Summary Basis for Regulatory Action

Date: March 16, 2011

From: Daryll L. Miller, ALM, Committee Chair

BLA/ STN#: 125296/0

Applicant Name: Teva Women's Health, Inc.

Date of Submission: September 30, 2008

Complete Response Letter Issued: July 16, 2009

Date of Resubmission: September 14, 2010

PDUFA Goal Date: March 16, 2011

Proprietary Name: None

Established Name: Adenovirus Type 4 and Type 7 Vaccine, Live, Oral

Indication: Active immunization for the prevention of febrile acute respiratory disease (ARD) caused by Adenovirus Type 4 and Type 7. For use in military populations 17 through 50 years of age.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Norman W. Baylor, Ph.D., Director, Office of Vaccines Research and Review

√ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**
Clinical Review	Lewis Schrager, M.D. – 3/2011
Statistical Review	Mridul Chowdhury, Ph.D. – 4/2009
CMC Review	Keith Peden, Ph.D. – 3/2011
Pharmacology/ Toxicology Review	Claudia Wrzesinski, Ph.D. - 5/2009
Advertising and Promotional Labeling	Loan Nguyen, Pharm D. – 1/2011
Biomonitoring Bioresearch Monitoring Review	Solomon Yimam – 4/2010
Facility Review and Inspection	Gang Wang, Ph.D. – 2/2011; 12/2010
Postmarketing Surveillance	Wei Hua, M.D., Ph.D. – 1/2011
DPQ Review	Rajesh Gupta, Ph.D. – 1/2011

1. Introduction

Duramed Research, Inc., a subsidiary of Barr Laboratories, Inc., submitted biologics license application (BLA) 125296 on September 30, 2008 for licensure of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, Enteric Coated Tablets, to prevent febrile acute respiratory disease in military populations caused by Adenovirus Type 4 and Type 7. This BLA included information on product development and characterization, manufacturing process validation and details of all in-process and quality control testing to ensure the safety, purity, potency of product intended for release to market and also included clinical data on safety and efficacy of the product. Efficacy and safety data in the BLA are from two clinical studies conducted under IND (b)(4), which was first submitted in July, 2004. Only a Phase 1 and a Phase 3 study were required since the vaccine previously produced by Wyeth was given to the military population for more than 20 years between the 1970's and the 1990's. Product licensing inspections were conducted in both production facilities (one of them, ----------(b)(4)-------, is a contract manufacturer). A Complete Response letter was sent to the applicant on July 16, 2009. Deficiencies identified in this letter related to several aspects of the review, but the critical deficiencies were related to product manufacturing and inspectional issues. In 2010, Barr Laboratories, Inc. was purchased by Teva Pharmaceuticals and Duramed's name was changed to Teva Women's Health, Inc. However, the manufacturing facility that produces the drug substance and drug product retained the name of the original company, Barr Laboratories. The applicant submitted a complete response to the Complete Response letter on September 13, 2010. The response reset the review clock to a due date of March 16, 2011. Teva Women's Health Inc. will hold the license.

This document includes summaries of each of the major review disciplines associated with the review of this BLA and highlights the major issues covered and brought to resolution during the review process for Adenovirus Type 4 and Type 7 Vaccine, Live, Oral. These include:

1. Manufacturing issues related to producing two live vaccines in a tablet form.
2. Labeling issues regarding age range for use.
3. Pregnancy Category determination.

2. Background

Adenovirus Type 4 and Type 7 Vaccine, Live, Oral is manufactured from the same human adenovirus type 4 and 7 strains propagated on WI-38 cells as Wyeth Laboratories, Inc. that (Wyeth) had developed, produced, and used in the military from 1971 to 1996. Wyeth transferred the type 4 and type 7 adenovirus seeds to Barr Laboratories, as well as the various production and testing documents necessary to produce the type 4 and 7 adenovirus drug substances.

The key starting materials and manufacturing processes for the drug substances are nearly identical between the Barr process and the process used by Wyeth to produce the previously licensed Adenovirus Type 4 and Type 7 drug substances. The virus strains have not been attenuated or otherwise genetically modified in any way so they are wild type virus strains with the potential to cause infection and disease. Three minor changes were made to the processing of drug substance in comparison to the Wyeth process: (1) antibiotics were not

used in the growth medium in the Barr process, ----------(b)(4)----------
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Adenovirus Type 4 and Type 7 Vaccine, Live, Oral is a two component vaccine. Each dose of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral contains one tablet of Adenovirus Type 4 component and one tablet of Adenovirus Type 7 component. Adenovirus Type 4 (ADV-4) and Adenovirus Type 7 (ADV-7) tablets each contain not less than 32,000 tissue-culture infective doses (4.5 log10 $TCID_{50}$). All tablets are manufactured with an inner core containing (b)(4) of Lyophilized Intermediate (drug substance). The outer layer of the ADV-7 tablet contains FD&C Yellow #6 Aluminum Lake dye to distinguish it from the Adenovirus Type 4 tablets. The final layer of all tablets is an enteric coating. The vaccine is supplied in a single 100-dose package containing one bottle of 100 tablets of ADV-4 and one bottle of 100 tablets of ADV-7. The proposed shelf life is 24 months at 2-8°C and the date of manufacturing starts from the date that the drug substance (lyophilized intermediate) is blended with the inner core excipients prior to inner core compression.

