



STN: BL 125296

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MEMORANDUM

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DATE: January 20, 2011

SUBJECT: Pharmacovigilance Plan Review
BLA Submission 125296 (Adenovirus Vaccine, Live, Oral, Type 4 and Type 7)

Reference: STN: BL 125296

Sponsor: Teva Women's Health, Inc. (Formerly Duramed Research, Inc.)

This memorandum is to provide you with a summary of my reviews regarding post-marketing safety evaluation for Teva Women's Health Biologics License Application (BLA) for the Adenovirus Type 4 & Type 7 vaccines.

(A) Summary of Safety Data Submitted by Sponsor: Acute respiratory disease (ARD) is the most common cause of morbidity and hospitalization among military recruits undergoing basic training (BT) in the United States (US) with adenovirus (ADV) types 4 and 7 constituting the two major causes of ARD in this population. For this reason, ADV type 4 and 7 live oral vaccine tablets produced by Wyeth Laboratories, Inc. (Wyeth) were routinely co-administered to military recruits from 1971 to the late 1990s. When production of the vaccine ceased and the tablets were no longer available, outbreaks of adenoviral respiratory disease reemerged in the military setting. Teva's Live, Oral, Type 4 and Type 7 enteric coated tablets were developed to be equivalent to the Wyeth vaccines with regard to virus strain, potency, manufacturing process, and delivery system. As with the Wyeth vaccines, the Teva vaccine is orally administered as two

tablets, one tablet each of type 4 and type 7 adenovirus vaccines, for the immunization of military populations in which epidemic respiratory disease due to ADV is likely to occur.

Vaccination with the Wyeth vaccines in previous clinical studies and during approximately 30 years of use in the US 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. The Wyeth ADV vaccines produced selective asymptomatic enteric infection sparing the respiratory tract. In recruits, no spread of the vaccine virus to the respiratory tract has been observed.

The Safety of Teva's vaccine was investigated in two clinical studies in military personnel: 1) a Phase 1, Randomized, Double-Blind, Placebo Controlled Study (BR-ADV-101) with 30 subjects in the vaccine group and 28 subjects in the placebo group, and 2) a Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study (DR-ADV-301) with 3031 subjects in the vaccine group and 1009 subjects in the placebo group. No comparative studies between the Teva and the Wyeth vaccines could be performed because the Wyeth vaccines are no longer available. Subjects in both studies were healthy adult males and females aged 17-42 years, who were in military training and confined to a military facility. Female subjects of childbearing potential had to have a negative urine pregnancy test prior to study medication administration.

(A.1) Adverse Events: No significant safety issues were identified during the clinical development of adenovirus type 4 & type 7 vaccines. The adverse events that were common in the vaccine treatment group across both Phase 1 and Phase 3 studies included: headache, arthralgia, pharyngolaryngeal pain, nasal congestion, cough, nausea, and diarrhea. Reported serious adverse events in both studies included 3 cases of pneumonia (2 vaccine group and 1 placebo group), 1 case of acute bronchitis (vaccine group), 1 case of acute tonsillitis (vaccine group), 1 case of upper respiratory tract infection (placebo group), 1 case of febrile ARD (placebo group), and 3 cases of gastroenteritis or gastritis (vaccine group). No statistically significant differences in adverse event frequency was noted between the vaccine and placebo groups in either study. No deaths were reported in either study, and no gender differences were apparent. .

(A.2) Virus Exposure and Pregnancy: Women of child-bearing potential represent a sizeable proportion of military personnel – approximately 50,000 out of 270,000 total civilians enrolled in military recruit training annually are reproductive-aged females. 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 & type 7 vaccines, there is a risk of unintentional exposure of an embryo or fetus to the battery of vaccines administered by the military during the in-processing procedure. No animal or human reproduction studies were conducted with the Wyeth or Teva vaccines and there is limited data on pregnancy outcomes in women inadvertently exposed to the vaccine virus. Human adenovirus does not replicate in rodents or rabbits; therefore, no relevant biological animal models are available to evaluate live type 4 and type 7 ADV vaccines for reproductive or developmental abnormalities. 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. No adverse pregnancy outcomes or congenital

abnormalities were observed in 4 subjects and their offspring. One vaccine subject remained pregnant at the time that the BLA submission was prepared.

