

## **MEMORANDUM**

FILE: STN 125296

TO: File

FROM: Keith Peden

THROUGH: Jerry Weir  
Robin Levis

DATE RECEIVED: September 30, 2008

DATE: May 23, 2009

REVISED: March 17, 2011

SPONSOR: Teva Women's Health

SUBJECT: CMC review

TITLE: Adenovirus types 4 and 7 live oral vaccines in enteric-coated tablets

PROPOSED USE: For the immunization of military populations in which epidemic respiratory disease due to adenoviruses type 4 and type 7 infections have been shown likely to occur

### **Overall Conclusion and Recommendation**

There were no significant issues identified in the CMC sections, and approval of the application is recommended. To make it clear, my description/comments are in Arial font, while the text and methods provided in the BLA are in Times New Roman font.

### **Background to Product**

This product (live oral Ad4 and Ad7 vaccine) was initially licensed in 1980 and was manufactured by Wyeth Laboratories until 1995. Its intended use is to prevent Ad4 and Ad7 infections in military recruits. In 1995, Wyeth Laboratories elected to cease production when faced with costly updating of manufacturing facilities for the vaccines. After supplies were depleted in 1999, there was an upsurge in adenovirus infections in recruits, and the Department of Defense contracted with Teva Women's Health, formally known as Duramed, Inc., a subsidiary of Teva/Barr Laboratories, in 2001 to develop replacement vaccines for Ad4 and Ad7. The technology and the vaccine viruses were obtained from Wyeth. The WI-38 cell substrate banks were generated from cells obtained from ----(b)(4)---.

## **Manufacturing Facilities for Commercial Batches**

### **Formulated Virus**

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The formulated virus batches are shipped ----- (b)(4) ----- to Virginia, USA, for the conversion to drug substance and drug product. -----  
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----- (b)(4) -----  
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### **Drug Substance and Drug Product**

Teva/Barr Laboratories  
1235 Mays Mill Road,  
Forrest, VA 24551,  
USA

## **Inspections of Facilities**

Inspection of the (b)(4) facility was done by Dr Steve Rubin  
Inspection of the VA facility was done by Dr Daryll Miller  
Reference is made to their reviews (not included here).

## **The Cell Substrate**

The human diploid cell line WI-38 was obtained ----- (b)(4) -----  
----- (b)(4) ----- WI-38 cells were amplified by ----- (b)(4) -----  
-----, under GMP conditions in EMEM-10 [EMEM medium with 10% fetal bovine serum (FBS)]. In 2005, a ---- (b)(4) ----- vials was established by ---- (b)(4) -----  
----- (b)(4) ----- This bank was designated ----- (b)(4) ----- The --- (b)(4) -----  
was described in IND (b)(4) and was tested, although this information is not included in the BLA.

From the WI-38 -- (b)(4) -- was prepared (b)(4) Master Cell Banks. ---- (b)(4) ----  
generated by -----  
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----- (b)(4) -----  
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However, as the products were manufactured in the tested MCB and as the virus



Several Ad4 and Ad7 genomes were sequenced to determine the similarity of the Teva viruses with the Wyeth viruses. In addition, some throat isolates were obtained and sequenced to determine what strains are circulating. This could have relevance to the effectiveness of the vaccine. The origin of these viruses is summarized in the Appendix Table E (Appendix page 4). -----

----- (b)(4) -----  
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In conclusion, because the Ad4 (and Ad7) seeds generated at Teva/Barr have the same sequence as the vaccine viruses obtained from the Wyeth vaccine tablets, then this is evidence that both Ad4 and Ad7 are stable to passage and the vaccines produced by Teva contain the same vaccine viruses as those produced by Wyeth.

The passage history of the adenovirus stocks is described in Appendix Tables F, G, and H (Appendix page 5 and 6).

The following table summarizes the cell banks used for the generation of seed stocks for Ad4 and Ad7 together with lot numbers and the dates of manufacture.