This vaccine is intended for use in the military population 17 through 50 years of age with an administration schedule of a single dose.

3. Chemistry Manufacturing and Controls (CMC)

The initial procedure for Adenovirus Type 4 and Type 7 Vaccine, Live, Oral was developed by the Department of the Army in the late 1960's under IND (b)(4) (Type 4) and IND (b)(4) (Type 7). These INDs were withdrawn in September 1980. After the vaccine manufacture was transferred to Barr Laboratories in 2004, a new IND -(b)(4)- was submitted in July, 2004. Barr refined the manufacturing process to modernize it. In addition, the dye that was originally used to distinguish Adenovirus Type 7 tablets (ADV-7) from the Adenovirus Type 4 tablets (ADV-4) was replaced because the original dye used by Wyeth caused hypersensitivity reactions. Vaccine tablets manufactured at the Barr facility were used for Phase 1 and 3 studies.

The manufacturing process for the production of the ADV-4 and ADV-7 Vaccine, Live, Oral is based on the inoculation of the human diploid cell line WI-38 with Adenovirus seed stocks ---------(b)(4)----------. The virus harvest is filtered and tested. ----------
----------(b)(4)----------

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

Manufacturing Facilities

Formulated Virus --------(b)(4)----------
-----(b)(4)-----
--------(b)(4)----------
-----(b)(4)--------

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

The formulated virus batches are manufactured by the contract manufacturer ----------(b)(4)---------- to Virginia, USA, for further manufacturing to drug substance and drug product.

Drug Substance and Drug Product	Barr Laboratories 1235 Mays Mill Road, Forrest, VA 24551, USA

There were no significant issues identified in the CMC sections of the BLA. Here is a summary of manufacturing process and the testing done at each stage, beginning with formulation of Master and Working stocks:

A. Product Quality

Critical elements of the product information, included in the BLA, are related to the novel aspects of the product, the characterization of the cell substrate and the Master Virus Seeds produced from the Wyeth Working Seeds, validation of the manufacturing process for the Bulk Virus, the Intermediate Drug Substance and the Final Drug Product, development of appropriate quality control testing plan to ensure manufacturing consistency and final container product quality, and stability data to support the hold times for intermediates and bulks, and to support the requested shelf life for the product once released for market distribution. Data and information included in the BLA demonstrate that the manufacturing process is well controlled. Below are some of the critical aspects of the product review. Details of each process can be found in the product review.

- **The Cell Substrate**

  The Master Cell Bank -----(b)(4)------ was manufactured at ---(b)(4)-------. The assays listed below have been reviewed for assay validation and the product reviewer found the results acceptable.

  Results Summary

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

- **Adenovirus Seeds**

  Wyeth Laboratories, Inc., Marietta, PA, supplied all virus-starting materials. From these Adenovirus Type 4 (ADV-4) and Adenovirus Type 7 (ADV-7) stocks, Master Virus Seeds of each were prepared in WI-38 cells by -----(b)(4)-------. Summaries of the passage history of the ADV-4 and ADV-7 seed viruses are provided in the submission.

- **Virus Seed Stocks**

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

2 pages redacted (b)(4)

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

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

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

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

Issues Identified with the Manufacturing Process

The applicant did not manufacture any lots of ADV-4 or ADV-7 between the initiation of the Phase 3 study and the pre-license inspection (PLI) for the BLA (2006 – 2009). The applicant manufactured one non-CGMP lot of ADV-4 during the inspection, which was considered to be non-CGMP because two of the bulk virus bottles used in the lyophilization step may have been contaminated. The applicant failed to demonstrate that they could consistently manufacture the product that met the CGMP requirement and product specifications. This failure prompted the review team to issue a Complete Response (CR) letter on July 16, 2009. Other issues identified during the inspection which had not been addressed by the date of the first review cycle Action Due date were also included in the CR letter. These issues included

incomplete cleaning validation studies and information requested at the inspection that were not provided prior to issuance of the CR letter.

With the submission of Amendment 30, on September 13, 2010, Teva completely responded to the CR letter and simultaneously submitted one lot each of ADV-4 and ADV-7 vaccine tablets for lot release. In the interim, Teva identified and corrected each issue. The investigation and subsequent corrections are described in Amendment 30, Module 3, Section 3.2.P.3.3 and are summarized here.

The first batch of ADV-4 tablets that was manufactured in 2009 was not considered manufactured under CGMP due to a possible contamination of two bottles of the virus. An investigation into the cause of the possible contamination was conducted and a new batch of virus was ordered from -----(b)(4)------. Once the new batch arrived, one batch of ADV-4 tablets was successfully manufactured under CGMP in 2009 and no further problems were encountered with ADV-4.

