

## Summary Basis for Regulatory Action

**Date:** March 15, 2017

**From:** Shuang Tang, Ph.D., Chair of the Review Committee

**BLA STN#:** 125123/1900

**Applicant Name:** Merck Sharp & Dohme (Merck)

**Date of Submission:** May 16, 2016

**Goal Date:** March 16, 2017

**Proprietary Name/Established Name:** ZOSTAVAX®/Zoster Vaccine Live

**Indication:** ZOSTAVAX is indicated for prevention of herpes zoster (shingles) in individuals 50 years of age and older.

**Recommended Action:** The Review Committee recommends approval of this clinical efficacy supplement to include implementation of the (b) (4) [REDACTED] method in the production of Varicella Zoster Virus (VZV) (b) (4) [REDACTED] for varicella-zoster virus (Oka/Merck strain) drug substance manufacture. We also recommend approval of revisions to the package insert labeling to comply with the 2014 Final Rule, *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*.

**Review Office Signatory Authority:** Wellington Sun, M.D., Director, Division of Vaccines and Related Products Applications, 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.**

The table below indicates the material reviewed when developing the SBRA.

<b>Document title</b>	<b>Reviewer name, Document date</b>
Clinical Reviews <ul style="list-style-type: none"><li>• Clinical</li><li>• BIMO</li></ul>	Ann Schwartz, M.D. (March 2, 2017) Haecin Chun (December 20, 2016)
Statistical Review	Lihan Yan, Ph.D. (January 10, 2017)
CMC Review	Shuang Tang, Ph.D. (February 28, 2017)

## 1. Introduction

This Prior Approval Supplement was submitted by Merck Sharp & Dohme (Merck) to the Center for Biologics Evaluation and Research (CBER) to support a change in the manufacture of varicella-zoster virus (Oka/Merck strain) drug substance (referred to as varicella drug substance) for Zoster Vaccine Live (ZOSTAVAX). The requested changes are intended to (b) (4) Merck's (b) (4) through implementation of a (b) (4) in the manufacturing of (b) (4) for varicella drug substance manufacture. It was concluded that the ZOSTAVAX drug product is not affected by these changes as there is no change to the critical process parameters (CPPs) and critical quality attributes (CQAs) including release specifications for both varicella drug substance and ZOSTAVAX drug product as a result of this manufacturing change. In support of this change in manufacture, Merck submitted studies on the process qualification, comparability, assay compatibility, and stability of varicella drug substance and ZOSTAVAX drug product manufactured using the (b) (4) and data from a clinical trial (Study V210-063) comparing VARIVAX manufactured using the 2007 process to VARIVAX (b) (4).

## 2. Background

The products in the varicella-zoster virus (VZV) family (VARIVAX®, ProQuad®, and ZOSTAVAX®) are (b) (4). ZOSTAVAX is a live attenuated virus vaccine for prevention of herpes zoster (shingles) in individuals 50 years of age and older. The lyophilized preparation when reconstituted with accompanying diluent yields a 0.65 mL dose containing a minimum of 19,4000 PFU (plaque forming units) of Oka/Merck varicella-zoster virus for subcutaneous administration.

Merck proposed plans for implementation of the (b) (4) process in the manufacturing of (b) (4) in order to (b) (4) Merck's (b) (4) in a Type C meeting briefing package submitted on November 1, 2013 (STN 125123/1521.0). In written feedback dated November 22, 2013, CBER agreed with the analytical comparability plan, the filing strategy, and the design of the proposed VARIVAX clinical study (V210-063). CBER recommended including, as a co-primary endpoint, a non-inferiority comparison of geometric mean titers (GMTs) for the VZV

antigen contained in the two products such that the lower bound of the 2-sided 95% confidence interval on the GMT ratio [VARIVAX (b) (4) / VARIVAX 2007] is > 0.67. CBER also recommended revising the clinical protocol to include additional measures to observe adverse reactions and revision of exclusion criteria to include history of seizure disorder and thrombocytopenia. Merck agreed with CBER's recommendations in written feedback dated on December 2, 2013 (STN 125123/1502.1).

### **3. Clinical/Statistical**

#### **a) Clinical Program**

The immunogenicity, safety and tolerability of VARIVAX (b) (4) (VARIVAX manufactured by the proposed (b) (4) manufacturing process) when administered concomitantly with M-M-R® II was evaluated in Study V210-063 in healthy subjects, 12 to 23 months of age. VARIVAX manufactured using the current manufacturing process (VARIVAX 2007 process) was used as active comparator in the study. In addition, non-inferiority immunogenicity between the VARIVAX (b) (4) group and the VARIVAX 2007 group 6 weeks post dose 1 was evaluated. Although CBER did not request this study to support the manufacturing change, Merck and CBER agreed upon the objectives and endpoint evaluations for this study.