(A.3) Viral Shedding and Risk for Transmission: Adenovirus type 4 & type 7 vaccines contain live adenovirus that is shed in the stool for up to 28 days after vaccination and is thus capable of being transmitted. In the Phase 3 trial, 1 of 1009 (<0.1%) placebo-treated subjects developed febrile ARD with a throat specimen positive for type 4 vaccine virus. There was no evidence of type 7 transmission. It is perceived that the health risks associated with the transmission of vaccine virus when used in the military recruit setting are minimal because the recruits are young and healthy and all recruits will be vaccinated and thus afforded protection from adenovirus types 4 and 7 ARD. However, the health risks associated 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 are present in the civilian population; if transmission occurs, the risk of virus exposure has not been fully assessed.

(B) Summary of the Pharmacovigilance Plan (PVP) Submitted by Sponsor (As of September 13, 2010): The Sponsor's proposal regarding the post-marketing safety evaluation of adenovirus type 4 & type 7 vaccines was outlined in Teva's submission of a Risk Management Plan (RMP) in original application to the BLA as of September 30, 2008 (formerly called Duramed Research Inc.) and again in the Complete Response to CBER's Letter (Amendment 30, dated July 16, 2009) as of September 13, 2010. The RMP includes 3 elements for post-marketing surveillance: 2 post-marketing studies (a sentinel surveillance plan and a pregnancy registry) and review of the Naval Health Research Center (NHRC) Febrile Respiratory Illness Surveillance Program publications.

(B.1) Sentinel Surveillance Plan (Protocol number DR-501-402)

There are several syndromes caused by different adenovirus serotypes. These include upper respiratory illness (types 1-3, 4, 5, 7, and 21), pharyngoconjunctival fever (types 1, 3, 4, 7, and 14), hemorrhagic cystitis (types 11, 21, 34, 35), GI infections (types 40 and 41), meningoencephalitis (type 7), epidemic keratoconjunctivitis (types 8 and 37) and disseminated disease. Adenovirus usually presents as self-limited ARD in immunocompetent individuals.

a. Study design and study population: The sentinel surveillance plan is intended 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 this vaccine during the first year post-approval through the use of the Defense Medical Surveillance System (DMSS). DMSS is a longitudinal database maintained by the Department of Defense (DoD) that electronically captures up-to-date and historical data on diseases and medical events on U.S. military personnel.

Recruits are young, healthy women and men who receive the standard battery of vaccinations before and during BT, live in standard barracks and eat similar diets, and have the same duration of rigorous physical training following their vaccinations which include live vaccines. One

exposed group and one historical control group will be selected. Each group will consist of 100,000 recruits.

Exposed group: Active duty military recruits, aged 17-42 years, at the outset of BT

- 1) Received adenovirus type 4 & type 7 vaccines,
- 2) Attended BT at a pre-specified basic training sites, and
- 3) Received a standard battery of concurrent mandatory vaccinations based on serologic testing and military component.

Historical control (unexposed) group: Active duty military recruits, aged 17-42 years, at the outset of BT

- 1) Did not receive adenovirus type 4 & type 7 vaccines,
- 2) Attended BT at the pre-specified basic training sites in the year prior to the exposed group and the same months of the year, and
- 3) Received a standard battery of concurrent mandatory vaccinations based on serologic testing and military component.

(Note: A concurrent control group was proposed in the original application submitted to BLA by Duramed as of September 30, 2008. The concurrent control group was removed from the September 11, 2010 submission by Teva.)

Matching: The exposed group and the historical control group will be group matched on the training site location and training month, and the composition of demographic characteristics including age, gender, and race.

b. Data collection: Each individual in the exposed and unexposed cohort will be followed for 42 days following the administration of the series of vaccinations for the occurrence of medical events of interest.

