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Biotest also supplied the complete defect set composition. This may be found in the submission, and the set is sufficient for its intended purpose. However, they did not provide any qualification or validation data demonstrating that they have completed the steps described above in order to qualify the visual inspection process and inspectors (see **Information Requests**, number 1, below). Biotest noted that during ----(b)(4)----- PAI (----- (b)(4) -----), performed for Biotest Pharmaceutical Corporation, STN 125389/0, CBER inspectors reviewed the visual inspection program, SOPs, defect libraries, training, and inspection boxes; in addition to observing an actual qualification test performed by an (b)(4) inspector. I agree that this information was reviewed and found acceptable, but Biotest’s current BLA should be updated to include this information.

3. *Cleaning validation is not adequate in that:*

- a) *Your use of a --(b)(4)--- cleaning validation limit of --(b)(4)----- is not appropriate for cleaning validation for equipment utilized in downstream process steps (b)(4), as use of this criterion would allow carryover of residual cleaning agents. Please reevaluate use of this cleaning validation acceptance criterion, select a criterion that would not allow for significant carryover of cleaning agent, and submit validation data demonstrating that you can meet the new acceptance criterion.*

Biotest responded as follows:

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Biotest also provided a table of cleaning testing values obtained during validation. A limit of ----(b)(4)----- for purification steps is acceptable for this equipment. For -----(b)(4)-----, see **Information Requests**, # 2, below.

- 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.*

Biotest performed a review of their validation data, and then submitted the following table listing new acceptance criteria:

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These criteria are supported by the data provided. All revised limits are acceptable with the exception of the criterion for cleaning of -----(b)(4)-----, as noted above, and that for the ---(b)(4)--- ----(b)(4)----- – see **Information Requests**, July 20 teleconference, below.

- 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)-----, and certain miscellaneous equipment (----- (b)(4)-----.) and submit the results of these runs for review.*

Biotest provided a high level summary of the cleaning validation performed for these (b)(4). However, the information provided was not sufficient to allow a full evaluation of cleaning of the (b)(4) (see **Information Requests**, Question 3, June 21, 2012, below).

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.*

Biotest submitted the results of a shipping validation study that utilized the actual shipper, containers, and modes of transportation normally employed to transport product. Biotest has adequately validated shipping of bulk drug product to their contract fill/finish facility, ---- (b)(4)-----.

Information Requests:

(Note that the numbers referenced below do not match the CR question numbers in this memorandum, as these numbers are derived from the full CR letter sent to Biotest, which included product office questions.)

Sent to the firm via email, June 21, 2012:

- 1) With respect to number 4:

Your description of the defect set used to qualify the 100 percent visual inspection procedure for Bivigam is sufficient. However, you have not provided complete qualification/validation data for the visual inspection program. As this is part of your license for the product, information demonstrating a validated visual inspection program is required to be present within your BLA. Therefore, please submit this information to your BLA.

This information request was accidentally omitted from the email sent on June 21, 2012. It was sent to Biotest July 18, 2012. Biotest responded on July 20, 2012, via submission of Doc. No.: 2- FF -034 (----(b)(4)----- SOP), "TRAINING AND QUALIFICATION OF VISUAL INSPECTION OPERATORS FOR FINAL DOSAGE FORMS" as well as the results of the most recent visual inspection qualification for all inspectors. The SOP and validation program appear appropriate.

- 2) With respect to number 5a:

For cleaning validation acceptance criteria for -----(b)(4)----- equipment, please consider using a ---(b)(4)----- limit of ----(b)(4)-----.

Biotest agreed to set the limit at the suggested value.

- 3) With respect to number 5c:

Please submit complete cleaning validation final reports for all equipment specified in this CR question.

Biotest submitted the document entitled, "Final Report for the Cleaning Validation of the -----(b)(4)-----"

Biotest performed one run on each of the (b)(4) that were not performed in VP-PQ-3673, specifically -----(b)(4)-----, as per their family approach to cleaning validation. Note that the validation was performed using the original cleaning validation

acceptance criteria, and not the new acceptance criteria listed above. This may have been acceptable given acceptable low validation actual values, but the post cleaning bioburden values reported were as follows (see **CR Question 1**):

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Given standard bioburden tests reported as CFU's per (b)(4), these results translate to values of -----(b)(4)-----; these values are unacceptably high, even for -----(b)(4)----- equipment. These values also call into question their reported low (b)(4) values for the same cleaning validation.

As a follow-up to this question, Biotest was asked to clarify their acceptance criteria for this validation on July 23, 2012, and asked to provide the rationale as why it is different from the one (---(b)(4)---) they have used for their ---(b)(4)--- process. Finally they were asked to include their calculation for bioburden results, if applicable.

Biotest confirmed that acceptance criteria for bioburden for the (b)(4) listed in the “Final Report for the Cleaning Validation of the -----(b)(4)----- is in (b)(4).

They further stated that their acceptance criteria units for ---(b)(4)---- equipment (-(b)(4)-) was set to match those of ---(b)(4)---- in process product bioburden acceptance criteria which is also in -(b)(4)--, likewise, the acceptance criteria units for ---(b)(4)---- equipment (---(b)(4)---) was set to match the bioburden acceptance criteria for ---(b)(4)---- which is also in ---(b)(4)-----.

SOP VAL3013 (Rinse ---(b)(4)--Sampling Procedure for Cleaning Validation) requires a -(b)(4)- --- rinse sample be collected for -----(b)(4)----- equipment, then per SOP QC2092 (Total Microbial Counts Test) --(b)(4)-- of the rinse sample is tested for -----(b)(4)-----.

The results are then converted to the -----(b)(4)----- bioburden units, respectively.

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

July 20, 2012 teleconference:

We acknowledge that you cannot meet a lower (b)(4) cleaning validation limit for the ---(b)(4)--- ----- due to residuals from the --(b)(4)-- solution (-(b)(4)-). Therefore, please consider evaluation of alternative metrics that will demonstrate your ability to effectively clean this -(b)(4)-.

Biotest responded that they were already considering development of a residual protein analysis for the ---(b)(4)---. At this time I requested that they formalize this test and submit a Post Marketing Commitment. Biotest responded as follows:

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Note: This commitment was agreed upon prior to completion of review of all the outstanding cleaning validation documentation requested in #3, above. Since Biotest's response to number three is not adequate and the file will be issued a CR letter, the PMC agreed to on July 20, 2012 will instead be included as a CR question (see **CR Question 2**).