Three ADV-7 GMP batches from 2009/2010 were rejected. During the dry coating of 2 of the GMP batches, inner cores were observed to be breaking during transfer from the -(b)(4)-- Several causes for the breaking inner cores were investigated. A summary of ---(b)(4)------- corrective actions are provided in Amendment 30.

Preventive actions from this investigation included the revision of SOP-904, *Set up and Operation of the* ---(b)(4)------- , to include two reference documents, to specifically outline the set-up for both the Type 4 and Type 7---(b)(4)----. A –(b)(4)- core batch was produced to investigate the root cause of the breaking inner cores and to verify the ------(b)(4)----------.

After the investigation and completion of preventive actions, production of another GMP tablet batch began. During the dry coating process on the (b)(4), low tablet yield was observed and during a routine AQL (Acceptable Quality Limit) inspection, a coreless tablet was observed. In addition, tablet breakage was observed ----------(b)(4)---------- ---------- Tablets were either breaking or being knocked off at this point of the process. Two deviation investigations were opened and a summary of corrective actions are provided in Amendment 30.

Conclusion of the investigations

The final conclusions regarding 2009-2010 adenovirus vaccine tablet production are as follows:

- The additional controls in place with alignment tools and set-up instructions, combined with software and recipe modifications will ensure the precise and reproducible operation of the ---(b)(4)------- moving forward.
- Other components of the tableting process, including the Lyophilizer, -(b)(4)- core tablet press, enteric coater, and imprinter are working properly.
- Three Adenovirus Type 7 Tablet batches have been rejected
- Adenovirus Type 4 Tablet batch --(b)(4)-- was acceptable and was submitted to the Agency for release
- Adenovirus Type 7 Tablet batch --(b)(4)-- was acceptable and was submitted to the Agency for release

With all manufacturing issues resolved, the product reviewer concluded that 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.

Stability of the ADV-4 and ADV-7 vaccine components has been shown for 24 months when stored under the recommended conditions, 2-8°C.

B. CBER Lot Release

A lot release protocol was submitted to the BLA for review. The initial protocol submitted for review included detailed in-process and final release tests performed for both Adenovirus Type 4 and Type 7 bulk viruses, intermediate formulated viruses and for the quality control release testing on the final container drug product. It was determined through discussion with the applicant that each of the final container drug products would be used for a single final container lot. Because the final container includes two components and batch sizes may not be equal, by considering each component separately, one lot of one component may be used in multiple lots of the final two component package. In addition to the requested changes in the format of the lot release protocol, we requested that the applicant remove some intermediate testing data sections and tables but to continue to perform the testing. The format for General Safety Test reporting was also changed. The applicant accepted all requested changes to the protocol and submitted the final protocol for review on February 18, 2011. CBER will release final container lots of Adenovirus Type 4 and Type 7 Vaccine Live, Oral.

Tablets of Type 4 lots ----------(b)(4)---------- and Type 7 lots ----------(b)(4)---------- were tested by CBER/OCBQ/Division of Product Quality for potency, identity and residual moisture. All specifications were met for the tablets. Internal discussions were held at CBER to determine the testing plan for lots submitted for release to market. The lot release testing plan was finalized on January 27, 2011. The final testing plan details the quality testing conducted by the applicant and makes recommendations of testing to be conducted at CBER. For routine lot release, the firm will submit samples and a Lot Release Protocol for each bottled sub-type to CBER. Any testing will be performed by CBER/OCBQ/DPQ.

Facilities review/inspection

Two inspections were held to support the review and licensure of this product. The first inspection was held at ----------(b)(4)---------- The inspection was conducted from ----------(b)(4)----------. The facility information for this site is:

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

This facility is where the Adenovirus Types 4 and 7 Bulk Viruses are grown and harvested and final bulks are formulated and filled under contract. In process and final container quality testing for the Adenovirus antigens is performed here. This inspection concluded with the issuance of an FDA Form 483 Inspectional Observations. These observations included: lack of media fill studies, written procedures and intervals for routine cleaning and environmental monitoring for out-of-use Class B clean rooms not specified, and lack of cleaning validation study reports. On

March 16, 2009, ---(b)(4)--- responded directly to CBER with a plan for addressing each issue. Final 483 observations were subsequently addressed by the applicant (detailed in an amendment to the BLA, submitted January 14, 2011) and the compliance status of this site was deemed acceptable to support license approval.

The second inspection was held at Barr Laboratories, Inc. in Forest, Virginia. The inspection was conducted from April 20 - 24, 2009. The facility information for this site is:

Barr Laboratories, Inc.
1235 Mays Mill Road
Forest, VA 24551
FEI # 3000718267

This facility is where the Adenovirus Types 4 and 7 Lyophilized Intermediate Drug Substance and Drug Product are manufactured. An inspection was conducted at this location to evaluate the manufacturing process for Lyophilized Intermediate Drug Substance and Drug Product. This inspection concluded with the issuance to the applicant of an FDA Form 483 Inspectional Observations. These observations included: inadequate cleaning validation studies, incomplete study of effectiveness of ----------(b)(4)---------- and lack of procedures for decontamination of virus spills in active manufacturing areas. The applicant submitted responses to the 483 (detailed in amendments to the BLA, submitted May 26, 2009, June 11, 2009, June 25, 2009, July 9, 2009, July 15, 2009, and September 13, 2010). All 483 observations were appropriately addressed and the compliance status of this site is deemed acceptable to support license approval.