Virus	Type of Stock	WI-38 Used	Lot Number	Date
Ad4	Master Virus Seed	---(b)(4)---	---(b)(4)---	---(b)(4)---
	Working Virus Seed	---(b)(4)---	---(b)(4)---	---(b)(4)---
	Working Virus Seed	---(b)(4)---	---(b)(4)---	---(b)(4)---
Ad7	Master Virus Seed	---(b)(4)---	---(b)(4)---	---(b)(4)---
	Working Virus Seed	---(b)(4)---	---(b)(4)---	---(b)(4)---
	Working Virus Seed	---(b)(4)---	---(b)(4)---	---(b)(4)---

The testing of Ad4 lot --(b)(4)-- is described in the Appendix Fig. D (Appendix page 6).

## Results Summary

----- (b)(4) -----  
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The tables are included in the Appendix to give examples of the --(b)(4)- assays used for the detection of adventitious agents that are used at multiple stages of vaccine manufacture: ----- (b)(4) -----  
(Appendix Tables I to V; Appendix pages 7 to 11).

Appendix Table W (Appendix page 12) summarizes the differences between the manufacturing processes of the original licensed Wyeth products and the Teva

vaccines. As can be seen, the changes are minor and do not negatively influence the safety of the products.

## **Manufacture of Bulk Virus Harvest**

A summary of the overall process is provided in Appendix Fig. E (Appendix page 13)(Section 3.2.S. Manufacture).

A summary of the production process for Ad4 and Ad7 bulk viruses is provided in Appendix Fig. F (Appendix page 14)(3.2.S. Manufacture).

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### **Detailed Protocol** **2.2.2 Initiation**

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----- (b)(4)

**Comment:** These reports have been evaluated and the formulated virus testing is complete and the results found to be satisfactory.

## Critical Control Steps in the Manufacturing Process

Only some of the parameters are included in this review. All were found to be satisfactory. The lot numbers for the bulk virus and formulated batches can be found in Appendix Table Y (Appendix page 17).

**Comment:** Several parameters were monitored during production to assure consistency of drug substance. For example, to obtain consistent amounts of virus, the -----(b)(4)----- . The former is shown in Appendix Fig. L (Appendix page 18), and the latter is shown in Appendix Fig. K (Appendix page 18). Table Z (below) summarizes the key process infection parameters.

**Table Z: Infection – Key Process Parameters Summary**

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### **3. DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS**

The drug product manufacturing process for Adenovirus Live Oral Type 4 and Type 7 tablets is performed in the Teva/Barr Laboratories Adenovirus facility dedicated to the manufacture of this product. -----

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[(b)(4)]

An overview of the steps and the major equipment involved in each step is provided.

The manufacturing process and equipment for the drug products consists of the (b)(4) major steps which are performed in a facility dedicated to the manufacture of the adenovirus drug products.

### 3.1. Blending Process for Drug Products

#### 3.1.1 Dry Coating Blending

In order to easily differentiate the two finished products, the dry coating blend for Ad7 drug product is slightly different from the dry coating blend for Ad4 drug product in that the dry coating blend for Ad7 drug product contains FD&C Yellow No. 6 Aluminum Lake. The raw material codes and theoretical weights for the dry coating process are provided in Table EE (below and in Appendix page25) for Ad4 and Table 4 (page 38) for Ad7. -----

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

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

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[(b)(4)]