Overall, in healthy children 12 to 23 months of age who receive either VARIVAX (b) (4) or VARIVAX 2007 process, the immunogenicity of VARIVAX (b) (4) vaccine was non-inferior to the immunogenicity of VARIVAX 2007 process vaccine for antibody response rates, GMTs and induced acceptable VZV antibody responses following the initial dose of vaccine. The VZV-specific antibody response was measured by gpELISA, a validated assay performed by (b) (4) lvania. The evaluation of safety showed that the adverse event profile was comparable between VARIVAX (b) (4) and VARIVAX 2007 process vaccines after each dose of vaccine.

#### **Study V210-063**

Clinical Study V210-063 was a phase 3, double-blind, randomized, multicenter, controlled study conducted to evaluate the immunogenicity, safety, and tolerability of VARIVAX (b) (4) compared with VARIVAX 2007 process. Details on the safety and reactogenicity results from this study can be found in Section 7 below. A total 611 healthy subjects, 12 to 23 months of age, were randomized into two study groups to receive a single dose of either VARIVAX (b) (4) or VARIVAX 2007 process at Visit 1, given concomitantly with MMR II. A second dose of vaccine was administered 3 months after the first dose; again concomitantly with MMR II vaccine.

The co-primary endpoints of the study were antibody responses rate, GMT responses and the acceptability of the antibody response rate at 6 weeks Post-dose 1. The primary objectives were to demonstrate that a single dose of VARIVAX (b) (4) induces VZV antibody responses, GMT responses, and acceptable antibody response rate to VZV 6 weeks Post-dose 1 that are non-inferior to those induced by VARIVAX 2007 process.

The secondary endpoints are to assess the safety and tolerability of the first and second doses of VARIVAX (b) (4) when administered to children 12 to 23 months of age and to summarize the antibody response to VZV among children after 1 dose of VARIVAX (b) (4) and among children after 1 dose of VARIVAX 2007 process.

**Analyses of Co-primary Endpoints:** Analysis of the risk difference in the response rates to VZV Post-dose 1 (percent of subjects with VZV antibody titer  $\geq 5$  gpELISA units/mL) between vaccination groups in the per-protocol population (Co-primary Objective 1) is shown in Table 1 below. A one-sided test for non-inferiority in 2 binomial proportions was performed at the  $\alpha=0.025$  (one-sided) level. This analysis was unstratified and the test statistic, p-value, and corresponding 95% CIs were calculated using the Miettinen and Nurminen method, an unconditional, asymptotic method. The response rate in subjects receiving a single dose of VARIVAX (b) (4) was considered non-inferior to the control group if the one-sided p-value for the associated non-inferiority test was  $<0.025$ . This criterion was equivalent to requiring the lower bound of the two-sided 95% CI for the difference in rates (Group 1 minus Group 2) exclude a decrease of 10 percentage points or more. The results as shown in Table 1 demonstrate non-inferiority of the response rate 6 weeks Post-dose 1 in VARIVAX (b) (4) as compared to VARIVAX 2007 process. Thus this co-primary endpoint was met.

**Table 1. Study V210-063: Non-inferiority Analysis of Risk Difference in Antibody Response Rates to VZV Between Vaccination Groups – Post-dose 1 (Per-Protocol Population)**

Parameter	Group 1: VARIVAX (b) (4) (N=306) n	Group 1: VARIVAX (b) (4) (N=306) Observed Response	Group 2: VARIVAX 2007 Process (N=305) N	Group 2: VARIVAX 2007 Process (N=305) Observed Response	Risk Difference (Group 1 – Group 2) (95% Confidence Interval)	Non- inferiority Conclusion
Percent $\geq$ 5 gpELISA units/mL	254	97.2% (247/254)	254	97.2% (247/254)	0.0 (-3.2,3.2)	Non- inferior

Source: STN 103552/6047.0,m5.3.5.1 Clinical Study Report, section 11.1, Table 11-1 (reviewer modified), page94/103.