C. Environmental Assessment

A request for a Categorical Exclusion from an Environmental Assessment under 21 CFR 25.31(c) was submitted to the BLA. It was concluded that the request was justified because the product is composed of naturally occurring substances, no extraordinary circumstances exist, and manufacturing of the product will not alter significantly the concentration or distribution of the natural substance, its metabolites, or degrade products in the environment.

The human adenovirus strains used in the vaccine are identical to the wild-type adenovirus that is or has widely circulated in the U.S. general population for the past 50 years. They are commonly widespread in the environment and a large percentage of the U.S. population, particularly in the military recruit population, has been infected by their late teens.

The firm has multiple measures in place to mitigate risk of virus entering the environment during production. In addition, Adenovirus Type 4 and Type 7, Vaccine, Live, Oral is only administered to U.S. military basic training recruits at the very beginning of basic training. Recruits are isolated from the general public during training for at least 5 weeks, thus allowing minimal risk that the virus can spread to the general population.

4. Nonclinical Pharmacology/Toxicology

No animal safety assessment studies were performed with Teva's Adenovirus Type 4 and Type 7 Vaccine, Live, Oral due to the lack of a suitable animal model. This vaccine was designed to be equivalent to the Wyeth vaccines in virus strain, potency, manufacturing process and delivery system. The safety of the Wyeth Adenovirus (ADV) Type 4 and Type 7 vaccines in humans is supported by clinical studies in more than 40,000 military recruits at

various military installations and use in millions of recruits in the U.S. military services from 1971 to 1999. No comparative studies between Adenovirus Type 4 and Type 7 Vaccine Live, Oral and the Wyeth vaccines could be performed because the Wyeth vaccines are no longer available.

The Phase 1 study of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral demonstrated that the current vaccines function in exactly the same manner as the Wyeth vaccines by selectively asymptomatically infecting the intestinal tract and bypassing the upper respiratory tract leading to a protective immune response. The Phase 3 study established the safety and efficacy of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral in over 4,000 military recruits. The clinical safety and efficacy data for Adenovirus Type 4 and Type 7 Vaccine, Live, Oral is consistent with the clinical experience with the Wyeth vaccines.

Summary of Oncogenicity

Various serotypes of ADV ----------(b)(4)----------were inoculated into 20-30 newborn hamsters either intraperitoneally or subcutaneous route. Necropsies were performed and tissues identified as being neoplastic were transplanted to naïve weanlings and/or newborn hamsters. Results of the oncogenicity study showed that an overall tumor frequency among the various ADV types was 7 tumors of 1557 tissues observed, or 0.45%.

Results of oncogenicity studies for ADV-7 were obtained in 466 days among 39 intact inoculated animals (3% tumor formation) and found only one tumor classified as lymphoma; however, 11 additional tumors were observed in hamsters that were thymectomized inoculees. In a second study a similar tumor incidence of 4% was observed when young hamsters were inoculated with ADV Type 7, and collectively, these preclinical findings show that these viruses possess a weakly oncogenic potential. Furthermore, Wyeth performed testing of the ADV-4 and ADV-7 strains selected for use in the ADV vaccines and found no evidence of oncogenicity using either ADV4-CL68578 or the ADV7-55142 vaccine strains based on the newborn hamster model.

Although a weak oncogenic potential may exist for some ADV strains in the hamster model, several million military recruits have been administered live Type 4 and/or Type 7 ADV vaccines, and as of 2004, there was no documented tumor incidence in humans resulting from ADV-4 and/or ADV-7 vaccines. Furthermore, wild-type human ADV-4 and ADV-7 strains are in widespread circulation in the general human population without known evidence for oncogenic potential.

Summary of Transmissibility in animals

ADV Type 4 given to monkeys by the intravenous and intranasal routes showed that the virus was shed in stool. Another monkey study showed no secondary transmission of ADV Type 4 from inoculated monkey to uninoculated cage mates.

Summary of Reproductive and Developmental Disorders

Human ADV does not replicate in rodents or rabbits, so no relevant biological animal models are available to evaluate live Type 4 and/or Type 7 ADV vaccines for reproductive or developmental disorders. For this reason, the FDA granted the applicant a waiver from conducting animal reproductive toxicity studies in a correspondence dated May 3, 2005. However, the safety of live adenovirus vaccines previously manufactured by Wyeth in

pregnant individuals has not been established. There is evidence in the literature that infection of human pregnant subjects with wild-type adenovirus can lead to placental infection and adverse fetal outcomes. Refer to the Risk Assessment and Post Marketing Commitments sections of this document for further information.

