

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: Daryll Miller, Biologist, Review Chair, OVRR/DVRPA/CMC2, HFM-478
File STN 125296/0

From: Gang Wang, Ph.D., Expert Biologist, OCBQ/DMPQ/MRB II, HFM-676

cc: Helen Gemignani, CSO, RPM, OVRR/DVRPA/CMC2, HFM-478

Through: Chiang Syin, Ph.D., Chief, OCBQ/DMPQ/MRB II, HFM-676

Subject: Review of the original BLA submitted by Teva Women's Health (formerly Duramed Research) to seek licensure of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, indicated for active immunization for the prevention of febrile acute respiratory disease caused by Adenovirus Type 4 and Type 7

This review memo contains the following two separate review memos:

1. Review memo (pages 1 – 13) recommending an approval for Teva's complete responses to the Completed Response (CR) letter issued by CBER on July 16, 2009.
2. Review memo (pages 14 – 65) recommending a CR letter for Teva's original BLA STN 125296/0 submitted on September 30, 2008.

FINAL REVIEW RECOMMENDATION

Based on the information submitted in Teva's complete responses to the CR letter issued on July 16, 2009 and their responses to my follow-up questions concerning the CR responses, I would consider that all DMPQ-related deficiencies identified in the CR letter as well as the 483 Observations resulted from the PLI conducted at the firm on April 20 – 24, 2009 have been adequately resolved. I recommend this BLA STN 125296/0 be approved.

REVIEW QUESTIONS

On October 22, 2010, CBER sent an Information Request (IR) containing two DMPQ-related follow-up questions regarding Teva's complete responses to the CR letter. On December 9, 2010, the sponsor submitted a written response (STN 125296/0/31) to CBER's IR. The IR questions (in *italics*), Teva's responses (in regular font) and my comments (in **bold**) are summarized below.

1. *Regarding your response to item 2d of CBER's Complete Response (CR) letter dated July 16, 2009, please clarify if you have revised your SOP for inspecting the incoming bulk viral bottles and proper handling of non-conformance samples should the "hissing bottle" or similar incident recur.*

Teva Response:

Based on the investigations conducted by ----(b)(4)---- (the contract manufacturer of the Formulated Adenovirus supernatant) on the "hissing bottle" incident, the firm concluded that -----(b)(4)----- to the virus bulk container did not adversely affect the Formulated Adenovirus material from a standpoint of quality (such as bioburden, titer, and pH, etc.). In addition, stability data of Adenovirus Tablets Type 4, Batch --(b)(4)-- (part of same batch with "hissing" bottles) has demonstrated no loss of titer for up to 12 months.

Thus, although -----(b)(4)----- was treated as a non-conformance for the purpose of investigation and reporting, the firm considered it an "abnormal" observation. They have added a note to the Master Manufacturing Batch Records (MBMR) for both Adenovirus Type 4, Lyophilized Intermediate and Adenovirus Type 7, Lyophilized Intermediate for the manufacturing technicians and supervisors which states:

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

MBMR 8108A027 was updated to MBMR 8108A037 and made effective August 12, 2009 for the Type 4 material. MBMR 8109A027 was updated to MBMR 8108A047 and made effective September 4, 2009 for the Type 7 material.

In addition, Teva/--(b)(4)--- committed to further investigating the use of ---(b)(4)--- ----- as an additional secondary packaging material for the Formulated Virus bottles. -----

-----The sponsor considered that this remedy may prove to be both straightforward and effective. The target completion date for the investigation of this "proof of concept" approach is February 2011.

CBER Comment:

The sponsor has conducted a thorough investigation on the "hissing bottle" incident and identified a reasonable root cause. The investigation concluded that the incident did not have adverse effects on the product quality. Detailed responses and my evaluations can be found in the section of REVIEW SUMMARY of this review memo (see Question 2d). The procedures taken by the firm appear to be acceptable. Overall, the responses to this question appear acceptable.

- 2. *Please submit an update report from ---(b)(4)--- on commitments made in their 483 responses to correct the deficiencies identified in the FDA Form 483 issued on February 17, 2009, and include the status of responding to those commitments within the specified timeframe.*

Teva Response:

In their responses, Teva provided a summary of the status of all outstanding FDA Form 483 observations issued to ---(b)(4)--- during the PLI conducted at the firm in ----(b)(4)---- in the following table.

below.

FDA 483 Observation #	(b)(4) Commitment	Status: Complete/Additional work in progress	Completion Date of initial 483 commitment	Additional study/work completion date
1	1.1	Complete	Jun 5, 2009	-
	1.2	Complete	Jun 5, 2009	-
	1.3	Complete	Feb 24, 2010	-
	1.4	Additional work in progress	Feb 26, 2010	Dec 31, 2010
	1.5	Complete	Jun 30, 2009	-
	1.6	Complete	Feb 17, 2010	-
2	2.1	Complete	May 27, 2009	-
	2.2	Complete	May 8, 2009	-
	2.3	Complete	May 28, 2009	-
3	3	Complete	Feb 16, 2010	-
4	4.1	Complete	Apr 1, 2009	-
	4.2	Complete	Jun 26, 2010	-
5	5	Complete	Feb 22, 2010	-
6A	6A	Complete	Apr 22, 2009	-
6B	6B	Complete	Mar 31, 2009	-
6C	Part of item 7A-C	See items 7A-C	See Items 7A-C	-
7 (A, B, C)	7.1	Complete	Dec 1, 2009	-
	7.2	Additional work in progress	Apr 9, 2010	Jan 31, 2011
	7.3	Additional work in progress	Jun 25, 2010	Jan 31, 2011
	7.4	Additional work in progress	Apr 9, 2010	Jan 31, 2011
	7.5	In progress	-	Jan 15, 2011
	7.6	In progress	-	Dec 20, 2010
8 (A, B, C, D)	8.1	Complete	May 6, 2009	-
	8.2	Complete	July 29, 2009	-
	8.3	Complete	July 17, 2009	-
	8.4	Complete	Jan 29, 2010	-
9	9.1	Complete	Feb 24, 2010	-
	9.2	Additional work in progress	Jun 24, 2010	Jan 15, 2011
10 (A, B, C)	10	Complete	May 4, 2009	-
	10A	Complete	Jun 23, 2009	-
	10B&C	Complete	Aug 18, 2009	-
11	11	Complete	Sep 25, 2009	-
12	12	Complete	Jul 20, 2009	-
13	13.1	Complete	Jun 10, 2009	-
	13.2	Complete	Oct 12, 2009	-
	13A-B	Complete	Jul 20, 2009	-
	13C, D, E	Complete	Mar 16, 2009	-
	13F	Complete	May 8, 2009	-

- For Commitment 1.4, the firm responded that they have developed a -----(b)(4)-----
----- test and have validated the test in line with the -----(b)(4)-----

The cleaning validation studies for the -----(b)(4)----- Tablet Press were submitted prior to receipt of the CR Letter, in Amendment 19 to BLA 125296 on June 25, 2009. Due to insufficient time for review the amendment before the Action Due Day, this deficiency was included in the CR Letter.

- Document 706016CR-1, Cleaning Validation Summary Report, Adenovirus Tablets, Type 4
- Document 706017CR-1, Cleaning Validation Summary Report, Adenovirus Tablets, Type 7

These reports include cleaning validation results for the -----(b)(4)----- Tablet Press as well as other pieces of equipment. Cleaning validation activities for the -----(b)(4)----- were abbreviated, as during the validation process, a decision was made to dedicate a -----(b)(4)----- to each adenovirus type so as to eliminate potential for cross-contamination. The reports contain results for

- A 3-batch cleaning validation for all other product contact processing equipment on both serotypes as specified in the respective protocols
- A 3-batch cleaning validation for the -----(b)(4)----- Tablet Press (excluding the -----(b)(4)----- due to product dedication) on both serotypes
- -(b)(4)-batch cleaning verifications for the ----(b)(4)---- on Adenovirus Type 4 prior to product dedication
- A -(b)(4)-batch cleaning verification for the ----(b)(4)---- on Adenovirus Type 7 prior to product dedication

Direct product-contact components of the -----(b)(4)----- Tablet Press such as the -----(b)(4)----- are dedicated to each adenovirus type.

