

## Summary Basis for Regulatory Action

**Date:** August 3, 2017

**From:** David C. Staten, Jr., CDR, USPHS, Chair of the Review Committee

**STN#:** 125123/1946

**Applicant Name:** Merck Sharp & Dohme Corp.

**Date of Submission:** 03-OCT-2016

**Goal Date:** 03-AUG-2017

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

**Reason for the Submission:** To include safety and immunogenicity data to support the concomitant administration of ZOSTAVAX and inactivated influenza vaccines, including quadrivalent inactivated influenza vaccines

**Recommended Action:** The Review Committee recommends approval of this supplement.

**Review Office Signatory Authority:** Wellington Sun, MD, 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.

Document title	Reviewer name, Document Date
Clinical Reviews <ul style="list-style-type: none"><li>• Clinical</li><li>• BIMO</li></ul>	Madan Kumar, MD, August 2, 2017 Haecin Chun, July 5, 2017
Statistical Reviews <ul style="list-style-type: none"><li>• Clinical data</li><li>• Non-clinical data</li></ul>	Sang Ahnn, July 27, 2017 Rong Fu, June 14, 2017
CMC Reviews <ul style="list-style-type: none"><li>• CMC/ VZV PCR assay and VZV gpELISA assay</li><li>• CMC/Influenza (QIV) strain specific HAI assay</li></ul>	Shuang Tang, July 27, 2017 Ewan Plant, March 13, 2017
Labeling Review (APLB)	Oluchi Elekwachi, July 27, 2017

## 1. Introduction

On October 3, 2016, the applicant submitted a supplement to their Biological License Application (BLA) for ZOSTAVAX (Zoster Vaccine Live) to seek an update to the ZOSTAVAX® US Prescribing Information (USPI) to update the information regarding the concomitant administration of Zoster Vaccine Live with inactivated influenza vaccines to include the quadrivalent inactivated influenza vaccine. The frozen formulation of the vaccine contains sucrose, phosphate, glutamate, and hydrolyzed (porcine) gelatin as stabilizers. When reconstituted as directed and stored at room temperature for up to 30 minutes, each 0.65-mL dose contains a minimum of 19,400 PFU (plaque forming units) of Oka/Merck varicella-zoster virus; 31.16 mg of sucrose, 15.58 mg of hydrolyzed gelatin, 3.99 mg of sodium chloride, 0.62 mg of monosodium L-glutamate monohydrate, 0.57 mg of sodium phosphate dibasic, 0.10 mg of potassium phosphate monobasic, 0.10 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of neomycin, and bovine calf serum. The product contains no preservatives. It is reconstituted with the sterile diluent that is supplied, and administered subcutaneously. A refrigerator stable formulation is also approved but not currently marketed in the United States (U.S.).

The current application includes clinical data from ZOSTAVAX® Protocol 062 that supports the safety and immunogenicity of Zoster Vaccine Live when administered concomitantly with quadrivalent inactivated influenza vaccine. As stated in both the original protocol submission on 01May2015 (BBIND 6840/0489) and the subsequent response to CBER questions on 29May2015 (BBIND 6840/0492), Protocol 062 was a double-blind, randomized controlled study that is similar in design to the study conducted previously to support the concomitant administration of Zoster Vaccine Live with licensed inactivated trivalent influenza vaccines (ZOSTAVAX® Protocol 011). In Protocol 062, 882 adults in the U.S., 50 years of age and older (median age =60 years), were randomized to receive quadrivalent inactivated influenza vaccine (QIV) and ZOSTAVAX® concurrently (N=440), or QIV alone followed 4 weeks later by ZOSTAVAX® alone (N=442). The antibody responses to both vaccines at 4 weeks post vaccination were similar in both groups. Results from Protocol 062 are submitted to update to the ZOSTAVAX® USPI statements regarding the concomitant administration of Zoster Vaccine Live with influenza vaccines to include quadrivalent inactivated influenza vaccines.