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

**4 pages redacted (b)(4)**

**Table KK: Composition of Adenovirus Tablets, Type 4**

<b>Ingredient</b>	<b>Function</b>	<b>Mg/Tab</b>	<b>%w/w</b>
<b><i>Inner Core: Type 4</i></b>			
Formulated Adenovirus Type 4, Lyophilized Int.	Active	-(b)(4)-	-(b)(4)-
Anhydrous Lactose, ----(b)(4)-----	Diluent	-(b)(4)-	-(b)(4)-
Microcrystalline cellulose, ----(b)(4)-----	Diluent	-(b)(4)-	-(b)(4)-
Polacrillin Potassium, ----(b)(4)-----	Disintegrant	-(b)(4)-	-(b)(4)-
Magnesium Stearate, (b)(4)	Lubricant	-(b)(4)-	-(b)(4)-
<b>TOTAL</b>		-(b)(4)-	-(b)(4)-
<b><i>Outer Tablet; Type 4</i></b>			
Anhydrous Lactose, ----(b)(4)-----	Diluent	-(b)(4)-	-(b)(4)-
Microcrystalline cellulose, ----(b)(4)-----	Diluent	-(b)(4)-	-(b)(4)-
Magnesium Stearate, (b)(4)	Lubricant	-(b)(4)-	-(b)(4)-
<b>TOTAL</b>		-(b)(4)-	-(b)(4)-
<b>TOTAL: COMPRESSION-COATED CORE</b>		-(b)(4)-	
<b><i>Enteric Coating</i></b>			
Core	Tablet	-(b)(4)-	-(b)(4)-
Cellacefate, ----(b)(4)-----	Enteric polymer	(b)(4)	-(b)(4)-
Castor Oil, ----(b)(4)-----	Plasticizer	(b)(4)	-(b)(4)-
Acetone, ----(b)(4)-----	Solvent	*	
Alcohol -----(b)(4)-----	Solvent	*	
<b>Target Weight Gain</b>		(b)(4)	-(b)(4)-
<b>TOTAL OF ENTERIC-COATED TABLET</b>		-(b)(4)-	-(b)(4)-

**Table LL: Composition of Adenovirus Tablets, Type 7**

<b>Ingredient</b>	<b>Function</b>	<b>Mg/Tab</b>	<b>%w/w</b>
<b><i>Inner Core: Type 7</i></b>			
Formulated Adenovirus Type 7, Lyophilized Int.	Active	-(b)(4)-	-(b)(4)-
Anhydrous Lactose, , ----(b)(4)-----	Diluent	-(b)(4)-	-(b)(4)-
Microcrystalline cellulose, , ----(b)(4)-----	Diluent	-(b)(4)-	-(b)(4)-
Polacrillin Potassium, , ----(b)(4)-----	Disintegrant	-(b)(4)-	-(b)(4)-
Magnesium Stearate, (b)(4)	Lubricant	-(b)(4)-	-(b)(4)-
<b>TOTAL</b>		-(b)(4)-	-(b)(4)-
<b><i>Outer Tablet: Type 7</i></b>			
Anhydrous Lactose, , ----(b)(4)-----	Diluent	-(b)(4)-	-(b)(4)-
Microcrystalline cellulose, , ----(b)(4)-----	Diluent	-(b)(4)-	-(b)(4)-
FD&C Yellow #6 Aluminum Lake, ----(b)(4)----- -----	Colorant	-(b)(4)-	-(b)(4)-
Magnesium Stearate, (b)(4)	Lubricant	-(b)(4)-	-(b)(4)-
<b>TOTAL</b>		-(b)(4)-	-(b)(4)-
<b>TOTAL: COMPRESSION-COATED CORE</b>		-(b)(4)-	
<b><i>Enteric Coating</i></b>			
Core	Tablet	-(b)(4)-	-(b)(4)-
Cellacefate, , ----(b)(4)-----	Enteric polymer	-(b)(4)-	-(b)(4)-
Castor Oil, , ----(b)(4)-----	Plasticizer	-(b)(4)-	-(b)(4)-
Acetone, , ----(b)(4)-----	Solvent	*	
Alcohol, , ----(b)(4)-----	Solvent	*	
<b>Target Weight Gain</b>		-(b)(4)-	-(b)(4)-
<b>TOTAL OF ENTERIC-COATED TABLET</b>		-(b)(4)-	-(b)(4)-

#### 1.8.4.1.7.3. Disintegration and Residual Solvent

Table 28 below presents the results for disintegration in (b)(4) - and residual solvents.