5. Clinical Pharmacology

Mode of Action

ADV Type 4 and Type 7 constitute the two major causes of acute respiratory disease (ARD) in U.S. military recruits. The incubation period for ADV is typically 4-5 days, after which illness caused by ADV is usually characterized by a fever of 100.5° F (38.06° C), cough, coryza, nasal congestion, headache, and chest pain; typically lasting 3-10 days. Physical examination would reveal pharyngitis, rales, and rhonchi. Approximately 7-10% of infections are complicated by pneumonitis, as noted on chest X-ray. Transmission from person to person is mainly by inhalation of respiratory droplets. Protection from ADV disease is associated with the presence of serotype specific serum neutralizing antibodies. There is no direct evidence that protection is mediated solely by neutralizing antibodies. Instead, it is likely that presence of serum-neutralizing antibodies serves as a specific marker of past infection that resulted in cellular and humoral immunity.

Military recruits were initially vaccinated in trials during the 1960s with only an ADV Type 4 live oral vaccine as this virus strain was the primary cause of ARD. R.M. Chanock developed a live ADV Type 4 vaccine using a selected wild-type 4 ADV virus (CL68578) isolated from a soldier at Camp Lejuene, South Carolina and grown in human diploid cells. The virus was administered in an enteric coated capsule, which caused selective infection in the lower intestinal tract, thus bypassing the upper respiratory tract. This type of selective infection is asymptomatic and stimulates the production of serum-neutralizing antibodies. The vaccine ADV Type 4 strain was excreted in the stool of more than 90% of vaccine recipients, and did not appear to spread from person to person among military recruits, and was only rarely recovered from the nasopharynx. The results of this study were reported in Chanock RM, Ludwig W, Heubner RJ, Cate TR, Chu LW. Immunization by selective infection with Type-4 adenovirus grown in human diploid tissue cultures. I. Safety and lack of oncogenicity and tests for potency in volunteers. JAMA. 1966;195(6):445-52.

The first study to report a protective effect of the oral ADV Type 4 vaccine was conducted in volunteers vaccinated at Camp Lejeune and transferred to Parris Island where an epidemic of ADV Type 4 was ongoing. None of the volunteers that received the ADV Type 4 vaccine developed ADV-associated illness requiring hospitalization, while 32 in the placebo group (one-third of the men who had Neutralizing Antibody titer <1:4) developed ARD caused by ADV Type 4 that required hospitalization.

In field trials, the ADV Type 7 vaccine was found to be protective against naturally occurring ADV Type 7 infection in susceptible individuals. A controlled field trial of live, oral ADV Type 4 and ADV Type 7 vaccines was conducted among Navy recruits at Great Lakes, Illinois during 1971. ADV infections in patients reporting to the dispensary with ARD were reduced 2- to 3-fold among vaccinated subjects compared to those who received placebo. Incidence of all respiratory-related hospital admissions among recruits receiving both vaccines was reduced by almost 40% as opposed to controls.

6. Clinical/ Statistical

Refer to the clinical and statistical reviews for details on the clinical studies included in this BLA to support the licensure of this vaccine. A brief summary based on these full reviews is provided below.

A. Clinical Program

Two clinical studies were conducted to evaluate the safety and efficacy of the applicant's ADV-4 and ADV-7 vaccines in preventing ARD in military recruits. The first, Study BR-ADV-101, a Phase 1, randomized, double-blinded, placebo-controlled study of the safety and immunogenicity of the ADV-4 and ADV-7 vaccines, was conducted in 58 subjects, 30 randomized to receive the vaccines and 28 randomized to receive placebos.

The second study, Study DR-ADV-301, was a Phase 3, multicenter, double-blind, randomized, placebo-controlled study in military recruits to evaluate the safety and efficacy of oral ADV-4 vaccine to prevent wild ADV-4-associated ARD and of oral ADV-7 vaccine to induce neutralizing antibody to ADV-7. Subjects were randomized to either the vaccine group or placebo group in a 3:1 ratio. A total of 4041 subjects were randomized and 4040 were analyzed.

The primary endpoints differed for determining the efficacy of the oral ADV-4 and ADV-7 vaccines. The primary endpoint for the oral ADV-4 vaccine was the reduction of attack rate of ADV-4 febrile ARD cases in the vaccine recipients compared with placebo recipients, defined as a subject with one or more clinical signs and symptoms of ARD, an oral temperature ≥ 100.5°F, and throat culture positive for wild ADV-4 infection. The primary endpoint for the oral ADV-7 vaccine was the rate of ADV-7 seroconversion in the vaccine group, defined as the development of ADV-7 neutralizing antibody at Day 26 after vaccination of at least 1:8 among those subjects whose baseline (Visit 0) ADV-7 titer was <1:4 (the limit of detection of the assay used).

Both the clinical reviewer and the statistical reviewer concluded that the pivotal study DR-ADV-301 met pre-specified endpoints for safety, efficacy and manufacturing lot consistency:

Efficacy
Among the 3031 recipients of the ADV-4 vaccine, one developed ARD. The vaccine efficacy (VE) estimate of 99.3% was greater than the prespecified success criterion of 80%, and the lower bound of the 95% confidence interval (CI) of 96.0% for VE was greater than 60% for the Intention To Treat (ITT) cohort, allowing one to conclude that the ADV 4/7 Vaccine is superior to the placebo and efficacious in reducing Wild-type ADV-4 febrile ARD cases. Additionally, the ADV-7 seroconversion rate (93.8%) for the vaccine group is greater than 75% and the lower bound of the 2-sided 95% CI (92.4%) is greater than 70%, allowing one to conclude that the ADV 4/7 Vaccine is effective with respect to ADV-7 seroconversion.