The results obtained to date indicate that the cleaning procedures specified in Table 8 of Document 706016CR-1 are effective at removing residual Adenovirus Type 4, and therefore, the cleaning procedures used in the manufacture and packaging of Adenovirus Tablets, Type 4 are considered validated using the specified cleaning agents.

Similarly, the results obtained to date indicate that the cleaning procedures specified in Table 14 of Document 706017CR-1 are effective at removing residual Adenovirus Type 7, and therefore, the cleaning procedures used in the manufacture and packaging of Adenovirus Tablets, Type 7 are considered validated using the specified cleaning agents.

CBER Comment:

The responses are acceptable.

- b. The cleaning efficacy study of -----(b)(4)----- to remove Adenovirus 4 (ADV-4) and Adenovirus 7 (ADV-7) residues from product-contact surfaces have not been validated.*

Teva Response:

Cleaning efficacy studies were conducted for -----(b)(4)----- . Reports for these studies are provided in Module 3.2.A of this Complete Response.

Cleaning Validation Summary Report for Efficacy of ---(b)(4)--- to Remove Adenovirus from Manufacturing Equipment (Document 70902CR-1) demonstrated that the cleaning procedure incorporating ----(b)(4)----- effectively removes Adenovirus residues from manufacturing surfaces sufficiently well to be approved for use in the Adenovirus production process.

Similarly, *Cleaning Validation Summary Report for Efficacy of -----(b)(4)----- to Remove Adenovirus from Manufacturing Equipment* (Document 709025CR-1) demonstrated that the cleaning procedure incorporating -----(b)(4)----- effectively removes Adenovirus residues from manufacturing surfaces sufficiently well to be approved for use in the Adenovirus production process.

CBER Comment:

The responses are acceptable.

c. The clean hold time for equipment and facility has not been validated.

Teva Response:

An analysis of equipment clean hold times was conducted and documented, and a corresponding SOP was created to define allowable hold times for equipment in the Adenovirus facility. These reports are provided in Module 3.2.A of this Complete Response.

Extensive EM of the facility has been conducted leading to the establishment of a clean hold time for the facility. These reports are also included in Module 3.2.A of this Complete Response.

Equipment Clean Hold Times

In order to establish clean hold times for equipment used in the manufacture of the Adenovirus tablets, Teva conducted a thorough analysis of bioburden data obtained from equipment that had been cleaned and held pending use in the next manufacturing campaign. This analysis, reported in document 709026CM-1 *Clean Hold Time Data for Equipment*, was used to create SOP-1796 *Adeno Equipment Clean Hold Times* which defines the allowable clean hold duration of equipment used in the manufacture of Adenovirus tablets. SOP-1796 is based on actual use data, generated from a limited number of manufacturing runs. Since the Adenovirus facility has not yet been manufacturing product on a routine basis, there has been limited opportunity to generate data that would allow extension of equipment hold times. Pending execution of prospective validation activities, SOP-1796 will assure that all cleaned equipment is used within a time-frame that has been demonstrated to result in an acceptable bioburden profile.

Facility Clean Hold Times

As part of the Adenovirus facility control program, monitoring activities for bioburden and non-viable particulates have been conducted starting in May 2006. All available information was reviewed during the PLI in April 2009. From May to November 2009, supplementary testing was performed to determine (i) whether the environmental controls and cleaning procedures were adequate to ensure that the facility is maintained as a -----(b)(4)----- environment, and (ii) to establish a facility clean hold time.

Report 709005ER-1 documents the results of the supplementary testing, and confirmed that the facility met the viable and non-viable airborne particulate and surface viable particulate requirements for ----(b)(4)---- classification for all product contact/non-floor samples as well as for non-product/non-floor samples. No data trends were observed for the air and non-floor surface samples. Floor sample results showed elevated bioburden levels. Corrective action was taken and the facility floors were re-surfaced. Prior to establishing a cleaning regimen for the newly re-surfaced floors, (b)(4)test sites were cleaned and monitored per protocol ARD_PRT-3603. Results from this study, reported in ARD_RPT-4485, demonstrated that the proposed cleaning procedures for the newly surfaced floors were effective at controlling bioburden. A more extensive confirmatory study was conducted on all the re-surfaced floors, per ARD_PRT-3663, and results are reported in ARD_RPT-4602. Data supports a facility clean hold time of (b)(4) days. The data generated from these studies was used to establish the EM program for the facility including sampling frequencies and alert/action limits for viable and non-viable particulates.

Two reports that provide an executive overview of the EM program and summarize the data for non-viable and viable particulate counts in the facility over a multi-year period are included. Report 710079ER, summarizes results of the non-viable particulate analyses, and report 710080ER summarizes the viable particulate analyses.

CBER Comment:

The responses are acceptable.

d. The viral inactivation study by (b)(4) at the Adenovirus facility has not been validated.

Teva Response:

The -----(b)(4)----- treatment was validated for viral inactivation. The report is provided in this Complete Response in Module 3.2.A.

Validation of viral inactivation using (b)(4) was conducted in the Adenovirus facility in July 2009. Results are reported in -----(b)(4)----- Viral Inactivation Study for the Adenovirus Tablet Oral Vaccine Manufacturing Facility Report (Document 709025ER).

Based on the results of the Virus Inactivity study, the use of (b)(4) treatment has been found acceptable as a means of kill live adenovirus in the facility prior to transitioning the facility from the manufacture of Adenovirus Serotype 4 to Adenovirus Serotype 7 (or vice versa).

The following critical -----(b)(4)----- must be implemented for future -----(b)(4)----- performed at the Adenovirus Tablet Oral Vaccine Manufacturing Facility:

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

To ensure that the ----(b)(4)---- was successful, the following conditions must result:

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

CBER Comment:**The responses are acceptable.**

2. *The following items pertaining to Barr Laboratories have not been submitted. Please submit the following:*
 - a. *Barr Laboratory's overall approach or plan to control and prevent contamination and cross-contamination.*

Teva Response:

The overall approach to the control and prevention of contamination and cross-contamination in the Adenovirus Facility was submitted in Amendment 19 to BLA 125296 on June 25, 2009 prior to receipt of the CR Letter. Due to insufficient time for review the amendment, this deficiency was included in the CR Letter dated July 16, 2009.

Two documents included in that submission have been updated and the current versions are included in this submission. Additionally, sections of the Site Master File have been revised to include supplementary information on contamination controls. This submission also includes a listing of SOPs that support facility controls to prevent contamination and cross-contamination. The Site Master File and other supporting documents are included in Module 3.2.A of this submission.

The specific documents included:

- 709022CJ-1 Sampling Site Location Risk Assessment, Adenovirus Tablets Type 4 and Type 7
- 709020CV-1 Cleaning Verification Monitoring Protocol, Adenovirus Tablets Type 4 and Type 7
- VAL_PG-10 Cleaning Validation and Verification Master Plan for the Adeno Facility

Sections of the Site Master File for the Adenovirus facility have been revised to include supplementary information on contamination controls, and a copy is provided in this submission.

- Site Master File, VAL_PG-18, Section C.3.11 (Sanitation)
- Site Master File, VAL_PG-18, Section C.3.12 (Cross Contamination).

In addition, a listing of SOPs that address facility controls and cross-contamination prevention is included with this submission.

- Cross Contamination Procedures and Control at the Adenovirus Facility

Two of the documents submitted in Amendment 19 have been updated:

- 709022CJ-2, Sampling Site Location Risk Assessment
- 709020CV-1a, Cleaning Verification Monitoring Protocol

Document 709022CJ-2, *Sampling Site Location Risk Assessment*, assesses the potential risks of product cross-contamination at different points in the manufacturing process and with different pieces of equipment. The updated document contains an amended calculation for the Risk Value of each of the sampling sites in the facility, and provides rationale for continuing to sample certain sites while eliminating others.