[(b)(4)]

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----- (b)(4) -----  
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#### 1.8.4.1.10. Conclusion

Teva/Barr Laboratories has developed and optimized an enteric coating process for the live Adenovirus tablets. The physical nature of the film coat has been investigated and found to exhibit reduction in possible defects when manufactured using the optimized coating process. The optimization of the coating process has resulted in --(b)(4)--- of the coating weight gain per tablet from ----(b)(4)----- . The optimized process results in a smoother, more even tablet coat that has been functionally tested using (b)(4) disintegration tests for delayed-release tablets. Results of (b)(4) disintegration testing

indicate that the optimized(b)(4) coat is comparable in functional performance to the un-optimized (b)(4) coat in terms of protection of tablet contents under testing conditions. The optimized (b)(4) weight gain per tablet brings the composition of the Barr product closer to that of the Wyeth product that has been used previously. The stability results for batches on stability with the -(b)(4)- coating weight gain are also acceptable over long-term storage at the recommended storage conditions.

### 1.8.5 Final Formula & Process

The major formulation and process changes compared to Phase I are:

- Use of lyophilized virus manufactured in-house in place of outsourcing
- -----(b)(4)-----
- Replacement of Microcrystalline Cellulose --(b)(4)-- with Microcrystalline Cellulose --(b)(4)--
- --(b)(4)-- of amount of Castor Oil in the coating composition
- Use of optimized process parameters for coating
- Use of equipment in all unit operations

The final formulae for the manufacturing of clinical batches for Phase III have been presented in the Table 18 and Table 19.

The Phase III formulations also represent the proposed commercial formulations.

### 1.8.7 Batch Evaluation

All batches of Adenovirus Tablets, Type 4 and Type 7 have been evaluated by the established test methods and specifications. Table NN and Table OO summarize the methods, specifications and results for two batches only.

**Table NN: Adenovirus Tablets, Type 4 Batch#: -----(b)(4)-----**

Tests	Methods	Limits	Results
Description	MTH-732	----- ----- (b)(4) ----- ----- -----	Conforms
Infectivity (Assay)		----- (b)(4) -----	5.5 logTCID50
Infectivity ----- (b)(4) -----		----- (b)(4) -----	Mean: 5.4 logTCID50 Max: 5.7 logTCID50 Mini: 4.8 logTCID50
Identification (b)(4)		----- (b)(4) -----	Positive
Identification (b)(4)		----- (b)(4) -----	Positive
Disintegration --(b)(4)--	--(b)(4)--	----- (b)(4) ----- -----	Conforms
Residual Solvents -(b)(4)- -(b)(4)- Water	MTH-732	-----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	0.3% 1.3% 3.3%
General Safety		(b)(4)	Pass
----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) ----- -(b)(4)- ----- (b)(4) -----		-----(b)(4)----- -----(b)(4)----- --(b)(4)-- --(b)(4)--	---(b)(4)-- --(b)(4)-- --(b)(4)-- --(b)(4)--



**Table OO: Adenovirus Tablets, Type 7 Batch#: -----(b)(4)-----**

Tests	Methods	Limits	Results
Description	MTH-732	----- ------(b)(4)----- -----	Conforms
Infectivity (Assay)		------(b)(4)-----	5.8 logTCID <sub>50</sub>
Infectivity -----(b)(4)-----		------(b)(4)-----	Mean: 5.6 logTCID <sub>50</sub> Max: 6.0 logTCID <sub>50</sub> Mini: 5.4 logTCID <sub>50</sub>
Identification (b)(4)		------(b)(4)-----	Positive
Identification (b)(4)		------(b)(4)-----	Positive
Disintegration SGF SIF	--(b)(4)---	------(b)(4)----- -----	Conforms
Residual Solvents -(b)(4)- -(b)(4)- Water	MTH-732	-----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	0.3% 1.3% 2.5%
General Safety		(b)(4)	Pass
------(b)(4)---- ------(b)(4)----- ------(b)(4)----- -(b)(4)- ------(b)(4)-----		-----(b)(4)----- -----(b)(4)----- -(b)(4)- -(b)(4)	--(b)(4)-- --(b)(4)-- -(b)(4)- -(b)(4)-

**Comment.** The lower and upper limits of Ad4 and Ad7 titer were the same as those used by Wyeth in their licensed product.