The predefined list of medical events of interest is comprised of potential, theoretical, and known adverse events of interest for live vaccines (including adenovirus type 4 & type 7 vaccines), including epilepsy, syncope and collapse, active infective polyneuritis (GBS, postinfectious ployneuritis), thyrotoxicosis with or without goiter, toxic diffuse goiter, pulmonary insufficiency, anaphylactic shock, encephalitis, myelitis, and encephalomyelitis, intussusception, acute pericarditis, pneumonia, symptoms involving skin and other integumentary tissue, and erythema multiforme.

c. Potential confounders and biases: The military recruit population limits the impact of confounding variables such as age, health status, and concurrently administered vaccines other than adenovirus type 4 & type 7 vaccines. Potential confounding variables include concurrent administration of other vaccinations (including live vaccines), seasonal variation in circulating pathogens at the time of vaccination and climate variation between the BT sites (both relates to viral pathogens present in the community at large and may infect the recruit population), and historical variability that may be due to annual variation related to viral pathogens circulating within a given community and changes in the BT regimen over time (including vaccinations and the recruit training program). Potential sources of bias include reliance on self-reporting of

medical events by recruits during BT, primary focus upon the 6-week period following vaccination, and psychological bias that recruits receiving adenovirus type 4 & type 7 vaccines may be more likely to report events given awareness of the surveillance plan. Also, the DMSS database only captures information for active duty recruits and data entry error might also occur.

d. Statistical analysis and signal detection: Incidence rate will be calculated as follows: total number of new events during the given time period / total number of recruits exposed during the given time period. Comparison of incidence rates between the exposed group and the control groups will be performed, using logistic regression, monthly for predefined medical events of interest and quarterly for all adverse events temporally related to vaccination. Each case of pre-specified medical event will undergo medical review. Additional logistic regression models will be run controlling for demographic and geographic confounders. The monthly and quarterly reviews will be conducted until 100,000 recruits have accrued. After 100,000 military recruits have accrued, a cumulative summary of the monthly and quarterly data will be provided.

e. Signal evaluation: Medical evaluation will be conducted for all spontaneously reported adverse events of medical significance and adverse events occurring within 42 days following vaccination with statistical significance compared to unexposed historical control group. Potential signals will be further evaluated in the DMSS database. If an unexpected and medically significant emergent signal is detected, the safety review committee will be consulted for appropriate course of action, including utilization of an additional 100,000 military recruits exposed to adenovirus type 4 & type 7 vaccines for signal evaluation.

f. Study termination: The sentinel surveillance plan will terminate after the first 100,000 military recruits have been exposed to adenovirus type 4 & type 7 vaccines in the first year post-approval.

g. Regulatory reporting: The outcome of the sentinel surveillance program will be included in a final study report. As part of routine safety surveillance and regulatory reporting by Teva for adenovirus type 4 & type 7 vaccines, Periodic Adverse Experience Reports (PAERs) will be submitted to the FDA quarterly for the first 3 years following approval and annually thereafter as per 21 CFR 600.80(c)(2)(ii). In addition, in accordance with 21 CFR 314.80(e), 15-day alert reports will be submitted to the FDA for serious, unexpected and reasonably possibly related adverse events from the sentinel surveillance plan.

(B.2) Pregnancy Registry (Protocol number DR-501-401)

a. Study design and study population: A prospective, observational, exposure-registration and follow-up study of pregnant women exposed to adenovirus type 4 & type 7 vaccines and their live born offspring through the first year of life. This is a prospective registry designed to detect potential safety signals, not to test a hypothesis.

Inclusion criteria for women:

- Female U.S. Military recruits in basic combat training, newly graduated from basic training and in active duty or discharged early from recruit training;
- Confirmed exposure to Adenovirus Vaccine;

- Received Adenovirus Vaccine while pregnant or had an estimated date of conception (DOC) within 6 weeks after receiving Adenovirus Vaccines;
- Positive β -hCG test or fetal ultrasound; and
- Oral informed consent obtained from the patient.