The analysis of the risk difference in GMT response to VZV post-dose 1 between vaccination groups in the per-protocol population (Co-primary Objective 2) is shown below in Table 2. A one-sided test for non-inferiority in the VZV antibody GMT was performed at the  $\alpha=0.025$  (one-sided) level. A ratio of 0.67 corresponds to a 1.5-fold decrease in GMT in Group 1 as compared to Group 2. Rejecting the null hypothesis ( $H_0$ :  $GMT_1/GMT_2 \leq 0.67$ ) at the 1-sided  $\alpha=0.025$  level corresponds to the lower bound of the 2-sided 95% CI for the GMT ratio (Group 1/Group 2) being  $>0.67$ . The non-inferiority criterion was demonstrated for the antibody GMTs (Table 2).

**Table 2. Study V210-063: Non-inferiority Analysis of Risk Difference in GMT Response Rates to VZV Between Vaccination Groups – Post-dose 1 (Per-Protocol Population)**

Parameter	Group 1: VARIVAX (b) (4) (N=306) n	Group 1: VARIVAX (b) (4) (N=306) Estimated GMT	Group 2: VARIVAX 2007 Process (N=305) n	Group 2: VARIVAX 2007 Process (N=305) Estimated GMT	Estimated GMT Ratio (Group 1 / Group 2) (95% Confidence Interval)†	Non- inferiority Conclusion
GMT	254	16.3	254	17.2	0.95(0.85,1.06)	Non- Inferior

Source: STN 103552/6047.0, m5.3.5.1 Clinical Study Report, section 11-2, Table 11-2 (reviewer modified), page96/105.

N = Number of subjects vaccinated in the vaccination group at Dose 1.

n = Number of subjects with seronegative antibody titer at baseline and postvaccination serology contributing to the per-protocol analysis.

Seronegative antibody titer - VZV: <1.25gpELISA units/mL.

VZV = varicella-zoster virus. GMT = Geometric mean titer.

The analysis of the acceptability of the antibody response rates of Group 1 (per-protocol population) to VZV post-dose 1 shows that acceptability was demonstrated for VARIVAX (b) (4). The 1-sample, 2-sided 95% CI for response rate is computed using the exact CI method for a single binomial proportion. The lower bound of the 95% CI being >76% for VZV implies that the value of the parameter is statistically significantly greater than the pre-specified acceptability criterion (76%) and allows for a conclusion of acceptability.

**Table 3. Study V210-063: Acceptability of Antibody Response Rates to VZV in Group 1 – Post-dose 1 (Per-Protocol Population)**

Parameter	Group 1: VARIVAX (b) (4) (N=306) n	Group 1: VARIVAX (b) (4) (N=306) Observed Response	Group 1: VARIVAX (b) (4) (N=306) 95% Confidence Interval	Acceptability Conclusion
Percent ≥ 5 gpELISA units/mL	254	97.2% (247/254)	(94.4%, 98.9%)	Acceptable

Source: STN 103552/6047.0, m5.3.5.1 Clinical Study Report, section 11.3, Table 11-3 (reviewer modified), page 97/106.

N = Number of subjects vaccinated in the vaccination group at Dose 1.

n = Number of subjects with seronegative antibody titer at baseline and post-vaccination serology contributing to the per-protocol analysis.

VZV = varicella-zoster virus.

Seronegative antibody titer - VZV: <1.25gpELISA units/mL.

gpELISA = Glycoprotein enzyme-linked immunosorbent assay.

**Analyses of Secondary Endpoints:** The VZV seroconversion rate (defined as subjects with baseline VZV titer <1.25 gpELISA units/mL and with postvaccination VZV titer ≥1.25 gpELISA units/mL) after the first dose was a secondary supportive analysis. As a result, with 100.0% of the VARIVAX™ (b) (4) group and 99.6% of the VARIVAX™ 2007 Process group achieving VZV titers ≥1.25 gpELISA units/mL post Dose 1 (99.8% of subjects overall).

Thirteen (13) subjects in the VARIVAX™ (b) (4) group and 19 subjects in the VARIVAX™ 2007 process group were initially seropositive to antibody and satisfied requirements for inclusion in the full analysis set population. Analysis results of these small numbers of subjects are not likely to provide meaningful conclusions and therefore are not presented in the review.

**Dropouts and/or Discontinuations:** The dropout rates were 14.1% and 11.5% in the VARIVAX (b) (4) group and the VARIVAX 2007 process group, respectively. About 17% of the subjects in each group were excluded from the primary immunogenicity analyses including subjects with positive VZV baseline. The rates are similar between the two treatment groups and were within the expectation (20%) at the planning of the study.