The major differences in the development pharmaceuticals of products from Wyeth, from Phase I clinical studies through Phase III clinical studies of Barr/Teva are tabulated in Table PP.

**[(b)(4)]**

#### **1.12. CONCLUSION**

The components, composition and process selected for Adenovirus Tablets, Type 4 and Adenovirus Tablets, Type 7 resulted in meeting most important attributes of a drug product – manufacturability, reproducibility, quality, stability, safety and efficacy.

1. The formulations and the processes discussed in this report for the manufacturing of Adenovirus Tablets Type 4 and Type 7 worked well to produce the final drug products.
2. The drug products met all the established acceptance criteria.

3. The parameters selected for each unit operation produced product that met its quality requirement.
4. Successful execution of 3 batches of each drug product has established the reproducibility in manufacturing and consistency in quality of the drug products.
5. Available data for stability studies for the Phase III clinical batches indicated that the Barr products were stable at 2-8 for in the primary packaging.
6. Stability of the drug product in an experimental packaging configuration can be predicted in an ambient condition (controlled room temperature).
7. Barr Adenovirus Tablets, Type 4 and Adenovirus Tablets, Type 7 have demonstrated desirable therapeutic effects in a Phase III clinical study.
8. Both the products have been found to be safe to use.

## 1. STABILITY SUMMARY AND CONCLUSION

To date, stability data have been generated on 3 batches each of Adenovirus Vaccine Live Oral Type 4 and Adenovirus Vaccine Live Oral Type 7 manufactured by the process described in 3.2.P.3.3. A summary of the batches of Adenovirus Vaccine Live Oral Type 4 and Type 7 is presented in Table 1. In addition, stability testing was carried out on the packaged Phase III clinical trial material (2 tablet bottle containing one tablet each of Ad4 and Ad7). The stability testing for the clinical trial material is summarized below in Table QQ. Protocols for all stability studies as listed below are provided in this section. Stability studies included testing for appearance, disintegration, water, infectivity and microbial limits. The methods and acceptance criteria for appearance, disintegration, infectivity and water are as provided in 3.2.P.5.1.

**Table QQ: Summary of Adenovirus Vaccine Live Oral Type 4 and Type 7 Batches Used in Stability Studies**

Batch Numbers	-----(b)(4)----	-----(b)(4)----	-----(b)(4)----	-----(b)(4)----	-----(b)(4)----	-----(b)(4)----
Batch Size (units)	-(b)(4)-tablets	-(b)(4)-tablets	-(b)(4)-tablets	-(b)(4)-tablets	-(b)(4)-tablets	-(b)(4)-tablets
Site of Manufacture	Adenovirus Facility, Forest VA	Adenovirus Facility, Forest VA	Adenovirus Facility, Forest VA	Adenovirus Facility, Forest VA	Adenovirus Facility, Forest VA	Adenovirus Facility, Forest VA
Date of Manufacture	19-Jun-2006	19-Oct-2006	01-Nov-2006	23-May-2006	23-Aug-2006	24-Aug-2006
Virus Type	Type-4	Type-4	Type-4	Type-7	Type-7	Type-7
Container Closure Description	Bottle: 60cc -(b)(4)- White, Wide Mouth, Round, 38/400 Cap: Plastic ----- ---(b)(4)----- -----	Bottle: 60cc -(b)(4)- White, Wide Mouth, Round, 38/400 Cap: Plastic ----- ---(b)(4)----- -----	Bottle: 60cc -(b)(4)- White, Wide Mouth, Round, 38/400 Cap: Plastic ----- ---(b)(4)----- -----	Bottle: 60cc -(b)(4)- White, Wide Mouth, Round, 38/400 p: Plastic ----- ---(b)(4)----- -----	Bottle: 60cc -(b)(4)- White, Wide Mouth, Round, 38/400 Cap: Plastic ----- ---(b)(4)----- -----	Bottle: 60cc -(b)(4)- White, Wide Mouth, Round, 38/400 Cap: Plastic ----- ---(b)(4)----- -----
Stability Study Number	ARD_PRT-1559	ARD_PRT-2091	ARD_PRT-2092	ARD_PRT-1558	ARD_PRT-1988	ARD_PRT-1989
Stability Study Start Date	27-Jun-2006	14-Dec-2006	14-Dec-2006	14-Jun-2006	13-Sep-2006	13-Sep-2006