Inclusion criteria for live born offspring:

- Infant born up until one year old to women with confirmed maternal exposure to Adenovirus Vaccine; and
- Oral informed consent obtained from the mother of the infant.

Exclusion criteria:

- Patients who refuse to provide oral informed consent to the Institutional Review Board (IRB)-approved informed consent;
- Females not exposed to Adenovirus Vaccine; or
- Patients not willing to meet registry study conditions and requirements.

b. Patient identification and enrollment: The primary source of identification is DoD during basic combat training and after completion of basic combat training through monthly DMSS database query. Alternative sources for identifying pregnant patients who are exposed to adenovirus type 4 & type 7 vaccines include pregnancies identified directly by Teva through spontaneous reporting, reports from the Vaccine Adverse Event System (VAERS), and reports from the scientific literature. Identified pregnancies will be evaluated to determine if the patient meets the inclusion/exclusion criteria for enrollment. Eligible pregnancy cases will be enrolled and followed-up.

c. Data collection: Pregnancies will be followed by a Registry Representative through the pregnancy outcome, and, if resulting in a live birth, continuing through the infant's first year of life. The scheduled follow-ups are: within 30 days of patient enrollment, 16-20 weeks gestation, 2 weeks after estimated date of delivery, 4 month old infant, and 1 year old infant. The following information will be collected at different stages of follow-up: general information, maternal demographics, maternal medical/obstetrical history, current pregnancy information, concomitant/historical medication, use of alcohol, tobacco, and/or drugs of abuse, and neonatal/infantile information.

d. Data analysis: Descriptive analysis of pregnancy outcomes and birth defects will be performed for all prospectively enrolled pregnancies with known exposure to adenovirus type 4 & type 7 vaccines. A total of 340 live births is planned to be enrolled. Birth defects will be evaluated using the CDC Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects and through independent review. Birth defect prevalence rates will be compared to the MACDP surveillance population or relevant comparison group (e.g. DoD Birth and Infant Health Registry). Retrospective reports will be included in a separate analysis.

e. Regulatory reporting: The Pregnancy Registry Status Report will be submitted to FDA annually in conjunction with the PSUR timeline. As part of the FDA post-marketing surveillance requirement under 21 CFR 314.80(e), all reports assessed as serious and unexpected and where a reasonable possibility exists that the product caused the adverse event will be reported within 15 calendar days. Meanwhile, the registry Representative will forward all adverse event reports, including birth defects, spontaneous fetal losses, and induced abortions, to

the drug safety surveillance department. All reports will be assessed and reported to regulatory authorities as required.

(B.3) Surveillance for vaccine-associated FRI due to viral shedding: Teva's Adenovirus Vaccine contains live adenovirus which has been shown to shed in the stool for up to 28 days. Therefore, there is a risk of febrile respiratory illness (FRI) due to vaccine-virus shedding and subsequent transmission to a susceptible population.

Viral shedding will be evaluated using the Naval Health Research Center (NHRC) Febrile Respiratory Illness (FRI) Surveillance Program. NHRC conducts active, laboratory-based surveillance of US military populations to quantify and study the etiology of respiratory illness, including FRI and pneumonia among military personnel. The NHRC FRI surveillance program is conducted at 8 military recruit training centers. At each training center, data on population size and FRI numbers will be collected, as well as throat swab specimens from a selected number of FRI patients who report for treatment. Samples are shipped on a regular basis to NHRC for virus isolation and identification including adenovirus serotyping. The NHRC is capable of differentiating between the vaccine viral serotype and the circulating wild-type viral serotype for ADV4. At this time, ADV7 serotype from the vaccine cannot be differentiated from circulating virus by the NHRC test algorithm. The potential for ADV7 shedding and transmission, however, can be inferred from the ADV4 vaccine strain data. The NHRC issues weekly reports. Teva plans to review reports on a monthly basis. The proportion of FRI subjects positive for ADV4 and ADV7 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. Upward trends or unusual patterns of adenovirus FRI will be discussed with NHRC. If either Teva or the NHRC interprets the trend as being related to vaccine safety, CBER will be contacted. 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.

