Summary Basis for Regulatory Action

Date: July 8, 2011

From: CDR Edward W. Wolfgang, MSA, BSN, Chair of the Review Committee

LT Juan C. Lacayo, Ph.D., Regulatory Project Manager

BLA/ STN: 125106/680

Applicant Name: GlaxoSmithKline Biologicals (GSK)

Date of Submission: September 20, 2010

Proprietary Name/Established Name: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed, (Tdap), Boostrix®

Proposed Indication: Active immunization against tetanus, diphtheria, and pertussis in individuals 65 years of age and older.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, DVRPA
√ 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.

Specific Documentation used in Developing the SBRA	Reviewer Name – Document Date
Clinical Review	Ann Schwartz, M.D.
Pharmacovigilance Review	Patricia Rohan, M.D.
Statistical Review	Lihan Yan Ph.D.
CMC Review	Leslie Wagner
CMC Review	Drusilla Burns, Ph.D.
Biomonitoring Review	Lillian Ortega
Electronic Integrity Review	David Schwab
Labeling Reviews	Maryann Gallagher Juan C. Lacayo, Ph.D. Ann Schwartz, M.D.

1. INTRODUCTION

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed, Boostrix® (Tdap) is currently approved for use in individuals 10 through 64 years of age for the prevention of diphtheria, tetanus and pertussis. On September 20, 2010, GlaxoSmithKline (US License 1617) submitted a supplement to their Biologics License Application (sBLA) for Boostrix to include immunogenicity and safety data to support the use of Boostrix in individuals 65 years of age and older. This supplement provides data from two clinical studies evaluating the immunogenicity and safety of Boostrix in adults aged ≥ 65 years of age. The first was a comparative study of GSK Biologicals' Boostrix vaccine vs. Sanofi-Pasteur's licensed tetanus and diphtheria toxoid adsorbed vaccine [Decavac®], when administered to adults aged 65 years or older. The second study was a supportive study assessing the co-administration of Boostrix with Fluarix® (Influenza Virus Vaccine, Trivalent, Types A and B; GSK) compared to Boostrix administered alone. The data from these studies are presented in the revised package insert.

2. BACKGROUND

In May 2005, Boostrix was licensed in the U.S. for active immunization against diphtheria, tetanus, and pertussis. At that time Boostrix was approved as a single booster dose for use in children and adolescents 10-18 years of age. Approval was based upon the demonstration of non-inferiority to a US-licensed Td vaccine with respect to immunogenicity for the diphtheria and tetanus components of the vaccine in a large U.S. study (Tdap 0.3–001), which enrolled 3000 adolescents 10-18 years of age who were administered Boostrix. Evaluation of the immune responses elicited by the Pertussis antigens [as measured by the anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations], demonstrated that the immune responses were non-inferior to those achieved by infants following a three-dose primary series of Infanrix® (diptheria and tetanus toxoids, and acellular pertussus vaccine adsorbed; GSK) in a previously conducted immunogenicity study. A subset of these infants formed the cohort for a German household contact study (APV-039) in which the efficacy of Infanrix against World Health Organization-defined typical Pertussis was demonstrated to be 88.7% [two-sided 95% confidence interval: 76.6%; 94.6%]. Similar safety profiles were observed for Boostrix and the US-licensed Td vaccine for the occurrence of both local and systemic adverse events. Subsequent to the initial approval, further studies in adults have supported the extension of approved use to include adults 19-64 years of age.

3. CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION

GSK submitted to CBER for concurrence the methodology and validation information for the clinical serologic assays for anti-Diphtheria and anti-Tetanus antibodies to demonstrate that the anti-Tetanus (anti-T) and anti-Diphtheria (anti-D) ELISAs are suitable for the intended purpose of measuring anti-T and anti-D antibodies ≥0.1 IU/mL. These assays were used in the assessment of the co-primary study objectives to demonstrate non-

inferiority of Boostrix compared to Decavac with respect to the percentage of subjects with sero-protective anti-D and anti-T concentrations ≥0.1 IU/mL and anti-T concentrations ≥1.0 IU/mL. CBER determined that sufficient validation information was not provided for measuring low-level anti-Diphtheria antibodies and thus its suitability for use could not be determined. Following communications between CBER and GSK it was agreed that the ----------(b)(4)---------- would not be considered supportive for licensure due to the absence of this validation information. A fully validated assay was not essential for approval because ----------(b)(4)---------- were only used to determine a secondary objective and not to assess the primary immunogenicity endpoints. In contrast, CBER did concur that the anti-Tetanus (anti-T) and anti-Diphtheria (anti-D) ELISAs are suitable for the intended purpose of measuring anti-T and anti-D antibodies ≥0.1 IU/mL.

GSK provided pertussis ELISA information used to measure the immune response in subjects to the pertussis components of Boostrix that included pertussis toxoid, filamentous hemagglutinin and pertactin. These assays were reviewed previously by CBER and were found to be appropriately validated and adequate for their intended purpose. In regard to evaluation of the assays for the purpose for which they were used in this pivotal clinical trial presented in this BLA efficacy supplement, CBER determined the pertussis ELISAs used in this study are adequate to support the conclusions of the study regarding antibody responses to the pertussis antigens contained in the vaccine.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Given the extent of human experience with Boostrix, non-clinical data were not required to support this sBLA.