**Table RR: Summary of Adenovirus Vaccine Live Oral Type 4 and Type 7 Clinical Trial Material Used in Stability Studies**

<b>Batch Numbers</b>	----- (b)(4) ----- ----- (b)(4) -----	----- (b)(4) ----- ----- (b)(4) -----	----- (b)(4) ----- ----- (b)(4) -----	----- (b)(4) ----- ----- (b)(4) -----
<b>Packaging Configuration</b>	Bottle (1 Type 4 and 1 Type 7)	Bottle (1 Type 4 and 1 Type 7)	Bottle (1 Type 4 and 1 Type 7)	Bottle (1 Type 4 and 1 Type 7)
<b>Date of Packaging</b>	14-Jul-2006	30-Nov-2006	15-Mar-2007	15-Jun-2007
<b>Container Closure System</b>	Bottle: 30cc (b)(4), White, Wide Mouth, Round, 28/400 Cap: Plastic ----- (b)(4) ----- -----	Bottle: 30cc (b)(4), White, Wide Mouth, Round, 28/400 Cap: Plastic ----- (b)(4) ----- -----	Bottle: 30cc (b)(4), White, Wide Mouth, Round, 28/400 Cap: Plastic ----- (b)(4) ----- -----	Bottle: 30cc (b)(4), White, Wide Mouth, Round, 28/400 Cap: Plastic ----- (b)(4) ----- -----
<b>Stability Study Number</b>	<a href="#">ARD_PRT-1911</a>	<a href="#">ARD_PRT-2120</a>	<a href="#">ARD_PRT-2317</a>	<a href="#">ARD_PRT-2318</a>
<b>Stability Study Start Date</b>	17-Jul-2006	23-Jan-2007	27-Jun-2007	27-Jun-2007

## 1.1. Stability Protocol

Adenovirus Vaccine Live Oral Type 4 and Type 7 has been and will continue to be tested according to the stability protocol summarized below in Table SS. The packaged Phase III clinical trial material was tested according to the stability protocol summarized below in Table TT.

**Table SS: Summary of Stability Testing of Adenovirus Vaccine Live Oral Type 4 & Type 7**

Storage Condition	Packaging Configuration	Testing Intervals
2-8°C	Bottle (100's)	0, 3, 6, 9, 12, 18 and 24 months
----- (b)(4) ----- -----	Bottle (100's)	0, 7 days, 14 days, 1 month, 2 months, & 3 months

**Table TT: Summary of Stability Testing of Clinical Trial Materials, Adenovirus Vaccine Live Oral Type 4 and Type 7**

Storage Condition	Packaging Configuration	Testing Intervals
2-8°C	Bottle (1 Type 4 and 1 Type 7)	0, 1, 3, 6, 9, 12, 14.7 and 15.9 Months
----- (b)(4) ----- -----	Bottle (1 Type 4 and 1 Type 7)	0, 1, 2 and 3 months

The results for Adenovirus Vaccine Live Oral Type 4 and Type 7 are presented in [3.2.P.8.3](#). The initial time point data in the tables represents the batch analysis data generated for each batch at the time of manufacture.