Document 709020CV-1a, *Cleaning Verification Monitoring Protocol*, has been amended to be consistent with both the Site Master File and 709022CJ-2, *Sampling Site Location Risk Assessment*. In addition, 709020CV-1a includes the rationale for a minor change to the acceptance criteria based on a change in the contract lab used to analyze swab samples.

As a result of the decision by -----(b)(4)----- to discontinue testing support to the Adenovirus project, Teva has contracted with ----(b)(4)---- to perform ongoing test of biological samples. In preparation for this transfer in testing responsibilities, ----(b)(4)----conducted studies, documented in KVPO1084.R02, Transfer and Qualification Report for -----(b)(4)----- Assays for the Identification of Adenovirus Types 4 and 7 in Biological Samples. Results from the qualification study indicate that the (b)(4) assay performance characteristics are comparable at both facilities.

During the PLI, the role of the -----
----- (b)(4) -----
----- was conducted per Protocol ARD_PRT-2726, and reported in Report ARD_RPT-3956.

CBER Comment:

The responses are acceptable.

b. An updated Site Master Plan for the room classification of the Adenovirus facility.

Teva Response:

The updated Site Master File was submitted in Amendment 21 to BLA 125296 on July 2, 2009. The Site Master File has since been updated and the current version is included in this Complete Response in Module 3.2.A. In addition, two documents, corresponding to pages 45 and 46 of the Site Master File, which describe the Process Areas and Pressurization and Production HVAC System, are provided as navigable PDF files for enhanced viewing.

- Site Master File, VAL_PG-18, version 3.0
- SMF, page 45, Attachment 1: First Floor Site Plan/ Process Areas and Pressurization
- SMF, page 46, Attachment 2: Production HVAC System Flow Diagram

CBER Comment:

The responses are acceptable.

c. Complete testing results of the "trial batch" manufactured during the PLI.

Teva Response:

The complete testing results of the Trial Batch were submitted in Amendment 19 to BLA 125296 on June 25, 2009. Due to insufficient time for review of the amendment, this deficiency was included in the CR Letter dated July 16, 2009.

The following documents were submitted:

- Batch Record ---(b)(4)---, Formulated Adenovirus Type 4, Lyophilized Intermediate

would think that this assumption was conceivable for that the containers are -----
------(b)(4)-----

---(b)(4)--- has previously performed validation studies on shipping and container/closure integrity. The results were previously submitted for review and deemed acceptable. The container/closure integrity testing that they used included -----(b)(4)-----
----- Although these testing methods may not provide sufficient sensitivity to determine the container/closure integrity, they are commonly acceptable methods practiced by the pharmaceutical industry. Another consideration that I would take into account for this deviation is that the virus bulk is not considered "sterile" but rather -----(b)(4)-----

The results of this investigation indicated that the bioburden level and other product specifications were not compromised due to the "hissing bottle". Based on these considerations, I would think that the risks associated with the "hissing bottle" or container/closure integrity caused by ---(b)(4)--- may be mitigated.

However, it is not clear if Teva has revised their SOP accordingly to inspect the incoming virus bulk bottles and properly handle the non-conformance samples should "hissing bottle" or similar incident recurs. This question has been conveyed to Teva in a follow-up Information Request (IR) dated October 22, 2010.

Note: Teva has responded this question on December 9 (STN 125296/0/31) and the responses appear to be acceptable (see REVIEW QUESTIONS section of this review memo).

- 3. *We agreed to allow the use of six clinical batches, three for ADV-4 and three for ADV-7, as consistency lots for your BLA. Samples from the six clinical batches were submitted for in-support testing. Since these batches expired in 2008, we requested that additional samples from the ADV-4 batch, manufactured during the April 20-24, 2009 PLI, be submitted for the completion of in-support testing. The ADV-4 batch manufactured during the April 2009 PLI was not considered a CGMP batch because of a manufacturing deviation. However, manufacturing proceeded as a trial batch. As a consequence, you have not demonstrated the ability to manufacture the product according to CGMP since the production of clinical batches in 2006. Please submit batch records showing complete testing results for one batch of ADV-4 and one batch of ADV-7 manufactured according to CGMP subsequent to the batch made during the April 20-24, 2009 PLI. Please submit 100 tablets for each batch. We may require additional batches for testing if our in-support testing results for the six clinical batches are out of specification.*

Teva Response:

An Executive Overview of the manufacturing activities, the manufacturing batch records, Summary Release Protocols, non-conformance and investigation reports are provided in Module 3.2.A of this submission and summarized below.

The document, Summary of 2009-2010 Production Activities, covers production activities for both the AdV4 and AdV7 tablets. It provides a history of all batches manufactured since the

2009 PLI, including product disposition, and provides an overview of the improvements made in manufacturing/equipment controls.

A CGMP batch of AdV4 was successfully manufactured following the manufacture of the trial AdV4 batch made during the pre-license inspection. The firm then encountered manufacturing challenges following the change-out of specific equipment components in preparation for the production of the AdV7 batch. Prior to successfully re-starting AdV7 production, a total of three AdV7 batches were manufactured and rejected. A detailed summary of the nonconformance investigations (NCI) into the three failed AdV7 batches are provided in Manufacturing Investigation Reports:

- RC_RPT-14797 (NCI 8000-10408 and -10490; Batches --(b)(4)-- and --(b)(4)--)
- RC_RPT-15200 (NCI 8000-12064 and -12183; Batch --(b)(4)--)

I have reviewed the NCI reports. The investigations appear to be adequate, the root causes have been identified and the corrective actions have been taken. As part of the investigation into the AdV7 batch failures, and to demonstrate that appropriate corrective actions had been implemented, the firm successfully manufactured several placebo batches, using lactose or DMEM media only, as part of its CAPA program. Details on these lactose-only batches are included in Manufacturing Investigation Report RC_RPT-15200.

Upon completion of these batches, successful production of the AdV7 batch was initiated.

The following records are provided for the AdV4 batch of Drug Product:

- Manufacturing Batch Record for AdV4 Drug Substance (Batch --(b)(4)--)
- Test results for AdV4 Drug Substance (Batch --(b)(4)--)
- Manufacturing Batch Record for AdV4 Drug Product tablets (Batch --(b)(4)--)
- In-process test results for AdV4 Drug Product (Batch --(b)(4)--)
- Finished Product test results for AdV4 Drug Product (Batch --(b)(4)--)
- Summary Release Protocol for AdV4 Drug Product (Batch --(b)(4)--)

The following records are provided for the AdV7 batch of Drug Product:

- Manufacturing Batch Record for AdV7 Drug Substance (Batch --(b)(4)--)
- Test results for AdV7 Drug Substance (Batch --(b)(4)--)
- Manufacturing Batch Record for AdV7 Drug Product tablets (Batch --(b)(4)--)
- In-process test results for AdV7 Drug Product (Batch --(b)(4)--)
- Finished Product Test Results for AdV7 Drug Product (Batch --(b)(4)--)
- Summary Release Protocol for AdV7 Drug Product (Batch --(b)(4)--)

I have reviewed the test results for both AdV4 and AdV7 batches and the data indicate that they meet specification requirements. Since the AdV4 batch was manufactured in 2009, this submission also includes, in the Summary of 2009-2010 Production Activities, the most recent stability data which confirms that the batch is stable and remains within specification.

In addition, samples of each batch are being concurrently shipped to CBER and are currently being tested by the Division of Product Quality at OCBQ.

Manufacture of these batches of Adenovirus utilized a new Working Seed Stock manufactured at --(b)(4)--. A copy of the GMP Compliance Certificate for each batch is provided for information.

- GMP Compliance Certificate, WVSS Adenovirus Type 4, Batch --(b)(4)--
- GMP Compliance Certificate, WVSS Adenovirus Type 7, Batch --(b)(4)--

CBER Comment:

I have reviewed the Summary of 2009-2010 Production Activities, NCI reports, and test results (including in-process and final product) for both Adv4 and Adv7 batches and found the responses acceptable. I did not review the batch records which are subject to product review. Based on the information I reviewed, I would consider that the responses are acceptable from DMPQ perspective.