Lot Consistency

Consistency of manufacture was evaluated in the Phase 3 study by comparing Geometric Mean Titer (GMT) among three manufacturing scale lots. For ADV-4, the 95% CIs for the GMT ratios Lot1/Lot2, Lot2/Lot3, and Lot1/Lot3 were (0.79, 1.05), (0.82, 1.09), and (0.75, 0.99), respectively. All were within the pre-specified boundaries of (0.50, 2.00), permitting a

conclusion that the antibody responses induced by each of the three vaccine lots were equivalent with respect to ADV-4 titer. For ADV-7, the 95% CIs for the GMT ratios Lot1/Lot2, Lot2/Lot3, and Lot1/Lot3 were (0.81, 1.09), (0.77, 1.03), and (0.72, 0.97) respectively. All were within the boundaries of (0.50, 2.00), permitting a conclusion that the three vaccine lots were equivalent with respect to ADV-7 titer. Taken together, these data provide clinical evidence supporting the consistency of manufacture.

Safety

In terms of safety, the study showed a comparable general safety profile with placebo. The incidence of any serious adverse events was 1.2% in both arms with no significant inter-arm difference (2-sided 95% CI on the rate difference: (-1.0%, +1.0%). Regarding the treatment emergent adverse event (AE) rates of 92.2% and 94.2% in the vaccine and placebo arms, respectively, the vaccine arm seemed to have a lower rate than in the placebo arm, with the 2-sided 95% CI on the rate difference being (-3.6%, -0.1%). Also, an overall 71.2% of the subjects had AEs requiring medications, but the rate did not differ across arms (2-sided 95% CI on the rate difference: -6.0%, +0.4%).

Risk Assessment:

Vaccination with the Wyeth vaccines in previous clinical studies and during approximately 30 years of use in the U.S. military services has not been associated with significant serious symptoms or adverse events. Diarrhea was noted as the most common possible side effect across studies. In recruits, no spread of the vaccine virus to the respiratory tract has been observed.

No significant safety issues were identified during the clinical development of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral. Refer to the epidemiological review for further information on typical adverse events and specific adverse events reported.

Although the military tests all female recruits for pregnancy before vaccination, and only those with a negative pregnancy test will be administered the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, there is a risk of unintentional exposure of an embryo or fetus. In the Phase 3 study, 5 pregnancies were reported in 1,488 women. Four of these women were randomized to the vaccine group and one to the placebo group. Pregnancies were conceived between two to thirteen days prior to vaccination to approximately twenty-one weeks after vaccination. No adverse pregnancy outcomes or congenital abnormalities were observed in any of the 5 subjects and their offspring.

Viral Shedding and Risk for Transmission: Adenovirus Type 4 and Type 7 Vaccine, Live, Oral contains live adenovirus, which is shed in the stool for up to 28 days after vaccination and is thus capable of being transmitted to others. The health risks associated with vaccine-virus transmission in the civilian population (probably through close contact) could be greater than that in the military. The specific populations at greater risk for severe disease include children less than 1 year of age and immunocompromised individuals. Pregnant women will likely be present in the civilian population; if transmission occurs, the risk of virus exposure has not been fully assessed.

The applicant proposed to provide targeted education, including a prevaccination verbal briefing and a vaccine information statement leaflet, at the time of vaccination. In addition, the applicant agreed to include targeted education on the risk of shedding adenovirus after

vaccination in the separation briefing that occurs before a recruit is separated from military service. CBER was satisfied that this plan would be sufficient to prevent unexpected transmission of the live viruses.

Post Marketing Commitments and Post Marketing Requirements:

The postmarketing plans, subject to reporting requirements of 21 CFR 601.70, as specified by the epidemiological safety reviewer from the Office of Biostatistics and Epidemiology, and agreed to by Teva Women's Health, Inc., are as follows:

1. To conduct a postmarketing sentinel surveillance study to detect potential safety signals and to monitor and analyze uncommon and unexpected medical events occurring within 42 days following vaccination in the first 100,000 military recruits exposed to Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, during the first year post-approval through the use of the Defense Medical Surveillance System (DMSS). The final study report will be submitted by
   January 31, 2013.

Final protocol submission date:	September 13, 2010
Study/trial completion date:	July 31, 2012
Final Report Submission date:	January 31, 2013

2. To conduct a prospective Pregnancy Registry study of pregnant women exposed to Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, and their live born offspring through the first year of life to detect potential safety signals. Approximately 340 live births are anticipated to be enrolled in an estimate of 2-4 years. The Pregnancy Registry Status Report will be submitted to CBER annually. The final study report will be submitted 6 months after the follow-up of the last subject is completed and no later than March 31, 2017.

