



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service  
Food and Drug Administration  
1401 Rockville Pike  
Rockville, MD 20852-1448

**MID-CYCLE MEETING SUMMARY**

|                   |  |
|-------------------|--|
| To:               | The File   |
| Date and Time:    | December 8, 2010 10:00–11:00 am                  |
| STN#:             | 125296/0   |
| Supplement Type:  | BLA  |
| Sponsor:          | Teva Women's Health, Inc.                        |
| Product:          | Adenovirus Type 4 and Type 7, Vaccine Live, Oral |
| Meeting Chair:    | Daryll Miller, M.A.                              |
| Meeting Recorder: | Helen Gemignani, B.S. and Darlene Hithe, B.A.    |
| Signature:        |  |

**CBER/FDA Attendees**

Marion Gruber, PhD, OVRR  
Wellington Sun, MD, DVRPA/OVRR  
Robin Levis, PhD, DVP/OVRR  
William McCormick, DPQ/OCBQ

**Review Team:**

Daryll Miller, Chair, DVRPA/OVRR  
Darlene Hithe, RPM, DVRPA/OVRR  
Helen Gemignani, RPM, DVRPA/OVRR  
Lewis Schrager, MD, Medical Officer, DVRPA/OVRR  
Claudia Wrzesinski, DVM, PhD, Toxicology, DVRPA/OVRR  
David Schwab, Electronic Integrity, DVRPA/OVRR (did not attend)  
Mridul Chowdhury, PhD, Biostatistics, DB/OBE  
Wei Hua, MD, PhD, MS, MHS, Epidemiology, DE/OBE  
Keith Peden, PhD, Product, DVP/OVRR  
Gang Wang, PhD, CMC Facility Inspection, DMPQ/OCBQ  
Loan Nguyen, Labeling, APLB/OCBQ  
Solomon, Yimam, Bioresearch Monitoring, DIS/OCBQ  
Karen Campbell, Product Testing, DPQ/OCBQ  
Rajesh Gupta, PhD, Product Testing, DPQ/OCBQ

**1.0 PURPOSE**

For the review team to present to management a summary of reviews and the resolution of issues.

## **2.0 BACKGROUND**

BLA 125296/0 was received by CBER on September 30, 2008 with the proposed indication for active immunization against acute respiratory disease by adenovirus type 4 and type 7. A Complete Response Letter was sent on the first Action Due on July 16, 2009. A Resubmission was received on September 14, 2010 and the new Action Due is March 16, 2011.

In 2010, Duramed Research Inc. changed the name of their company to Teva Women's Health, Inc.

### **2.1 Review Committee**

The review committee is as follows: (See meeting participants above.)

### **2.2 Milestones**

#### **First Review Cycle:**

|               |                    |
|---------------|--------------------|
| BLA Received: | September 30, 2008 |
| CR Letter:    | July 16, 2009      |

#### **Resubmission:**

|                                    |                    |
|------------------------------------|--------------------|
| Received:                          | September 14, 2010 |
| 1st Draft Reviews Due:             | November 13, 2010  |
| 2 <sup>nd</sup> Draft Reviews Due: | December 28, 2010  |
| Final Reviews Due:                 | January 27, 2011   |
| Final Action Due:                  | March 16, 2011     |
| Action Pkg for Posting Due:        | March 16, 2011     |

### **2.3 Meetings**

|                          |   |
|--------------------------|---|
| First Committee Meeting: | October 1, 2010   |
| PeRC:                    | May 7, 2009 (full waiver)   |
| VRBPAC:                  | N/A   |
| Monthly Team Meetings:   | October 29, 2010<br>January 28, 2011<br>February 25, 2011<br>March 25, 2011 |
| Labeling Meetings:       | October 28, 2010, January 14, 2011  |
| Midcycle Review Meeting: | December 8, 2010  |
| SWG:                     | TBD   |

### **2.4 Information Requests**

Most Information Requests have been in the area of testing and reagent requests. Others were for Proprietary Name resolution, scale up procedures, request for stability data, PM safety plan, and 483 items.

### **2.5 Amendments**

The sponsor submitted 24 amendments during the first review cycle, one in the second review cycle, and five administrative amendments during that interim period.

### **3.0 DISCUSSION TOPICS**

During the first review cycle the sponsor had difficulty with manufacturing. A Complete Response (CR) letter was issued due to manufacturing problems in July 2009. The sponsor's resubmission was received in September 2010.