This portion of the review memo (pages 14 – 65) was completed and resulted in the issuance of a CR letter in 2009 for the original BLA STN 125296/0 submitted by Duramed on September 30, 2008. Duramed was often referred below in the early part of review memo.

REVIEW RECOMMENDATION

I have completed my review of all the DMPQ-related information submitted in this original BLA STN 125296/0.

This BLA contains two sets of manufacturing facility information on Barr Laboratories (Barr Labs) and -----(b)(4)-----, respectively. The latter is a contract manufacturer of Formulated Virus Bulk used for manufacturing of the lyophilized drug substance and the final tablet product of --(b)(4)-- at Barr Labs.

CBER conducted two pre-license inspections (PLIs) at -----(b)(4)-----, and Barr Labs in Forest, VA on April 20 – 24, 2009, respectively. Two separate Form FDA 483 Inspection Observations were issued to the two corresponding firms, and two separate Establishment Investigational Reports (EIRs) were drafted as well.

The major review issues identified in this BLA include incomplete cleaning validations at Barr Labs (the final cleaning validation report has not been completed due to incomplete cleaning validation on two pieces of critical manufacturing equipment), inadequate environmental monitoring performance qualification (EMPQ) of the Adenovirus Facility at Barr Labs, incomplete validation study on mixing/formulation of adenovirus bulk at (b)(4) scale at ---(b)(4)----, and inadequate validation study on lyophilization at (b)(4) scale at Barr Labs. These issues were convened to the sponsors and were subsequently followed up during the PLIs. The mixing/formulation study at (b)(4) scale was later submitted as an amendment to the BLA. The request for lyophilization at (b)(4) was withdrawn by the sponsor. Details about these issues are also discussed in EIRs.

Based on my review of the information provided, the submission package appears to be complete, the facilities and equipment appear to be adequately qualified, and the validation studies appear to be properly designed and executed (with the exceptions mentioned above). Most of the review issues were adequately addressed. Some of the review issues were further followed up during the PLIs. The inspectional issues were discussed in more details in two separate EIRs. The sponsor committed to resolving the remaining issues as post-market commitments (PMC).

I must point out that this BLA was put together in a poor quality in that many information and data submitted by Barr Labs were scanned copies of the original documents with poor legibility. Some diagrams/illustrations were illegible. Numerous documents submitted under hyperlinks did not have brief descriptions or summaries to facilitate review. Many raw data and hand writing data shown to be illegible or difficult to interpret were submitted without further elaboration. I was told by the Barr Labs management during the PLI that many of the information/documents submitted were put together in a rush in order to meet the submission deadline.

In summary, despite the fact that most review issues have been adequately addressed, several major issues remain to be resolved before the BLA can be approved. Specifically,

1. Barr Labs has not manufactured a single CGMP batch of Adenovirus 4 (ADV-4) or Adenovirus 7 (ADV-7) in their Adenovirus Facility in the last three years since 2006. The six clinical batches (three ADV-4 and three ADV-7), which were also used as

consistency lots, were manufactured in 2006. Since then, no CGMP batches have ever been manufactured in the facility. The ADV-4 "trial batch" manufactured during the PLI was not considered a CGMP batch due to a manufacturing deviation. As a result, I am not convinced that the sponsor has demonstrated the capability of manufacturing the product in compliance with CGMP requirements under the current condition.

2. The following inspectional issues from the Barr Labs' PLI have yet to be resolved:
 - a. Equipment cleaning validation studies for the -----(b)(4)----- Tablet Press have not been completed and the final report on cleaning validations for all equipment have not been submitted for evaluation.
 - b. The cleaning efficacy study of -----(b)(4)----- to remove Adenovirus 4 (ADV-4) and Adenovirus 7 (ADV-7) residues from product-contact surfaces has not been validated.
 - c. The clean hold time for equipment and facility has not been validated.
 - d. The viral inactivation study by (b)(4) at the adenovirus facility has not been validated.
3. The following items pertaining to Barr Labs have yet to be submitted:
 - a. Barr Laboratory's overall approach or plan to control and prevent contamination and cross-contamination.
 - b. An updated Site Master Plan for the room classification of the adenovirus facility.
 - c. Complete testing results of the "trial batch" manufactured during the PLI.
 - d. Investigation report of the two "hissing" bottles of discolored Formulated Virus.

Based on the significant deficiencies identified above, I recommend that a Complete Response (CR) letter be issued to the sponsor.

REVIEW QUESTIONS

On December 19, 2008, CBER sent the following 27 review questions to Duramed. These questions involve issues related to both Barr Laboratories (Barr) and its contract manufacturer ---(b)(4)----- . On January 29, 2009, Duramed responded the questions. I subsequently reviewed their responses. Some of the questions were further reviewed and followed up during the two pre-license inspections (PLI) at -----(b)(4)-----, and at Barr in Forest, VA, respectively. My review questions are listed in *italics*, Duramed's responses are summarized in plain text, and my comments are summarized in **bold**.

1. *You intend to --(b)(4)-- the lyophilization capacity from----- (b)(4)----- of lyophilized intermediate for commercial production of the product after approval. To achieve this, you plan to --(b)(4)-- the formulated virus manufacturing process to formulate a ----- (b)(4)----- of Adenovirus 4 and Adenovirus 7. However, validation data for -----(b)(4)---- lyophilization and mixing studies have not been submitted. We would like to advise you that without the validations for -----(b)(4)--- lyophilization and mixing, CBER can only consider approval of the currently submitted (b)(4) validated procedure.*

Barr Responses

Duramed responded that they had performed the lyophilization validation at (b)(4) scale for four times, three times with a placebo and once run with ADV7. Additional questions were further raised concerning the lyophilization validation study. Duramed later withdrew their request for lyophilization at the (b)(4) scale.

The mixing validation at the -----(b)(4)-----
Based on what was described in the response letter, the mixing study appears to be designed and executed adequately. The results were further evaluated during the PLI and deemed to be acceptable.

CBER Comments

The issue is resolved.

2. *You state that the final report for cleaning validation for Adenovirus 4 and Adenovirus 7 and residual solvents in Barr Laboratories has not been completed. Only an interim report for cleaning validation has been submitted in this BLA. Please submit a summary of the final report for cleaning validation for each piece of product-contact equipment, lyophilizer, and the facility.*

Barr Responses

Duramed responded that because the cleaning validations of ---(b)(4)--- for ADV4 and the cleaning validations of -----(b)(4)----- Tablet Press for ADV7 were incomplete, the final cleaning validation summary report for ADV4 and ADV7 are still not complete. The interim reports are written and approved when further data is required to complete the summary report. This deficiency was cited in the 483 during the Barr PLI and is discussed in EIR and 483 responses review memo.

Barr does not perform facility cleaning validation, but rather uses -----(b)(4)----- during changeover from ADV4 to ADV7 manufacturing and vice versa. The viral inactivation by (b)(4) at the facility was not verified, which resulted in a 483 citation during the Barr PLI. This issue will be discussed in EIR and 483 responses review memo.

CBER Comments

The issues have not been fully addressed at this time and will be followed up in the 483 review memo as inspectional issues.

3. *Cleaning/disinfecting validation for rooms of lyophilizing, blending, core compression, core coating compression and coating were not performed. It was stated that -----(b)(4)----- cleaning and disinfection of rooms were performed per SOP. Please explain why cleaning validations were not performed for these rooms.*

Barr Responses

Barr does not perform facility cleaning validation, but rather performs cleaning validation on product-contact, processing equipment. They use -----(b)(4)----- agent during changeover from ADV4 to ADV7 manufacturing and vice versa. The cleaning validation activities were performed on product-contact, processing equipment prior to the -----(b)(4)----- and data provides evidence that demonstrates the adequacy of Barr cleaning procedures to prevent cross-contamination of serotypes even before the

---(b)(4)--- procedure is executed. Barr performed one cleaning verification execution on equipment and manufacturing areas subsequent to the ---(b)(4)--- process. EM is performed to ensure that the environment is suitable for use and Bioburden is controlled.