(C) CBER's Response to PVP (Dated 04/15/2009 and 05/15/2009)

The original application was submitted to CBER by Teva (formerly called Duramed) dated September 30, 2008. On September 13, 2010, an updated PVP (called Risk Management Plan by the sponsor) was submitted in Amendment 30 with revised and supplemental information based on CBER's response to the original PVP.

CBER responded to the sponsor's original PVP on the following issues:

(C.1) Sentinel Surveillance Plan: In the original application, the Sponsor indicated that the exposed group and the unexposed comparison groups (concurrent and historical) will be matched on the timing of vaccination and the training site location. The comparison groups will consist of military recruits who never received the Adenovirus Type 4 & Type 7 vaccines but received concurrent mandatory vaccines, either in the prior year (historic control group) or within the same year (concurrent control group) but at different training sites. On April 15, 2009, CBER requested the Sponsor to 1) clarify what the concurrent mandatory vaccines were referred to and when those vaccines would be administered; 2) clarify whether the same set of mandatory

vaccines were given to the historic control group following the same vaccination schedule in the prior year; 3) provide additional information on matching criteria and matching procedure for each control group; 4) clarify what sample size would be used for each control group; 5) clarify how long the cohorts (one exposed group and two unexposed groups) would be followed after vaccination; and 6) clarify whether censoring would be taken into account in the measure of incidence.

In addition, in Appendix A-Predefined List of Medical Events of Interest, ICD-9 code 995.0 for other anaphylactic shock was listed as the only code for anaphylaxis. Since anaphylactic shock is referred as the most severe manifestation of anaphylaxis, on May 15, 2009, CBER requested the Sponsor to add additional ICD-9 codes to expand search for anaphylaxis.

(C.2) Pregnancy Registry: On April 15, 2009, CBER requested the Sponsor to 1) provide additional information to define new graduates from basic training as mentioned in the inclusion criteria; 2) clarify the inconsistency in the definition of retrospective cases in section 5.4 and section 8.1 of the BLA submission Module 1.16 Appendix 3; 3) clarify how duplicate reports would be specifically labeled to differentiate them from other invalid reports in analysis; and 4) provide an estimated time frame for recruiting 340 live births for the Pregnancy Registry study.

(C.3) Viral Shedding and Risk for Transmission: The Sponsor proposed to provide targeted education, including a prevaccination verbal briefing and a vaccine information statement leaflet, at the time of vaccination. While educating vaccinees to viral shedding and transmission risks at the time of vaccination is important, it would seem equally important to provide an additional targeted education session as to those risks at the time of military discharge to those individuals who are discharged from the military during the 28 day shedding period. On April 15, 2009, CBER requested the Sponsor to clarify whether a risk education session provided at the time of discharge to those who were discharged from the military during the 28 day shedding period was included in the risk management intervention and how this type of targeted educational session may be added if not included in the current plan.

(D) Sponsor's Response to CBER (04/15/2009 and 05/15/2009) Comments

(D.1) Responses to CBER April 15, 2009 comments regarding post-marketing surveillance were submitted to the BLA as of April 28, 2009 (Amendment #11). The responses adequately addressed CBER's concerns and questions. The Sponsor also 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.

(D.2) Responses to CBER May 15, 2009 comments regarding additional ICD-9 codes to expand search for anaphylaxis were submitted to the BLA as of May 22, 2009 (Amendment # 15). The following Medical Events of Interest and ICD-9 codes will be added to the predefined list of events in the Sentinel Surveillance Plan to expand the search for anaphylaxis: 995.3 for allergy unspecified, 995.2 for other and unspecified adverse event of drug, medical and biological substance (due) to correct medical substance properly administered, 999.4 for anaphylactic shock due to serum, and 977.9 for unspecified drug or medical substance.