#### **3.1 Product - Keith Peden, DVP/OVRR**

No additional product issues have been identified since the resubmission. The submission includes stability data up to 24 months which will be addressed in the final product review memo.

#### **3.2 Inspection – Gang Wang, DMPQ/OCBQ**

The original CR issues involved cleaning validation, manufacturing deviations, and the inability of the sponsor to manufacture a GMP lot. The sponsor has addressed each of these issues in the resubmission. The root cause of the manufacturing deviations which caused discoloration of the bulk and a hissing sound of the bulk bottles was not thoroughly identified. The sponsor believes that -----(b)(4)----- in the shipping container could have caused a pH deviation. We have requested an SOP from the sponsor which addresses how they will conduct manufacturing deviation investigations in the future to include how they will handle the product in the event of a similar investigation. The batch records for one lot of each Type 4 and Type 7, manufactured since the CR, have been reviewed and everything appears ok. These two lots along with the six lots manufactured in 2006 will be used to support consistency. The sponsor will not need to manufacture very many lots each year as each lot yields approximately --(b)(4)--- tablets, and at (b)(4) lots manufactured per year, should provide sufficient supply for military use.

#### **3.3 Testing - Rajesh Gupta, DPQ/OCBQ**

Review of the resubmission revealed that the sponsor changed the Identity test without informing CBER. The testing the sponsor is using is more than what is required. CBER will only use a simplified method for in support and release testing. All in support testing is now complete and the testing plan and lot release protocol are being finalized and should be done by the end of December. It is anticipated that release testing will take approximately 5 – 6 weeks. DPQ has some items for discussion with Teva in regard to the Lot Release protocols. A telecom will be scheduled with Teva.

#### **3.4 Clinical - Lewis Schrager, MD, DVRPA/OVRR**

Revision of clinical review nearly completed and Dr. Schrager awaits receipt of response to his Information Request for separate solicited AE and unsolicited AE tables. Clarification of the sponsor's definition of seronegativity and what is counted as seroconversion has been requested from the sponsor. Additionally, we have some concern that there is no clinical endpoint for ADV7 disease and we have never requested a level of neutralizing antibody for ADV7. CBER will need to determine if a post-marketing study should be requested since ADV7 is essentially being approved with only a surrogate endpoint. We have asked the sponsor to formulate a rationale to extrapolate the clinical data from ADV4 to support the approval of ADV7. We may be able to avoid what appears to be a "precedent setting" approval by following what was done to support the approval of several other products with multiple serotypes all of which did not have clinical endpoints. This will be further explored by the clinical reviewer.

The last clinical issue discussed involved the population described in the label which states for “military populations”. This may be too restrictive but may be in alignment with the original Wyeth Adeno and JEVAX labels. The clinical reviewer will confirm the population description in the original label.

### **3.5 Biostatistics - Mridul Chowdhury, DB/OBE**

There are no statistical issues. Review of the data supports 99% efficacy of ADV4 and a 92% seroconversion rate for ADV7.

### **3.6 Bioresearch Monitoring - Solomon Yimam, DIS/OCBQ**

The Bioresearch Monitoring final review memo was issued on April 20, 2010. Two bioresearch monitoring inspections were conducted by the Baltimore District Office in support of the BLA.

### **3.7 Epidemiology/Postmarketing - Wei Hua, MD, MPH, DE/OBE**

Based on the review of the pharmacovigilance plan, DE/OBE recommends approval.

### **3.8 Toxicology - Claudia Wrzesinski, DVRPA/OVRR**

The sponsor proposed a pregnancy category C. After a literature review regarding adenovirus infections in pregnant women which documents adenovirus being found in the amniotic fluid, CBER recommends pregnancy category D.

### **3.9 Proprietary Name - Loan Nguyen, APLB/OCBQ**

The sponsor has withdrawn the request for a proprietary name; therefore only the proper name will be used on packaging and labeling. There is a concern with the carton text since the name TEVA was added. The company name is too prominent and may be confused as the drug name. The sponsor will be asked to revise the carton.

### **3.10 Labeling/SBRA – Daryll Miller, DVRPA/OVRR**

Labeling comments will be sent to the sponsor by December 17<sup>th</sup>. The SBRA will begin at the end of December. The clinical and inspection final reviews are still required for the completion of the SBRA.

### **3.11 Action Status - Helen Gemignani, DVRPA/OVRR**

Approval is targeted for mid February.

## **4.0 CONCLUSION**

The review is progressing on schedule and it is anticipated that the product will be approved.

## **5.0 SUMMARY OF ACTION ITEMS - None**