CBER Comments

Multiple deficiencies were identified during the Barr PLI and were cited in the 483. The issues have not been fully addressed at this time and will be followed up in the 483 review memo as inspectional issues.

- 4. *The cleaning validations of residual solvents in the Barr facility do not appear to be complete. Cleaning validations for some equipment were not included in your submission. Please provide a list of product-contact and solvent-contact equipment and indicate which ones have been validated and which ones have not been validated for cleaning/disinfecting and provide data for those that are missing.*

Barr Responses

Again, cleaning validation for some equipment was not complete.

The -----(b)(4)----- are cleaned with (b)(4) and therefore did not require cleaning validation activities for removal of -----(b)(4)----- . Because -----(b)(4)----- no cleaning validation activities for removal of solvents were performed on this equipment.

Cleaning validation activities were not performed for removal of the -----(b)(4)----- , used in the manufacturing process as -----(b)(4)----- .

Cleaning validation activities were not performed for removal of the -----(b)(4)----- .

CBER Comments

This justification provided was not acceptable. The firm should provide data to demonstrate that residual solvents are effectively removed or demonstrate that residual chemicals – -----(b)(4)----- – will not react with components of the in-process or the final product and have no adverse effects on the in-process or the final product.

As stated above, multiple deficiencies in cleaning validation were identified during the Barr PLI and were cited in the 483. The issues have not been fully addressed at this time and will be followed up in the 483 review memo as inspectional issues.

- 5. *Please clarify if aseptic process validation has been done at the ----(b)(4)---- facility. If so, please submit a summary of the final report.*

Barr Responses

Duramed argued that ADV4 and ADV7 drug substances are non sterile. The drug substance manufacturing process is -----(b)(4)----- . The aseptic process validation for the (b)(4) scale formulation / fill process used in production of Phase III batches was completed in August 2007, with 3 successful full scale media fill batches executed –

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

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

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

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

CBER Comments

The -----(b)(4)----- issues were extensively discussed during the PLIs at ---(b)(4)----- and Barr and detailed in EIR. Barr agreed to -----(b)(4)----- the formulated virus bulk received from ---(b)(4)----. The overall responses are acceptable.

- 7. *You have used two different sized -----(b)(4)-----, to conduct stability studies of the drug product. Please clarify which size bottles will be used for commercial product and justify that the bottles and caps used during stability studies are comparable to those used in the final product.*

Barr Responses

Duramed clarified that the container closure for the commercial product is the -----(b)(4)-- bottle with the -----(b)(4)-----, and includes 100 of each type of virus and a --(b)(4)--. This configuration is identical to the commercial container. The ---(b)(4)---- bottles were used for the clinical and supportive stability studies.

Drug product stability data for the commercial container was provided in 3.2.P.8.3 and was summarized in 3.2.P.8.1. The data demonstrate the drug products remain stable for up to 18 months at the recommended storage condition, 2-8°C.

CBER Comments

The responses are acceptable.

- 8. *Please provide a summary of validation studies for the filters used for filtration of the -----(b)(4)----- followed by a -----(b)(4)-----.*

Barr Responses

The filtration -----(b)(4)-----
----- was a direct technical transfer from the previously approved
Wyeth process. The filtration (b)(4) is used as -----(b)(4)-----
-----.

The following manufacturer's filter validation packages are provided in Module 3.2.S.2.5:

- Validation Guide ---(b)(4)-----
- Validation Guide -----(b)(4)-----

The flow rates used in Bulk Virus harvest filtration ---(b)(4)--- are well within the recommended flow rates based on suppliers validation documentation.

Furthermore, filter integrity testing by ----(b)(4)---- method is performed following the ----(b)(4)-----, with a specification of ---(b)(4)--- to indicate an intact filter. No filter integrity test failures were encountered during the six Phase III consistency batches, nor did any filters require replacement due to clogging.

CBER Comments

The responses are acceptable.

9. *In section 3.2.S.6 Container Closure System, you stated that for the commercial process, (b)(4) of Formulated Adenovirus will be filled into -----(b)(4)-----
-----In section 3.2.A.2 Manufacture, you stated that for commercial manufacturing, -----(b)(4)-----
----- . You also mentioned that you have used -----
-----(b)(4)----- . Please clarify what size bottles you will use for commercial product. Please provide a summary report of validation studies for all the containers and closure integrity and bulk shipment.*

Barr Responses

Duramed clarified that for the commercial process, -----
----- (b)(4) -----
----- . This information was submitted in 3.2.S.2.2.7 and 3.2.S.2.3.2.

With regard to the container closure testing of the containers used to store the intermediates manufactured at -----(b)(4)-----

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

The following attachments are provided with the response to Question 9.

- Validation Plan VP0001.R1.0 – Final Product Container Closure Systems
- EVR005.08 – Validation of Final Product Container/Closure Systems
- EVP035.R00 – Validation of Container Closure Integrity, Long Term Microbial Challenge, Aseptic Filling Process

Once again, Duramed emphasized that ADV4 and ADV7 Live Oral Tablets are non-sterile solid oral dosage forms. In addition, the lyophilized drug substances are also not sterile, -----(b)(4)-----.

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

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

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

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

CBER Comments

Because the product is non-sterile, the sterility becomes less an issue. Although Barr did not perform an integrity test of the -----(b)(4)----- test of the drug substance, they did perform stability test on the --(b)(4)- drug substances.

13. *The leak testing for -----(b)(4)----- bottles is performed by the vendor when an -----(b)(4)----- is applied internally to the container. Does this pressure represent the pressure encountered during the -----(b)(4)-----, i.e., does this condition represent the worst case condition? For commercial product, --(b)(4)-- will be used for shipment. Does the leak testing condition performed on --(b)(4)-- also represent the worse case condition for shipment of the product in --(b)(4)---*

Barr Responses

Duramed justified that the -----(b)(4)----- bottles used for clinical supplies and the ----- (b)(4)----- bottles that will be used for commercial manufacturing share the same materials of construction and have the same neck diameter. Because the container closure mechanism is the same for both bottles, they believed that the leak testing performed by the vendor on the (b)(4) bottles is applicable to the (b)(4)bottles and represents the worst case conditions for both bottles.

1 page redacted (b)(4)

CBER Comments

The responses appear to be adequate. The product reviewer/inspector accepted the (b)(4) moisture level.

- 20. *In the Barr facility, the EM samples were taken under both dynamic and static conditions and sampled -----(b)(4)----- . Please justify the sampling frequency and why you think---(b)(4)--- is sufficient.*

Barr Responses

An additional Environmental Monitoring Study for the Adenovirus Tablet Oral Vaccine Manufacturing Facility (Protocol #709005EM) will be performed to support the initial EM studies that were previously performed at the Adenovirus Facility.

This additional EM study will be performed -----(b)(4)-----
----- sample frequency used during the initial EM study.

The sample frequency for the additional EM study will encompass sampling all selected sites -----(b)(4)----- under dynamic conditions. A -----
----- (b)(4)-----

Sampling will be performed -----(b)(4)----- treatment of the facility. In addition, samples will be collected at all sites during each step of tablet manufacture over the course of a GMP run from lyophilization to packaging. At a minimum, a total of (b)(4) samples must be collected at each sample site during the sampling period.

CBER Comments

During the PLI at Barr, I verified the Phase II EMPQ study and pointed out that their sampling plan including sampling number and frequency was inadequate. Barr responded that they had drafted a revised Phase III EMPQ validation study which will include increased sampling locations and frequency. The EM sampling will cover the entire process of the production at dynamic as well as static conditions. The revised Phase III EMPQ will monitor the manufacturing facility for -(b)(4)- in order to establish profiles of viable and non-viable particles for alert/action limits. Although the revised Phase III EMPQ protocol still lacks consideration of worst-case scenarios, it is an improvement over the previous Phase II EMPQ. Details of this issue are further discussed in Barr EIR.