## 1.2. Discussion

The stability data demonstrate that the Adenovirus Tablets, Type 4 and Type 7 remain within acceptable physical, chemical and biological limits when stored for 18 months at

the recommended storage conditions of 2-8°C. Although the drug product batches stored at 2-8°C meet all acceptance criteria, the 100 count bottles stored at (b)(4) fail infectivity criteria after 1 month. [See Appendix Tables UU and VV Appendix pages 34 and 35)] for one batch of Ad7 tablets. Similar results were found for other batches of Ad7 and for the Ad4 tablets.] This is in contrast to the 2 count bottles and the 50 count bottles stored at (b)(4) data, which meet all acceptance criteria. This loss of titer in the 100 count bottles stored at (b)(4) is likely due to an interaction between humidity and temperature that is not well understood. Moisture data would indicate that humidity is controlled appropriately in our commercial packaging. However, ---(b)(4)----- in the 2 count and 50 count bottles respectively indicate that moisture may play a part in the degradation pathway. Overall, the stability data indicate that Adenovirus Tablets, Type 4 and 7 will remain in acceptable physical, chemical and biological limits when stored at 2-8°C for the duration of the stability studies. Therefore the recommended storage condition is 2-8°C.

### **Date of Manufacture**

The dating period for Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture (DOM) shall be defined as the date that the drug substance (Adenovirus Type 4 lyophilized intermediate or Adenovirus Type 7 lyophilized intermediate) is blended with the inner core excipients (anhydrous lactose, microcrystalline cellulose, polacrillin potassium and magnesium stearate) prior to inner core compression. For example, for an Adenovirus Type 4 batch blended on April 24, 2011, and taken through tableting on April 28, 2011, DOM of this bottle of 100 tablets would be April 24, 2011. For a product with a 2-year expiry, the expiration date for this bottle would be 04/2013 (as expiry occurs on the last day of the month of manufacture). The dating period for your drug substance shall be 24 months when stored at 2-8°C. The expiration date for the packaged product, Adenovirus Type 4 and Adenovirus Type 7 Vaccine, Live, Oral, shall be dependent on the shortest expiration date of any component.

### **1.3. Storage Conditions**

The recommended storage conditions for Adenovirus Vaccine Live Oral Type 4 and Type 7 is 2 - 8°C, protected from light.

**CBER Comment:** Results submitted in Module 3.2.P.8.3 described stability data for up to 24 months at 2 to 8°C for the Ad4 and Ad7 drug substances and the Ad4 and Ad7 final tablets. The data indicated that the products were stable under the storage conditions for 24 months.

## **2. ADVENTITIOUS AGENTS SAFETY EVALUATION**

The final dosage form of this vaccine is a unique oral tablet containing live adenovirus. The tablet is not sterile, but is tested and controlled for bioburden. In addition, the tablets are tested for General Safety as a release specification. In order to control the risk of introduction of adventitious agents into the tablet, all the raw materials and intermediate products making up the drug substance are extensively tested to exclude the presence of viral and non-viral adventitious agents. The adventitious agents testing was based on FDA Draft Guidance for Industry:

Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases - 9/28/2006. Furthermore, the excipients used to make the drug product are controlled for bioburden and the magnesium stearate is sourced from US origin material.

