information is present elsewhere in the BLA, please specify that location.*

Biotest provided more detailed descriptions of most process equipment; some of the major process equipment was not provided, however that information was provided in validation reports to sufficient detail. This information was requested for the purposes of streamlining the review. Information provided is summarized as follows:

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

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

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

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

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

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

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

STN 125389/0

1 Page Determined to be Not Releasable: (b)(4)

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

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

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

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

Supplied process equipment descriptions are adequate, and provide sufficient information to aid in the review of cleaning validation studies performed in support of this equipments' use.

3) *With respect to Cleaning Validation:*

- a. *Please justify use of (b)(4) cleaning validation acceptance criteria of either ---(b)(4)-final rinse sample) or ---(b)(4)----- sample) for cleaning of all product contact equipment used from ---(b)(4)-- of the manufacturing process on. Similarly, please justify use of a bioburden acceptance cleaning validation criteria in excess of ---(b)(4)----- specifications for all product contact equipment used from --(b)(4)- of the manufacturing process on. Finally, please justify use of a ----(b)(4)----- acceptance criterion of ---(b)(4)----- for all process equipment.*

-(b)(4)-

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

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

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

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

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

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

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

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

Overall, Biotest stated that, based on continuous monitoring data demonstrating process capability showing consistently lower values, it may consider the use of more stringent limits for future validation protocols.

Comments: A ----(b)(4)---(final rinse) and ----(b)(4)----- acceptance criteria are acceptable for cleaning of product contact equipment involved in steps ----(b)(4)----- . A ----(b)(4)---- limit of ---(b)(4)-- is not appropriate for cleaning validation of this type of equipment, as use of this criterion would allow carryover of residual cleaning agents. Also, given the actual values Biotest achieved during cleaning validation, particularly for bioburden, endotoxin, and ---(b)(4)----, use of their selected acceptance criteria does not reflect process capability (see **CR Question #3**)

b. Please define the method by which you choose locations to be (b)(4) sampled for (b)(4) and Bioburden.

Biotest provided adequate rationale for selection of (b)(4) sampling sites, and provided the locations of all actual (b)(4) sites.

- c. *Please specify that all equipment was soiled with a worst case soil with respect to what the equipment is used for.*

Biotest confirmed that all equipment was soiled with a worst case soil with respect to the intended use of the equipment. Soiling materials for the purpose of cleaning validation is representative of the natural process soil for equipment in each respective area. Furthermore, all cleaning validation protocols incorporate a minimum ---(b)(4)--- soiling period (dirty hold time) to present a “worst case” challenge to the cleaning procedure. Table 3 of their response describes the soiling materials used for performing cleaning validation for equipment in each area of production.

- d. *You state that due to Deviation DEV-7307 associated with the Final Report for the Cleaning Validation of the ---(b)(4)--- Cleaning of Fractionation Miscellaneous Equipment and Components, you will need to complete a, t least one additional cleaning validation run in 2012. Please specify if this run has been performed, and submit the results of this run.*

Biotest stated that the equipment associated with this deviation is not associated with Biotest IGIV, and therefore this is not pertinent to this review.

- e. *Please provide all actual numbers that are listed as “(b)(4)” from all Cleaning Validation reports if those numbers were associated with any (b)(4) negative control value deviation.*

Biotest provided all values. All values were ----(b)(4)-----, and therefore easily met (b)(4) specifications as well as the cleaning validation acceptance criteria.

- f. *You state that you “utilized a family approach to accomplish cleaning validation. Multiples of like equipment that are equivalent, in both process use and physical structure, were grouped into like equipment groups. After grouping, representative worst case units were selected for use in the testing. Once the cleaning validation is completed and approved, all units included in the group are considered as validated.” Please define all individual equipment that cleaning has not been actually validated for.*

Biotest revealed that -----(b)(4)----- certain miscellaneous equipment (----- (b)(4)-----, etc.) have not undergone cleaning validation (see **CR question #3**)

- g. *In relation to deviation DEV-7133, you state that the (b)(4) Rinse Control was collected from port ----(b)(4)----- on 3-11-2011. On the same day as the failure, a sample was collected from a different port (----(b)(4)---). Please justify using results from a different (b)(4) port to establish that port contamination of the port you actually used had not occurred.*

Biotest stated that DEV-7133 relied on (b)(4) monitoring data from port ----(b)(4)----- bracketing the date of the negative control failure (3-7-11 and 3-18-11) as the primary factor to conclude that the root cause of the deviation was not port contamination. Information

related to port ----(b)(4)---- which is in the same area as ----(b)(4)--- was included in the deviation to provide supplemental information on the state of the (b)(4) system used for cleaning validation on 3-11-11. Please note that cleaning validation protocols VP-PQ-3672 and VP-PQ-3673 also were performed on the 3-11-11 and each required negative control sample collection from the same point of use port as DEV-7133 (----(b)(4)-----); the control samples from each validation were well within the (b)(4) bioburden acceptance criteria, thus providing further evidence that port ----(b)(4)---- was not a source of contamination.

This conclusion is appropriate, and it is unlikely that port ----(b)(4)---- was a source of the observed contamination.

h. Please specify that, for any alteration of cleaning methodology found necessary to meet cleaning validation acceptance criteria, you have incorporated the necessary alteration into your routine practices.

Biotest confirmed that they have incorporated cycle changes into routine practice.