- 21. -----
----- (b)(4) -----

Barr Responses

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

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

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

CBER Comments

The responses are adequate.

22. *Please provide a summary report of validations on the computer system. Please clarify your statement about computer validation as described in VMP Final Report. What do you mean “this risk analysis and assessment is not documented explicitly in a separate document or within the protocol but was performed as a function of protocol development as required by the original master plan.”?*

Barr Responses

The Adeno Validation Master Plan required that a risk analysis/assessment document would be issued to define the level of documentation and computer validation testing required to demonstrate reliable testing and performance of all Computerized Systems that had impact on product or Production at the Adenovirus facility.

At the time the VMP was issued the Computerized Systems that had impact on product or Production at the Adenovirus facility were:

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

A decision was made to perform computer validation testing on all the Computerized Systems listed above therefore the risk assessment/analysis documents were not issued. The Computerized Systems were qualified utilizing the traceability matrices to link the Functional Requirement Specifications to the Protocol tests.

The computer systems listed above met the criteria of 21 CFR Part 11 and met all validation criteria upon resolution of any deviations that occurred during the execution of the qualification protocols.

One additional computerized system that was not included in the VMP at the time the document was issued is the -----(b)(4)----- . This system met all validation criteria upon resolution of all deviations that occurred during execution of the qualification protocols. For the recipe portion of the -----(b)(4)-----, 21 CFR Part 11 compliance was met through revisions to the Standard Operating Procedures.

CBER Comments

The responses are adequate.

23. *In your Amendment to VMP Final Report (Document # 406060EM-1), you stated that EM testing (PQ) for Rooms -----(b)(4)----- met the Class --(b)(4)- static requirements. What are the EM testing results under dynamic conditions?*

Barr Responses

The EM protocol and reports listed below were provided in the BLA in 3.2.A.1.1.4.

- ARD_PRT-1743, Special Studies Protocol – Protocol for Phase II of the Environmental Monitoring Program at the Adenovirus Tablet Oral Vaccine Manufacturing Facility
- ARD_RPT-2346, Special Studies Report Adenovirus Environmental Monitoring: Phase I/II Interim and Phase II Data
- ARD_RPT-2842, Special Studies Report Adenovirus Environmental Monitoring: Phase II Second Quarter Data
- ARD_RPT-2953, Special Studies Report Adenovirus Environmental Monitoring: Phase II Fourth Quarter Data

The following report (data for the third quarter) was inadvertently omitted in the BLA and is provided as an attachment to this response.

- ARD_RPT-2844, Special Studies Report Adenovirus Environmental Monitoring: Phase II Third Quarter Data

A summary of the EM reports and data (Table 1) is provided. In these reports, the Class --(b)(4)-- results for air sampling performed under static and dynamic conditions were provided. A summary of the data is provided. The maximum cfu is listed in these tables -----(b)(4)----- . The (b)(4) acceptance criteria for Class --(b)(4)-- conditions for air cleanliness are ---(b)(4)--- ----- The EM data for rooms -----(b)(4)----- demonstrates that the air in these rooms is consistent with Class --(b)(4)-- dynamic air requirements.

CBER Comments

The responses appear to be adequate. During the PLI at Barr, the sponsor reaffirmed that you only intended to classify the -----(b)(4)-----and the -----(b)(4)----- as Class ---(b)(4)--- under static conditions. They would like to classify the rest of the Adenovirus Facility as “unclassified” for the reason that it is solid tablets facility.

24. *Please provide a summary of results of the container closure testing for -----(b)(4)----- used to store inner core, outer core coated inner core, and enteric coated tablets.*

Barr Responses

Container closure studies have not been performed for the intermediates in the non-sterile oral dosage forms. During process, intermediates are stored in -----(b)(4)----- For the consistency batches, after the inner cores are compressed, the time to out core coating was --- (b)(4) ---. The time between outer core coating and the enteric coating process averages was ----(b)(4)----.

In the Adenovirus Facility, in process materials are controlled as documented in SOP-54, Time Limitations for Re-Evaluation between Production Stages. In summary, the time between processing steps should not extend ---(b)(4)---. In the event that this in-process period is extended, the in-process material is re-tested prior to use in further manufacturing.

In process intermediate materials in the drug product manufacturing processes, are tested for in-process controls as detailed in 3.2.P.3.4 in the BLA and that all batches met in-process acceptance criteria. Additional sampling during the tableting process was performed during the validation of the tableting process, as provided in 3.2.P.3.5 in the BLA, and all in process validation parameters were met. There are no changes to the tableting process validated in the BLA and the intended commercial process.

The following attachment is provided as 3.2.P.3.4.:

- SOP-54, Time Limitations for Re-Evaluation Between Production Stages

CBER Comments

Given that the drug is a solid tablet form and the stability of the drug tablets has been validated, the responses appear to be adequate.

25. *The --(b)(4)-- facility has -----(b)(4)-----, for manufacture of Adenovirus 4 and Adenovirus 7. Please clarify what the other -----(b)(4)-----, are used for? If they are used for other products, please provide the name of the products and describe the segregation, containment and procedural controls that you have in place to prevent contaminations and cross-contaminations.*

Barr Responses

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

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

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

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

1 page redacted (b)(4)

CBER Comments

The responses appear to be acceptable.

- 4. *Please describe how you perform the-----(b)(4)----- test for each lyophilized tray.*

Barr Responses

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

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

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

CBER Comments

The responses appear to be adequate.

- 5. *Please justify the discrepancy of moisture specifications between Wyeth and Barr labs ---(b)(4)-----*

Barr Responses

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

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

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

CBER Comments

The responses appear to be acceptable.

REVIEW SUMMARY

I. Introduction

The purpose of this BLA (STN 105296/0) submitted by Duramed Research, Inc. is to seek approval by CBER for their proprietary drug product -----(b)(4)----- Enteric Coated Tablets (Adenovirus Vaccine, Live, Oral, Type 4 and Type 7). -----(b)(4)----- is indicated for the immunization of military populations in which epidemic respiratory disease due to adenovirus, types 4 and 7, has been shown likely to occur. Acute respiratory disease (ARD) is the most common cause of morbidity and hospitalization among military recruits undergoing basic combat training in the United States with adenovirus (ADV) types 4 and 7 constituting the two major causes of ARD in this population.

The Formulated Bulk Virus Adenovirus Type 4 and Type 7 is manufactured in Duramed's contract manufacturer -----(b)(4)----- It is shipped to Duramed's Barr Laboratories' manufacturing facility located at Forest, Virginia for further processing The Formulated Bulk Virus is lyophilized to Lyophilized Intermediates (Drug Substance) and then blended, compressed and enteric coated to the final tablet drug product.

Duramed is a wholly owned subsidiary company of Barr Labs and is responsible for marketing Barr Labs' proprietary products. Barr Labs is mainly for manufacturing of generic drugs.

The Formulated Bulk Virus Adenovirus Type 4 and Type 7, Lyophilized Intermediates, and the six GMP consistency lots of the Phase 3 Adenovirus Vaccine, Live Oral Tablets, Type 4 and Type 7 were manufactured, tested and released at:

Barr Laboratories, South Facility
1235 Mays Mill Road
Forest, Virginia, USA 24551

The Master and Master Working Cell Banks, Master and Master Working Virus Seeds, Bulk and Formulated Virus Intermediates for Adenovirus Type 4 and Type 7 were manufactured, tested and released at:

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

Commercial drug substance intermediates and drug product will be manufactured, tested and released at the same sites in -----(b)(4)----- and Barr, respectively.

II. Facilities & Equipment

A. Drug Products

Formulated Adenovirus Type 4 and Type 7, lyophilized intermediates (drug substances) and Adenovirus Vaccines, Live Oral Tablets Type 4 and Type 7 (drug products) are manufactured at Barr Laboratories Inc., 1235 Mays Mill Road, Forest, VA 24551. The Site Master File for the Barr VA Site is provided in BLA.