(E) Sponsor Request for Changing Regulatory Reporting Format

(E.1) On May 15, 2008, the Sponsor requested that periodic reports be prepared according to CFR 600.80 rather than PSUR per ICH E2C Guidelines.

(E.2) In the Complete Response (CR) letter dated June 30, 2009, CBER requested the Sponsor to submit a detailed plan of post-marketing safety reporting per 21 CFR 600.80, for each of the three post-marketing surveillance studies including the Sentinel Surveillance Plan, the viral shedding evaluation using the Naval Health Research Center Febrile Respiratory Surveillance Program, and the Pregnancy Registry.

(E.3) Response to CBER 06/30/2009 request regarding regulatory reporting was submitted to the BLA as of July 10, 2009. The response clarified that

a. The Sentinel Surveillance Plan and Pregnancy Registry are post-marketing studies. Per 21 CFR 600.80, the Periodic Adverse Experience Reports (Periodic Reports) will not include events from these studies unless the event is considered serious, unexpected and determined to have a reasonable possibility that it was caused by the vaccine [600.80(c)(2)(ii) and 600.80(e)(1)].

b. Study events classified as 15-day Alerts will be included in the Periodic Report.

c. Reporting quarterly for 3 years: Periodic Report as per 21 CFR 600.80(c)(2)(ii); Evaluation of data from Sentinel Surveillance Plan (until end of program); Overall risk-benefit assessment of above data.

d. Reporting annually with Periodic Report: Pregnancy Registry status report (until closure of Registry); Evaluation of data from Sentinel Surveillance Plan (until end of program); Confirmation that annual review of NHRC Febrile Respiratory Illness Surveillance Program weekly reports has been conducted and whether or not a signal was detected. If signal is detected, plans for evaluation of signal and any action to mitigate risk will be included; Overall risk-benefit assessment of Periodic Report data and above.

e. Upon completion of Sentinel Surveillance Plan, Cumulative Summary Report will be submitted to CBER.

f. Upon completion of Pregnancy Registry, final report of Pregnancy Registry will be submitted to CBER.

(F) Sponsor Submission of Updated PVP Dated 09/13/2010

On September 13, 2010, the sponsor submitted Complete Response to CBER's Letter dated July 16, 2009 (Amendment 30), in which the following revisions to PVP were included:

(F.1) Sentinel Surveillance Plan: Removed concurrent control group in study design (only one, instead of two, unexposed control group in the current protocol), updated ICD-9 codes for pre-

specified outcomes of interest, and updated contact information and company name (former Duramed, now Teva).

(F.2) Pregnancy Registry: Included minor administrative changes, and updated contact information and company name (former Duramed, now Teva)

(G) CBER Review of Updated PVP: DE review of the proposed PVP has identified the following safety concerns, and actions planned by the sponsor to mitigate these safety concerns are listed below.

Safety Concerns	Proposed Pharmacovigilance Activities
Identified Risks	
Viral Shedding and Risk for Transmission	NHRC FRI Surveillance Program Vaccine indicated for recruits who will all be vaccinated and will have limited contact with unvaccinated individuals for 28 days post vaccination Risk education for individuals discharged less than 28 days post vaccination Routine Reporting to VAERS
Potential Risks	
Predefined events of interest of concern with live vaccines	Sentinel Surveillance Plan DR-501-402 Routine reporting to VAERS
Important Missing Information	
Pregnancy outcomes after Vaccine Virus Exposure	Labeling Screening for pregnancy by military health system prior to vaccination Pregnancy Registry DR-501-401 Routine Reporting to VAERS
Safety Database based on young adult population only	Safety database reflects the age range of basic military trainees for whom the product is indicated Routine reporting to VAERS

Because no serious risk or signal of serious risk has been identified related to the use of the vaccine and there is no available data indicating the potential for a serious risk, a Post-Marketing Requirement will not be necessary at this time.