4) *Please define all tests performed as part of your -----(b)(4)----- Test, as noted in your report entitled, “Final Report for the Installation/Operational Qualification of the ---(b)(4)-----.” Additionally, please define the key performance aspects of the -----(b)(4)----- System, and state how you determine that the system met these aspects’ acceptance criteria.*

Biotest state that for the Performance Test, the -(b)(4)-- system temperature and ability to deliver ---(b)(4)- was tested. First, the -----(b)(4)-----

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

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

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

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

The specified acceptance criteria for the performance test were met with no deviations; therefore the system met the key aspects’ acceptance criteria as defined in the protocol.

- 5) *For the -----(b)(4)-----, please define all process steps where ----(b)(4)-- is in contact with the product, and if ---(b)(4)-- is filtered through a ----(b)(4)--- filter either systemically, or at points of use.*

This response is acceptable, as all product contact points for ---(b)(4)--- have assurance that the ---(b)(4)--- is sterile, and in most instances that assurance is gained by -----(b)(4)-----.

- 6) *For the -----(b)(4)-----, please specify environmental conditions required while these ----(b)(4)-----are in use, and then provide data that demonstrates that you are able to achieve said environmental conditions.*

Biotest provided environmental data that supports chosen classification, with no excursions.

- 7) *For your empty chamber temperature distribution study performed in support of Validation number VP-FR-3242-2 for Autoclave (b)(4), please define your temperature setpoint, and please explain the large temperature variation between thermocouples, more than (b)(4), observed during the study.*

This response is acceptable, and the thermocouple data supports this claim.

- 8) *With respect to the -----(b)(4)-----, please define normal -----(b)(4)-----, and then relate this normal ----(b)(4)----- to the -(b)(4)-- evaluated in the -----(b)(4)---- (see section 6.2.8, Table 7).*

Biotest stated that the -----(b)(4)----- only runs at full (b)(4) which is ---(b)(4)---. This is the normal ----(b)(4)----- used for production and is the (b)(4) that was evaluated in the -----
----- (b)(4)-----.

- 9) *For all ----(b)(4)---- units, please specify -----(b)(4)----- storage conditions, and provide data that support number of maximum uses for the ----(b)(4)---.*

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

*10) Please provide evidence that the ----(b)(4)----- at the -----(b)(4)-----
----- steps were part of the originally validated process, as you claim in your
response to CR question 4. You may direct us to previously submitted process descriptions
to respond to this question.*

Biotest noted that, as previously stated, ----(b)(4)----- at the -----(b)(4)-----
----- steps are part of the original validated process and do not represent any
change or deviation to the manufacturing process. Biotest provided old batch records to provide
direct evidence that this is the case.

Pankaj Amin's February 13, 2012 information request (starting from #13 of the actual
information request with #1 - #12 from OBRR reviewers):

Regarding Computer System

*13. Please verify that (b)(4) validated computer systems (----- (b)(4) -----)
were used during manufacturing of last two conformance lots.*

Biotest verified that ----- (b)(4) ----- were used during the manufacturing
of the last two (Phase II) conformance lots.

*14. Please provide rationale for not performing performance qualification for these new
systems.*

-(b)(4)

-(b)(4)

Testing performed in the OQ for these systems is sufficient, given the description of testing.

15. Please provide copies of the protocol that lists all functional testing, sequential testing, stress testing and/or network testing that were performed as part of the ----(b)(4)---- qualification including acceptance testing.

Biotech provided a complete copy of the protocol entitled, "Installation / Operational Qualification of the Main Process -----(b)(4)-----." Review of this 394 page protocol indicates that testing described is sufficient to evaluate operation of the system. -----(b)(7)(e)(b)(5)-----
-----,

16. Please provide all deviation and investigation reports relate to -----(b)(4)-----
----- noted during conformance lots (for example -incident of power lost, data lost,
wrong recipes used, tank overflows, computer lost connection with controller, system locks
up, a list of critical alarms, wrong product pathway).

Biotest stated that one deviation (DEV7362) has occurred that is potentially related to -----

-(b)(4)

This response is acceptable.

17. We noted that you have experienced several deviations during IQ/OQ performance, please provide if you have run any additional tests to verify that system is working without any additional deviations/comments?

Biotest noted in the final report summary that additional testing had been performed to verify that the system was working properly, post deviation and correction. Biotest confirmed this in their response.

Regarding Transport Validation

18. Please provide copy of study protocols and transport validation data for the minimum and maximum or worst case product load size including longest travel time for the multiple runs (typical three consecutive shipments tested on different days) to demonstrate that the product will remain under defined conditions during transport.

Biotest stated that because the -----(b)(4)----- temperature controlled trucks are intended to function as a moving cold room, ---(b)(4)--- does not normally conduct customer specific transport validation studies. The summary reports for an Installation/Operational Qualification and Performance Qualification for a representative temperature controlled truck are provided in the original BLA. The data represented by the summary reports were collected from the cargo hold of a truck containing -----(b)(4)----- during a temperature controlled shipment. This cargo load represents a worst case condition because a small amount of cargo leaves the most amount of empty cargo space to cool down.

This response is not adequate, and considered with other documents regarding transportation validation provided either in the original BLA documentation or in subsequent amendments, transportation of bulk product between Biotest Boca Raton and -----(b)(4)----- facility has not been validated (**see CR question #4**). This situation renders Biotest's response to Question 19, below, not relevant.

19. Please provide copy of quality agreement and your plan to perform an audit of the vendor's (---(b)(4)---) quality system.

Biotest provided a copy of quality agreement and it was considered inadequate to support transport validation.