### **Control of Components of the Drug Substance**

The bulk virus and formulated virus are produced at -----(b)(4)----- cGMP virus production facility, which is described in section 3.2.A.1. This facility is designed with air handling to meet class(b)(4) specifications with all open manipulations in --(b)(4)-- biological safety cabinets. All media, sera and (b)(4) are tested for viral and non-viral adventitious agents prior to release as described in 3.2.S.2. All bovine sera are sourced from -----(b)(4)----- and is irradiated. All (b)(4) is sourced from the USA. All other components of the media are free from mammalian derived materials. The WI-38 cell banks and Ad4 and A7 Master Virus Seeds and Working Virus Seeds have been extensively tested for the presence of potential contamination with both viral and non-viral adventitious agents. The testing and results are outlined in 3.2.S.2.3. The Ad4 and Ad7 viruses used for production of the Master Virus Seeds were supplied by Wyeth Laboratories and was produced using bovine sera collected before Jan. 1, 1980. Every bulk virus lot produced for the vaccine is extensive tested for the absence of viral and nonviral adventitious agents prior to release. These tests and results are outlined in 3.2.S.2. The formulated virus contains Human Serum Albumin supplied by -(b)(4)- using US sourced sera and that is extensively tested for viral and non-viral adventitious agents as outlined in Section 3.2.S.2.

### **Control of the Drug Product**

The final dosage form is an oral tablet and is produced in a dedicated facility that only lyophilizes the formulated virus to make the drug substance and produces the enteric-coated tablet. The adenovirus facility is described in 3.2.A.1 and is designed to isolate adenovirus within an active zone to prevent cross-contamination or introduction of excessive bioburden during the manufacturing process.

### **Lot-Release Protocol**

This was the subject of separate discussion with Barr/Teva and the protocol was reviewed by OVR and comments conveyed to the sponsor. The final lot-release protocol for both the Ad4 and Ad67 components contains:

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**CBER Comment.** This protocol was discussed with the BLA team and with Barr/Teva. It seems appropriate to this reviewer.

**CBER Comment.** This additional section describes the development of the enteric coating process by Barr/Teva. It is not necessary for the review but it is inserted for the completeness of information for the reviewer.

#### 1.8.4.1. Development Of Enteric Coating Process

#### 1.8.4.1.1. Overview

Adenovirus Tablets contain a live virus formulated in a compressed tablet to be administered orally. The product is designed to disintegrate in the intestine. Hence, protection of the live virus from the acidic environment in the stomach is critical to product performance. The formulation accomplishes this protection through enteric coating. The protection afforded to the product by enteric coating is based on the presence of an acid-insoluble film on the surface of the product. The presence of this acid-insoluble film prevents the stomach acid from coming in contact with and deactivating the product. Typically, coating dosage forms with a polymeric film that is insoluble in the stomach but dissolves rapidly in the intestine has conferred enteric properties. The predominant mechanism by which such behavior is achieved is through the use of polymeric film coats, which exhibit pH-dependent water solubility. Enteric polymers currently used to coat pharmaceutical dosage forms include cellulose, vinyl, and acrylic derivatives. These polymers exhibit resistance to gastric fluids yet are readily soluble or permeable in intestinal fluid. Enteric polymeric materials are primarily weak acids containing acidic functional groups, which are capable of ionization at elevated pH. In the low pH of the stomach, the enteric polymers are un-ionized and, therefore, insoluble. As the pH increases in the intestinal tract, these functional groups ionize, and the polymer becomes soluble in the intestinal fluids. Thus, an enteric polymeric film coating allows the coated solid to pass intact through the stomach to the small intestine, where the dosage form disintegrates and allows the drug release for absorption. Enteric coating is the process of depositing this film of acid insoluble polymer on the surface of the tablet. The performance of the enteric-coated tablet is dependent upon the quality of film formation on the tablet and the quantity of enteric coating on the tablet as it relates to film thickness. The required film thickness will be dependent upon the quality of the formed film. Optimal film formation corresponds to a smooth, continuous film coating that uniformly covers the entire tablet surface. The presence of fissures and imperfections in the continuous film coating has a negative impact on the integrity of the film and can result in film failure at low pH. Under these circumstances, greater film thickness will be required to assure the presence of a continuous barrier around the tablet. -----

-(b)(4).



3 Pages redacted (b)(4)