Final protocol submission date:	September 13, 2010
Study/trial completion date:	September 30, 2016
Final Report Submission date:	March 31, 2017

3. To conduct a surveillance study for vaccine-associated febrile respiratory illness (FRI) due to Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, viral shedding. Vaccine viral shedding will be evaluated using data from the Naval Health Research Center (NHRC) Febrile Respiratory Illness Surveillance Program. The NHRC FRI data will be reviewed on a monthly basis. The proportion of FRI subjects positive for Adenovirus Type 4 and Type 7 will be evaluated on a quarterly basis and cumulatively throughout the study period to identify if there are upward trends or unusual patterns of adenovirus FRI indicating a potential signal for the transmission of the virus to the respiratory tract, thereby resulting in FRI. This surveillance will be conducted concurrently with the Sentinel Surveillance Plan which covers the first 100,000 recruits exposed to the vaccine during the first year post-approval. The final report will be submitted with the Sentinel Surveillance study final report by January 31, 2013.

Final protocol submission date:	September 13, 2010
Study/trial completion date:	July 31, 2012
Final Report Submission date:	January 31, 2013.

Bio-Research Monitoring:

----------Withheld due to Privacy ACT----------

---------- Withheld due to Privacy ACT----------

B. Pediatrics

Adenovirus Type 4 and Type 7 Vaccine, Live, Oral is intended for use in military personnel, primarily military recruits, for prevention of acute febrile respiratory disease due to ADV-4 and ADV-7. Accordingly, this product is not intended for use in individuals below the age of conscription (i.e., <17 years of age).

Teva Women's Health, Inc. requested a full waiver of pediatric studies pursuant to 21 CFR 314.55, section (c)(2) pertaining to the following:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

The applicant notes that, although ADV-4 and ADV-7 are being used among U.S. military recruits in training, there does not appear to be sufficient evidence to suggest that adenovirus infections with these adenovirus serotypes pose a serious, enduring threat to the pediatric community that would warrant the use of live, oral vaccines.

On May 6, 2009, the review team met with the Pediatric Review Committee (PeRC) committee to discuss the waiver requested by the applicant as outlined above. The PeRC agreed with the applicant's request. CBER agrees with the age indication of a minimum age of 17 for receipt of this vaccine and that pediatric studies are not required.

C. Other Special Populations

Teva Women's Health, Inc. requested a Waiver of the Labeling Requirements as per 21 CFR 201.58, as no pregnancy category fits the teratogenicity criteria as specified in 21 CFR 201.57(c)(9)(i)(A). The waiver was granted. Based on a risk benefit assessment, the requested pregnancy category will be as follows: Pregnancy Category: Contraindicated

D. Overall Comparability Assessment

Based on the results of the Phase 3 pivotal study, including a safety cohort and a lot-to-lot consistency study, the applicant has shown that this product is efficacious, safe for the recommended population, and consistent from one lot to another.

7. Safety

Refer to the clinical and statistical reviews for details of safety in each study.

Overall Safety Conclusions
No safety signal was noted in either the Phase 1 or the Phase 3 studies. Shedding was confirmed to occur in the treatment recipients in the Phase 1 study but only one out of 1009 placebo recipients had a positive throat swab for the vaccine strain of ADV-4, demonstrating the efficacy of the vaccine and highlighting the need for the vaccine in vulnerable populations.

The percentage of AEs and serious adverse events (SAEs) were comparable in both the treatment and placebo recipients in both studies. No specific event was identified as being caused by receipt of the vaccine, including pyrexia or viremia. Five pregnancies occurred during the Phase 3 study, 4 were vaccine recipients, and 1 received the placebo. All 5 pregnancies resulted in healthy babies.

The only safety concern associated with the vaccine is the possibility of infection of the unprotected population. A risk-management plan includes an education program for all recruits to explain the importance of personal hygiene during the 28-day shedding period. Prior to receipt of the vaccine and, if necessary, again prior to leaving the military during the 28 day shedding period, the recruits will be educated of the possibility of infecting vulnerable populations, such as children under the age of 7 years old, pregnant women, and immunocompromised individuals.

8. Advisory Committee Meeting

The application was not referred to the Vaccines and Related Biological Products Advisory Committee because the review of information submitted in the Biologics License Application (BLA), including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

9. Other Relevant Regulatory Issues

No other significant regulatory issues were identified during the review of this file.

10. Labeling

Proprietary Name Review

Several proprietary names were submitted by the sponsor but none were approved by CBER. The proposed proprietary names were considered to be fanciful and posed potential significant risk for medication errors with the proprietary names of other currently marketed products when taking into account similarity in spelling, pronunciation, handwriting, storage, dosage form, setting of use, route of administration, and marketing status. The applicant withdrew the Proprietary Name requests and made a decision to only use the proper name, Adenovirus Type 4 and Type 7 Vaccine, Live, Oral because the vaccine will only be used for the military population and will not be available for other populations.