The Barr VA site is a facility dedicated to the GMP manufacture, storage, testing, release and packaging of Adenovirus Type 4 and Type 7 drug substances and drug products.

The commercial drug substances and products will be manufactured at the Barr VA site, which is the same facility as the consistency batches were manufactured.

The Validation Master Plan (VMP) for the Adenovirus Oral Vaccine Tablet Manufacturing Facility was originally approved in 2003. All of the requirements from the VMP were completed and the Validation Master Plan Final Report for the Adenovirus Oral Vaccine Tablet Manufacturing Facility Report was approved in June 2006.

The scope of the VMP and the VMP Final Report includes manufacturing rooms, equipment, utilities, processing and packaging areas, computerized systems, cleaning and disinfecting validation, process validation, calibration and preventive maintenance, SOPs, training and change controls.

Validation studies and reports are completed for the utilities, process equipment, analytical equipment, packaging equipment, cleaning, and computer systems as provided in the VMP Final Report. An Amendment to Validation Master Plan Final Report for the Adenovirus Oral Vaccine Tablet Manufacturing Facility was written in July 2008 to discuss the overall operation -----
-----(b)(4)----- after engineering modifications and the Performance Qualification Environmental Monitoring Study (EMPQ). Results of the studies are included in the Amendment to VMP Final Report. Data show that the -----
------(b)(4)-----
-----.

Based on what was described in Barr's Site Master File (SMF), the lyophilization room including the loading/unloading area of the lyophilizer was designed to meet ISO Class (b)(4) requirements for cleanroom operations under static conditions. There was no description on the classifications of the rest of the facilities. During the PLI at Barr conducted from April 20 – 24, 2009, I was told that after the Phase II EMPQ, Barr decided to classify only the -----
---(b)(4)-- and the -----(b)(4)----- as Class -(b)(4)- under static conditions, whereas the rest of the facilities were classified as unclassified. Room (b)(4) is used to -----(b)(4)-----
----- and Room (b)(4) is used to -----(b)(4)-----
----- . Other rooms in the facility are mainly used for tablet compressions, enteric coating, and packaging operations, etc.

I reviewed the VMP Final Report (#406060EM) which listed the equipment, utilities, computer systems and cleaning/disinfecting validation documents performed to validate the Adenovirus Oral Vaccine Tablet Manufacturing Facility (Adenovirus Facility). The PQ for the (b)(4) did not meet protocol criteria for humidity. As a result, the PQ was suspended until further investigation. I raised this issue to Duramed in an Information Request (Question #21) dated December 19, 2008. Duramed responded to the IR on January 29, 2009 stating that they have since re-qualified, between May 5 and June 9, 2008, and the (b)(4) and all the PQ criteria were met and the (b)(4) was released for CGMP used. The Final Report (Report #708060 ER): Performance Qualification Protocol -----(b)(4)----- – Mechanical Asset No: 010088 was included.

The VMP Final Report contains an Amendment pertaining to the EMPQ study performed in the Adenovirus Facility to evaluate the effects of facility controls, namely HVAC, utilities, equipment, and process control systems on the manufacturing process and product quality. The

[(b)(4)]

Cleaning Validation

Barr stated that cleaning validation for ADV 4 and ADV 7 and residual solvents were conducted according to approved protocols as listed in the following tables (Tables 3 & 4). Final cleaning validation reports will be provided once all the protocol requirements have been assessed. Barr stated that the interim reports indicated that the cleaning validation requirements have been met for those that have been tested.

It should be noted that some deficiencies in cleaning/disinfection validations were observed during the PLI and cited in 483 (see details in EIR).

Table 3: Cleaning Validation Protocols and Interim Reports

	Adenovirus Type 4	Adenovirus Type 7
Protocol	706016CV and Amendment 1a	706017CV and Amendments 1a and 1b
Interim Report	706016CV-IR-1	706017CV-IR-1

Table 4: Residual Cleaning Validation Protocols and Summary Report

Protocols	705008 CV, 705008 CV-2
Report	705008 CR

The “Interim Report” 706016CV-IR-1 (ADV 4) and 706017CV-IR-1 (ADEV 7) provided in this submission looked like a lab note with hand writing notes that were very difficult to read. No general descriptions or summaries were provided, and therefore, I was not able to provide a meaningful evaluation on the cleaning validation.

The deficiency in cleaning validation has been forwarded to Duramed via an Information Request (Question #2 on IR) dated Dec. 19, 2009. Duramed responded the IR on Jan. 29, 2009 stating that the final cleaning validation summary report for ADV4 and ADV7 was incomplete. Barr’s current policy dictates that a summary report should be written and approved upon completion of the validation of all protocols for the entire product-contact equipment train. Once sampling is complete, a final cleaning validation report will be authored for the entire product contact equipment train and submitted. This deficiency resulted in a 483 citation during the PLI at Barr (see details in EIR).

Environmental Monitoring

Environmental monitoring in the Barr’s Adenovirus Facility was performed according to Special Studies Protocol ARD_PRT-1743. Samplings took place in both dynamic and static conditions and were sampled -----(b)(4)----- in order to establish a profile of the viable and non-viable bioburden present in the areas of the facility where product was exposed to the environment.

Duramed did not provide justifications for the EM sampling frequency at -----(b)(4)----- ----- . I raised this question to the firm in an IR dated Dec. 19, 2009. In their Responses dated Jan. 29, 2009, Duramed proposed to perform an additional Phase 3 Environmental Monitoring Study for the Adenovirus Tablet Oral Vaccine Manufacturing Facility (Protocol #709005EM) to support the initial EM studies. This additional Phase III EMPQ study will use -----(b)(4)----- ----- . However, it was not clear how this frequency will fit into their production schedules. What if the facility is not in production or shut down for an extended period of time or there is a long interval between two productions. How can they maintain the specified specification of the facility under such conditions? These issues were further discussed with the firm during the PLI and detailed in Barr EIR.

Table 5: Environmental Monitoring Protocol and Reports

Protocol	ARD_PRT-1743.
Reports	ARD_RPT-2842, ARD_PRT-2953, ARD_RPT-2346

I reviewed the EM Protocol and the Phase II EMPQ Reports (ARD_RPT-2842, ARD_RPT-2953 and ARD_RPT-2346). The Reports summarized EMPQ results from execution of a Phase II EM Protocol (ARD-PRT-1743) from Oct. 1 to Dec. 31, 2006, April 1 to June 30, 2007, and from May 25 to September 30, 2006, respectively. The EM samples, including non-viable airborne particulates, viable counts, viable surface and floor, and product contact and non-product contact surface were collected under both static and dynamic conditions.

The Phase I EMPQ study at Barr consisted of gathering (b)(4) days of data from each sampling site. -----(b)(4)-----

Barr decided to continue a Phase II EMPQ that included collecting EM samples at each sample site -----(b)(4)-----

----- . The study was designed to evaluate the effects of facility controls, namely HVAC, utilities, equipment and process control systems, on the manufacturing process and product quality. The data collected would establish a limited profile of the viable and non-viable bioburden present in the areas of the facility where product is exposed to the environment.

The EM Protocol was not an actual EM validation protocol. Rather, it was used to collect EM samples to establish a limited profile of the viable and non-viable bioburden present in the areas within the facility where product was exposed to the environment. Sampling of the Phase II EMPQ took place during both dynamic and static conditions. The sampling frequencies under dynamic or static conditions -----(b)(4)----- . For example, if there was a production going on in the facility, the samples collected would be counted as dynamics; if there was no production going on in the facility, the samples collected would be counted as static.