**Subpopulation Analyses:** Although not powered for the comparison, an analysis of Post-dose 1 antibody responses to VZV by gender and race in the per-protocol population was done. Antibody responses across races and between vaccination groups were generally comparable, with >94% of all races achieving VZV antibody titers  $\geq 5$  gpELISA units/mL at 6 weeks Post-dose 1 and VZV antibody GMTs being similar between vaccination groups.

**Bioresearch Monitoring (BIMO) inspection:** BIMO inspections were completed at two clinical study sites conducting Study V210-063. A review of the inspection results did not reveal any significant issues that impact the data submitted in this supplement.

## **b) Pediatrics**

ZOSTAVAX is not indicated for prevention of primary varicella infection (Chickenpox) and should not be used in children and adolescents.

## **c) Other Special Populations**

ZOSTAVAX is contraindicated for pregnant women and women planning to become pregnant within 3 months of administration of ZOSTAVAX, individuals who are immunosuppressed or immunodeficient and individuals with a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin or any other component of the vaccine.

## **4. Chemistry Manufacturing and Controls (CMC)**

Manufacturing sites for the varicella drug substance and ZOSTAVAX drug product:

Merck Manufacturing Division

(b) (4)

Merck Manufacturing Division

(b) (4)

The (b) (4) for the manufacturing of VZV (b) (4) is proposed to (b) (4) the (b) (4). Based on the information submitted, use of the (b) (4) by applying the (b) (4) process in the manufacturing of the (b) (4) does not negatively impact product quality.

**a) Product Quality**

In the current procedure, (b) (4)

The key manufacturing process change in (b) (4)

To support the proposed changes, information was provided on the (b) (4) consistency batches and stability batches for VARIVAX Refrigerated manufactured using the (b) (4) drug substance lots produced using the (b) (4) met CPPs and CQAs including release specifications. Three VARIVAX drug product lots

manufactured from the (b) (4) also met release specifications. Thus, the process validation studies for the (b) (4) are acceptable.

It is noted that the clinical trial materials, demonstration batches and stability batches were manufactured using the (b) (4) procedure, which does not include all of the requested changes. The (b) (4) process contains additional process improvement changes, including (b) (4)

These additional changes in the (b) (4) were previously included in the Type C meeting briefing package submitted on November 1, 2013 (STN 125123/1521.0). (b) (4) is a new process analytical technique recently approved by CBER for use in determining (b) (4)

The drug product manufacturing process remains the same as licensed for final bulks and final containers. The applicant re-qualified the process and characterization assays that may be potentially affected as a result of the change, all of which were found acceptable for use. There is no change to the CPPs and CQAs including the release specifications for both varicella drug substance and ZOSTAVAX drug product as a result of this manufacturing change.

Accelerated stability studies and long-term stability studies for (b) (4) varicella (b) (4) drug products including both ZOSTAVAX and VARIVAX are provided in the submission. Briefly, results of the accelerated stability studies at 5°C, (b) (4) for (b) (4) varicella (b) (4) batches (b) (4) met all stability comparability criteria. The long-term stability data for the (b) (4) varicella (b) (4) batches for storage at (b) (4) met all stability specifications through (b) (4). The long-term stability study of the (b) (4) is still ongoing and will be monitored through a period of (b) (4). The accelerated stability study and the long-term stability study for (b) (4) VARIVAX drug products were performed using (b) (4) VARIVAX Refrigerated lots manufactured using the (b) (4) batches. The



degradation slopes of the accelerated stability studies for the (b) (4) VARIVAX Refrigerated batches at (b) (4) are within the 95%/95% tolerance interval established by the historical VARIVAX Refrigerated (b) (4) accelerated slope range. The long-term stability testing for (b) (4) VARIVAX Refrigerated batches at 5°C was completed through (b) (4) (expiry) and all results were within their respective stability specifications. Accelerated stability studies were performed on (b) (4) ZOSTAVAX Refrigerated batches manufactured using the (b) (4). The accelerated stability testing results for these (b) (4) ZOSTAVAX batches are comparable to the historical experience. Long-term stability studies on the (b) (4) ZOSTAVAX Refrigerated batches are still ongoing and will be monitored for a period of 18 months. Testing through three months is complete, and the results met the specification limits.

### **b) CBER Lot Release**

There were no revisions to the existing ZOSTAVAX Lot Release Protocol under this supplement. A review of Product Release Branch records indicated that there are no pending lots or issues that would affect approval of the submission.