Carton and Container Labeling

This vaccine is a two-component product, containing individual tablets for both Adenovirus Type 4 and Type 7. One tablet of each type must be taken to provide one dose of the vaccine. The

final package contains one bottle of 100 tablets of the Type 4 component and one bottle of 100 tablets of the Type 7 component. The original cartons did not emphasize the fact that the vaccine was two separate components and the need to take one tablet of each for one complete dose. The container labels and carton label now reflect that information.

Package Insert (PI)

The package insert (PI) originally submitted to the BLA and all subsequent amendments related to the label were reviewed by all relevant reviewers on the file. Several rounds of changes were made to the label submitted by the applicant. Many of the changes were minor, however several critical changes were made.

- **Age range**

  The package insert submitted with the BLA original submission contained an indication with no age range provided, only the indication for use in military populations. Subjects included in the Phase 3 trial ranged in age from 17 through 42 years. An agreement was reached between the applicant and CBER to specify an age range of 17 through 50 years of age for the use of indication. This age range would include the youngest recruits and those considered to be at the upper limit of the normal healthy population. In addition, the upper age for military recruitment eligibility is 42.

- **Caution to avoid contact with children**

  The package insert submitted with the BLA original submission contained a caution to avoid contact with children less than one year of age. Recent North American data demonstrated that the highest rate of all ADV infections as detected by PCR occurs among children between the ages of six months to six years. The ADV- 7 component included in the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral is not safe for use in infants and younger children as it is a live vaccine, and would pose a risk to the vaccine recipient of causing an active case of respiratory infection if the contents of the oral vaccine were released in the oral cavity and aspirated. In light of these safety concerns, the proposed label for Adenovirus Type 4 and Type 7 Vaccine, Live, Oral carries this warning: "Vaccinees and individuals who come into close contact with vaccinees may be exposed to the viruses shed in stool for up to 28 days. Vaccinees should avoid close contact with children less than seven years of age, immunocompromised individuals, and pregnant women during the 28 days following vaccination."

- **Pregnancy category**

  The original package insert proposed a Pregnancy Category C because of the lack of animal studies and lack of controlled human studies to provide safety data to the pregnant population. Teva Women's Health, Inc. requested a Waiver of the Labeling Requirements (21 CFR 201.58) as no pregnancy category fits the teratogenicity criteria as specified in 21 CFR 201.57(c)(9)(i)(A). Because a risk benefit assessment, based upon literature reports of fetal harm due to adenovirus infection with unspecified serotypes and the intended use of this vaccine primarily among military recruits, does not support the use of the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral in pregnant women, the requested pregnancy category will be as follows: Pregnancy Category: Contraindicated.

- **Solicited vs. Non-solicited Adverse Events**

The subjects in the Phase 3 study were military recruits participating in basic training. Their schedules did not permit them much time to complete a 14-Day Patient Diary, which was requested by the clinical reviewer. A compromise was reached to require the first 780 enrolled subjects (safety cohort) to complete a 14-day diary and if no safety signal was seen by the Data Monitoring Committee, the rest of the subjects would only be required to complete a 7-day diary. In addition, the subjects were not able to monitor their daily temperature so pyrexia was not listed as a solicited adverse event on the diary. Pyrexia could be an expected event because the subjects were receiving a live vaccine.

In order to present the data in a meaningful manner, the definitions of solicited vs. non-solicited adverse events need to include the time period being discussed vs. the population being discussed. The definitions are as follows:

- **Solicited adverse events**: Safety cohort – days 0 to 14, all others – days 0 to 7
- **Non-solicited adverse events**: Safety cohort – days 15 to 56, all others – days 8 to 56
- **Pyrexia** was reported as an adverse event if the subject reported to the clinic and the subject's body temperature was confirmed to be ≥ 100.5˚F and only during the period that solicited adverse events were recorded: Safety cohort – days 0 to 14, all others – days 0 to 7.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

Following the review of all supportive product and clinical data, it is the recommendation of the review committee to approve this product for licensure.

b) Risk/ Benefit Assessment

The quality, efficacy, and safety of this vaccine have been thoroughly reviewed and have been determined to be acceptable for use of this vaccine as indicated in the label. The benefits from using this vaccine are related to the high efficacy for the prevention of Adenovirus Type 4 and Type 7 infection in military populations as demonstrated in the results of the clinical studies.

c) Recommendation for Postmarketing Risk Management Activities

There was no recommendation for postmarketing risk management activities. See below for the postmarketing activities associated with the licensure of this product.

d) Recommendation for Postmarketing Activities

Postmarketing activities include studies that will be performed post-licensure. These studies are classified as either postmarketing requirements under Section 505(o) of the Food Drug and Cosmetic Act (FDCA), postmarketing commitments subject to 21 CFR 601.70 or postmarketing commitments not subject to 21 CFR 601.70. During the review of the BLA it was determined that no postmarketing requirement studies were necessary.

Three postmarketing studies to follow safety were discussed with Teva Women's Health. The first study is a sentinel surveillance plan to detect potential safety signals in the first 100,000 vaccinees. The second study is a pregnancy registry and the third study is surveillance for vaccine-associated Febrile Respiratory Illness (FRI) due to viral shedding. No other PMC's were requested.