There were no justifications for sampling frequencies, sites and numbers for the Phase II EMPQ study. During the PLI, I asked Barr if the sampling sites represented the worst-case locations in the facility and the answer was uncertain. I pointed out the deficiencies to the Barr management during the PLI. Barr recognized the deficiencies in the Phase II EMPQ study and is planning a Phase III EMPQ that will include increased sampling frequencies and sampling sites under both dynamic and static conditions. The collected data will be used to establish a reference profile of the viable bioburden and non-viable particulates present in the manufacturing areas of the Adenovirus Facility. Details about the Phase III EMPQ can be found in the Barr EIR.

I reviewed the limited EMPQ data collected during Phase II EMPQ. The airborne viable counts and non-viable particulates appeared to be within the specifications. The sponsor claimed that no excursions were observed during the Phase II EMPQ. Barr also measured the surface viable counts, but stated -----(b)(4)----- . No major deficiencies were noted. Based on the Phase II EMPQ results, Barr classified the -----(b)(4)----- and the -----(b)(4)----- as Class -(b)(4)- and the rest of the facilities as unclassified. I was informed that it is not uncommon for a tablet drug manufacturing facility. Details can be found in EIR.

Site Master File

I reviewed the Adenovirus Oral Live Vaccine Tablet Manufacturing Facility Site Master File (VAL_PG-18). This SMF contains specific information about the quality assurance, the production and quality control of pharmaceutical manufacturing operations carried out at the facility. The SMF also details on general information, personnel, premises, documentation, production, quality control, contract manufacture and analysis, distribution, and appendices.

During the PLI, I suggested to the Barr management that they should amend the BLA to clearly state the classifications of the each room and the facility.

General Information

Barr Laboratories (Barr) was founded in 1970 in New York and launched its first generic product in 1972. In 2004, the company was reincorporated in Delaware as Barr Pharmaceuticals Inc. with established subsidiaries, Barr Laboratories, Duramed Research and Duramed Pharmaceuticals.

Barr is focused on developing, manufacturing and marketing quality generic and proprietary pharmaceuticals. The Company's generic products are marketed under the "Barr" label, and proprietary products are marketed under the "Duramed" label. With its corporate Headquarters located in Montvale, New Jersey, Barr has facilities in nine locations in New York, New Jersey, Ohio, Pennsylvania, Virginia and Washington, D.C. The Company's generic pharmaceutical research and development operations are headquartered in New York, while proprietary research and development activities are headquartered in Pennsylvania.

State-of-the-art manufacturing facilities are located in New York, New Jersey, Ohio and Virginia, with distribution operations located in Virginia. The Virginia operations includes the Main Manufacturing facility as well as the Adenovirus Facility with the latter being the focus of this BLA. The Adenovirus Facility which is built on Barr's property in Forest, VA and its contents, are presently classified as Government Owned and Contractor Operated (GO-CO).

The site is pending approval and licensure for the manufacture of Type 4 and Type 7 Adenovirus Oral Live Vaccine Tablets and is the subject of this BLA.

Manufacturing Activities

Two biological finished products in the form of non-sterile solid dosage, live vaccine tablets for human use, are manufactured at this site. Manufacture of these products requires the use of actives containing live infectious human viruses. As a result of the unique safety issues of handling infectious virus, the facility was designed to meet (b)(4) requirements and is dedicated for the manufacturing of Type 4 and Type 7 Adenovirus Oral Live Vaccine Tablets. The Adenovirus Facility is located independently from other Barr Virginia manufacturing facilities.

Site Description

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

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

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

 • -----(b)(4)-----

2 pages redacted (b)(4)

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

Sanitation (Cleaning)

Approved cleaning procedures define the various steps required for each type of cleaning, as well as the preparation and specification of approved cleaning agents for each cleaning application.

The cleaning validation program is governed by a Cleaning Validation Master Plan to ensure appropriate procedures and controls are in place. Cleaning validation protocols are generated to ensure that equipment cleaning procedures are appropriate to remove active ingredients and detergent residuals to below pre-defined acceptable levels. The effectiveness of the cleaning program was demonstrated using clinical viral inactivation log reduction studies and safety factors.

In addition, the cleaning and sanitization as well as identification of status of rooms are performed in accordance with approved procedures to ensure appropriate cleaning, inspection and release of rooms prior to set-up and use for manufacturing. Area cleaning between productions of different virus serotypes requires a -----(b)(4)----- as defined by approved procedures.

Validation Master Plan

I reviewed the “Validation Master Plan for Adenovirus Oral Vaccine Tablet Manufacturing Facility (Barr Laboratories)” which was approved in August 2003. The VMP contains the following eight sections and one appendix.

1. Validation Master Plan – Review, Approvals and Revisions
2. Introduction
3. Scope
4. Regulatory Requirements
5. Validation Approach and Management
6. Equipments/Systems to Be Qualified
7. Qualification Criteria
8. Training and Qualification

Appendix A: Definitions and Abbreviations

Duramed states that all of the requirements from the VMP were completed and the Validation Master Plan Final Report for the Adenovirus Oral Vaccine Tablet Manufacturing Facility Report (Report #406060EM) was approved in June 2006. The Final Report contains the following six sections and one appendix.

1. Validation Master Plan – Approvals
2. Introduction
3. Scope
4. Validation Approach and Management
5. Completion Status Summary
6. Exceptions and Clarifications to Master Plan

Appendix A: Definitions and Abbreviations

The following major areas associated with Stage A of the Adenovirus Oral Vaccine Tablet Manufacturing Facility:

- Manufacturing rooms
- Equipment and utilities
- Processing and packaging
- Computerized systems
- Cleaning/disinfecting validation
- Process validation
- Calibration and preventive maintenance
- Standard Operating Procedures
- Training
- Change control and periodic review

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Amendment to Validation Master Plan Final Report for the Adenovirus Oral Vaccine Tablet Manufacturing Facility Location: Forest, VA (Document #406060EM-1)

I have discussed the Phase II EMPQ issues in the previous section. For the purpose of completeness, I summarized the EMPQ study again in this section.

The Phase II EMPQ study was performed per Document #ARD-PRT-1743, Special Studies Protocol for Phase II of the Environmental Monitoring Program at the Adenovirus Tablet Oral Vaccine Manufacturing Facility. The study results were summarized in the Amendment to VMP Final Report (Document #406060EM-1) and approved in July 2008. This Amendment pertained to the EMPQ study that was performed in the Barr facility to evaluate the effects of facility controls, namely HVAC, utilities, equipment, and process control systems on the manufacturing process and product quality.

The data collected from the EM also verified if Room -----(b)(4)----- and Room -----(b)(4)----- were consistent with Class -(b)(4)- requirements under static conditions.

IQ/OQ of the Process Air Handling System (b)(4) for the Facility was performed in 2003 and 2004. Qualification of room temperature, relative humidity, and differential pressure for Room (b)(4) and Room (b)(4) were performed under the (b)(4) PQ for the Facility per protocol 03084EP which was approved on 12/29/03. A second (b)(4) PQ protocol 708060EP was issued to address the overall operation of the facility after the engineering modifications were made and was executed in May of 2008.

Based on the results of the IQ/OQ testing and the (b)(4) PQ, the Facility was found to be consistent with Class -(b)(4)- static requirements. The IQ/OQ tests and associated engineering documents also confirmed the process area met design requirements (i.e., -----(b)(4)-----).

Deficiencies of this Phase II EMPQ study were discussed in the previous section and raised to the attention of the Barr management during the PLI. The firm is currently planning a Phase III EMPQ study by collecting more data at more sampling sites at increased sampling frequencies.

A PQ Protocol for (b)(4) – Mechanical (Protocol #708060EP) and a Final Report for PQ Protocol for -----(b)(4)----- (Report #708060ER) were provided. The Final Report of (b)(4) PQ summarized and discussed the results of PQ of -----(b)(4)----- . The results showed that the acceptance criteria for test instruments, temperature, humidity and pressure monitoring were all met. No deviations were observed.

II. Drug Substance

The Master and Master Working Cell Banks, Master and Working Virus Seeds, Bulk and Formulated Virus Intermediates for Adenovirus Type 4 and Type 7 are manufactured at:

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

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