5. CLINICAL PHARMACOLOGY

No clinical pharmacology data were provided in the supplement.

6. CLINICAL/ STATISTICAL

Clinical data from two studies provide evidence supporting effectiveness and safety of Boostrix administered as a single intramuscular dose in adults 65 years of age and older.

Pivotal Study 011
Pivotal Study 011 was a Phase IIIb, observer-blind, randomized, controlled, multi-center study to evaluate the immunogenicity and safety of GSK Biologicals' Boostrix compared to Sanofi Pasteur's tetanus and diphtheria toxoid adsorbed vaccine (Decavac®), when administered to adults 65 years of age and older. This study was conducted in 24 centers in the United States from January 2009 through October 2009. A total of 887 adults aged 65 years and older were vaccinated with Boostrix in Study 011.

The primary objectives in Study 011 were: 1) to demonstrate non-inferiority (margin=10%) of Boostrix compared to Decavac with respect to proportions of subjects

with anti-D and anti-T ≥ 0.1 IU/mL and anti-T ≥ 1.0 IU/mL, one month after vaccination; and 2) to demonstrate non-inferiority (margin for ratio =0.67) of Boostrix compared to 3-dose Infanrix series in study APV-039, with respect to anti-PT (pertussis toxoid), anti-FHA (filamentous hemagglutinin) and anti-PRN (pertactin) geometric mean concentrations (GMCs) one month after vaccination.

The proportions of subjects with anti-D and anti-T concentrations at least 0.1 IU/mL and anti-T concentrations at least 1.0 IU/mL at one month after a single Boostrix vaccination were 84.9%, 96.8% and 88.8%, respectively. The GMCs for anti-PT, anti-FHA, and anti-PRN at one month after a single Boostrix vaccination were 48.9 EL.U/mL, 689.1 EL.U/mL, and 104.7 EL.U/mL, respectively. All of the pre-specified non-inferiority criteria were met.

Supportive Study 008
Supportive study 106323, Study Tdap 0.3-008 (referred to as Study 008), was an open-label study of GSK Biologicals' Boostrix vaccine co-administered with GSK Biologicals' influenza vaccine, Fluarix® compared to Boostrix administered alone, one month after administration of Fluarix, in healthy adults. This study included a cohort of 217 subjects 65 years of age and older for exploratory analyses. Within this subset, 112 received concomitant administration of Boostrix and Fluarix, and 105 received Fluarix followed one month later by Boostrix. The immunogenicity results appeared to be similar between the two treatment groups and within the same range of the results observed in Study 011. However, no formal statistical hypothesis tests were planned or performed.

Safety
In Study 011, the reactogenicity profile of Boostrix appeared to be comparable to that of the control Decavac, with slightly lower rates for local symptoms in the Boostrix group. However, the overall adverse event rate in the Boostrix group was slightly higher than that in the Decavac group (20.7% vs. 16.6% for all AEs, 17.1% vs. 14.4% for all AEs occurring within Day 0-30). In Study 008, there appeared to be slightly higher rates of local reactions at the Boostrix injection site among subjects who received Boostrix and Fluarix compared with subjects who received Boostrix one month after Fluarix. The overall AE rates were similar between the two treatment groups in this study. The safety data in the sBLA support the approval of Boostrix for use in individuals ≥ 65 years of age as a single dose.

Data Quality
Under FDA's Compliance Program Guidance Manual 7348.811, Inspection Program for Clinical Investigators, three clinical investigators in Study 111413 Tdap 0.3-011 were inspected. The inspections focused on specific questions concerning clinical protocols submitted. The inspection revealed no deviations from applicable regulations to impact the data submitted in the sBLA.

PREA
This supplement did not trigger PREA.

7. SAFETY

The pharmacovigilance plan was found to be adequate. GSK proposes to continue routine safety monitoring for Boostrix. This monitoring includes routine reporting and submission of annual Periodic Safety Update Reports to FDA. Serious unexpected or unlabeled events will be submitted to FDA as 15 day reports. Other unlabeled events, as well as events described in the medical literature, and available data from relevant studies (non-clinical, clinical, epidemiology) will be monitored by GSK and reported as required by applicable regulations. GSK reports that it maintains the capability to conduct evaluations in response to ad hoc queries from regulatory authorities to address safety concerns that might arise in the future. In addition, GSK will submit safety summaries in support of any future marketing applications.

8. ADVISORY COMMITTEE MEETING

It was determined that presentation of data in the sBLA for Boostrix to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was not required because of CBER's experience with Boostrix. Furthermore, because our review of information submitted in the supplement, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion, it was agreed that review of this sBLA by the VRBPAC was not necessary.

9. OTHER RELEVANT REGULATORY ISSUES

There are no other relevant regulatory issues of note.

10. LABELING

Review of the prescribing information (PI) in Physician Labeling Rule format identified some deficiencies, most of which required only minor modifications to the text. CBER's Advertising and Promotional Labeling Branch (APLB) was consulted for labeling comments. These labeling comments from APLB and other sBLA review team members were discussed and comments determined to be acceptable by the review team were communicated to the sponsor. After labeling negotiations with GSK, it was determined by the clinical reviewer and the entire committee that the prescribing information for Boostrix is acceptable.

11. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

The committee recommends approval of this sBLA.