### **c) Facilities Review/Inspection**

No information related to any of the manufacturing facilities was included in this supplement. Such information is not required as there are no manufacturing facility-related changes. The varicella drug substance and ZOSTAVAX drug product are manufactured at both the (b) (4) sites.

### **d) Environmental Assessment**

No information related to environmental assessment was included in this supplement. The FDA concluded that an environmental re-assessment is not needed since there is no change to the scale of manufacturing for the drug product as a result of the requested manufacturing change.

### **e) Product Comparability**

Comparative studies were performed using comparability/characterization methods including characterization tests and routine release tests measuring the CQAs of (b) (4). All the (b) (4) lots met the CQA acceptance criteria and are within historical experiences. (b) (4) results show that there are (b) (4) lots. The (b) (4) is similar to those from the current process and is within historical experience. There are no changes to the (b) (4), which are related to (b) (4). The CQAs including potency, antigen content, potency/antigen ratio, (b) (4) level, as well as quality control release testing for the (b) (4) lots are within the historical range. In addition, all the (b) (4) VARIVAX lots met the release specifications and there were no changes to the stability profiles for (b) (4) varicella (b) (4) drug products according to the ongoing long-term stability study and accelerated stability study. Comparative studies

demonstrated that the (b) (4) varicella drug substance and drug products including both VARIVAX and ZOSTAVAX are comparable to the drug substance and drug products produced using the 2007 process.

## **5. Nonclinical Pharmacology/Toxicology**

No new nonclinical pharmacology/toxicology data were submitted or required in support of this supplement.

## **6. Clinical Pharmacology**

No new clinical pharmacology data were submitted or required in support of this supplement.

## **7. Safety**

All subjects were followed for safety (daily temperatures, injection-site adverse events, and systemic adverse events) for 42 days after each vaccination. All subjects were followed for serious adverse events from the time of enrollment until the end of the study. In addition, medically-attended events were collected through 180 days after completing the 42-day safety follow-up post Dose 2. Although no formal hypothesis was tested regarding safety, a summary of safety results following each dose of vaccine demonstrated that the safety profile of the two vaccines was similar. Overall, the two vaccination groups were comparable in terms of the incidence rates of adverse events overall, systemic adverse events, injection-site adverse events, vaccine-related adverse events, and serious adverse events.

## **8. Advisory Committee Meeting**

A Vaccines and Related Biologics Products Advisory Committee (VRBPAC) meeting was not held for this supplement, as there were no issues or concerns that presented during the course of review of the supplement that required consult from the advisory committee.

## **9. Other Relevant Regulatory Issues**

There are no other relevant regulatory issues.

## **10. Labeling**

No clinical data from Study V221-063 were added to the package insert. Two ZOSTAVAX package inserts were submitted by the Applicant in the PLLR format as required by the Final Rule: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling (PLLR) published December 4, 2014, and effected June 30, 2015: one for Frozen formulation and the other for Refrigerator-stable formulation. Revisions to the content and format of information presented in the package insert in the Physician Labeling

Rule (PLR) format under section 8 Use in Specific Populations were included and removal of the pregnancy letter categories was completed based in part on data submitted from the completed pregnancy registry (1995-2013). Revisions to the package insert were agreed upon by the Applicant and CBER. The committee concurred that the Final Draft Labels submitted on March 10, 2017, were acceptable.

## **11. Recommendations and Risk/Benefit Assessment**

### **a) Recommended Regulatory Action**

The safety and immunogenicity data from the clinical study V221-063 support a recommendation for approval of the manufacturing process changes for ZOSTAVAX. This implementation of the (b) (4) using a (b) (4) method in the production of VZV (b) (4) of VZV (b) (4) used in the production of all varicella-zoster virus containing vaccines produced by Merck (VARIVAX, ProQuad and ZOSTAVAX). BLA supplements were submitted for VARIVAX and ProQuad under the respective files, and were reviewed separately. The supplement for VARIVAX was approved on February 17, 2017.

### **b) Risk/Benefit Assessment**

The risk/benefit profile of varicella drug substance and ZOSTAVAX drug product manufactured with the (b) (4) in the production of (b) (4) is unchanged from that of the currently approved ZOSTAVAX vaccine (2007 process) based on process qualifications and comparability studies, and safety and immunogenicity data from the clinical study V221-063.

### **c) Recommendation for Postmarketing Activities**

No PMCs or PMRs are currently in place for any varicella-zoster containing vaccine, including ZOSTAVAX. At this time, maintenance of routine pharmacovigilance is planned after approval of this manufacturing change.