## 2. Background

This Application does not propose any change to the indication or dosing schedule for ZOSTAVAX®. In the U.S., ZOSTAVAX® is indicated for the prevention of herpes zoster (shingles) in individuals 50 years of age and older. Concomitant administration of ZOSTAVAX® and trivalent inactivated influenza vaccine was approved in the US on 06-Jul-2007. In Protocol 011, 374 adults in the U.S., 60 years of age and older (median age =66 years), were randomized to receive trivalent inactivated influenza vaccine (TIV) and ZOSTAVAX® concurrently (N=188), or TIV alone followed 4 weeks later by ZOSTAVAX® alone (N=186). The antibody responses to both vaccines at 4 weeks post vaccination were similar in both groups. The study results from Protocol 011 were

submitted in supplemental BLA 125123/90 which was approved on July 12, 2007. The modification sought in this Application is to obtain approval for the concomitant administration of ZOSTAVAX® with inactivated influenza vaccines, including quadrivalent inactivated influenza vaccines.

### 3. Clinical/Statistical

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

Prior to ZOSTAVAX there were no FDA licensed vaccines for the prevention of herpes zoster. VARIVAX, a vaccine licensed for use in the U.S. for prevention of varicella in individuals 12 months of age and older, uses a smaller dose of the same live, attenuated Oka/Merck vaccine virus. ZOSTAVAX, manufactured by Merck & Co., is a live, attenuated virus vaccine that is licensed in the U.S. for persons 50 years of age or older for the prevention of herpes zoster. ZOSTAVAX was initially approved on May 25, 2006, for active immunization and prevention of herpes zoster in persons 60 years of age and older in a single dose (0.65 ml subcutaneous injection) regimen. Approval for use in persons 50-59 was granted on March 24, 2011. Merck submitted a BLA supplement on October 03, 2016, requesting approval for changes in the ZOSTAVAX USPI to reflect data from Protocol 062 on its concomitant use with quadrivalent influenza vaccines.

Protocol 062: A Phase 3, double-blind, randomized, multicenter study to evaluate the immunogenicity, safety, and tolerability of ZOSTAVAX administered concomitantly versus nonconcomitantly with quadrivalent influenza virus vaccine. In this study 882 healthy adults 50 years of age and older were randomized 1:1 to two vaccination groups (one administered Fluzone Quadrivalent and ZOSTAVAX together, and one administered ZOSTAVAX four weeks after influenza vaccination).

VZV-specific primary immunogenicity endpoints for this study evaluated VZV Ab GMT ratios at four weeks post vaccination (concomitant/nonconcomitant) and the Geometric Mean Fold Rise (GMFR) from prevaccination to four weeks post vaccination in the concomitant group. Total anti-VZV IgG antibody concentration was determined by a validated VZV gpELISA assay. The primary endpoints used to assess the immune response to the quadrivalent influenza vaccine were the strain specific HAI GMT ratios (concomitant group vs. nonconcomitant group) for each of the four strains in the influenza vaccine at four weeks post vaccination. Study success was defined as meeting preset criteria for noninferiority for all of these respective endpoints (lower bound of the 95% CI around each GMT ratio > 0.67, and lower bound of the 95% CI around gpELISA GMFR > 1.4). Safety endpoints evaluated (N=882) were the proportions of subjects reporting SAEs within 28 days after any study vaccination, injection-site AEs (redness, swelling, and pain/tenderness/soreness) occurring within 5 days after any study vaccination, injection-site AEs within 28 days after any study vaccination, elevated temperatures ( $\geq 100.4^{\circ}\text{F}$  [ $\geq 38.0^{\circ}\text{C}$ ] oral or equivalent) within 28 days after any study vaccination, and SAEs throughout the study duration of eight weeks.

## Efficacy

Efficacy in this study was inferred from analyses of primary immunogenicity. Overall the data from Protocol 062 demonstrate no evidence of immune interference and no safety concerns for concomitant administration of ZOSTAVAX with Fluzone quadrivalent influenza vaccine.

The results of the primary immunogenicity analyses for the per protocol population are summarized below:

The following table shows VZV gpELISA GMTs overall and with age stratification.

**Table 1: VZV gpELISA GMTs for Participants in Protocol 062**

Age Stratum (Years)	Endpoint	Time Relative to ZOSTAVAX	Concomitant Group			Non-concomitant Group		
			n	Observed Responses	(95% CI)	n	Observed Responses	(95% CI)
50 to 59	GMT	Prevaccination	210	195.2	(167.4, 227.7)	199	222.4	(192.6, 256.8)
	GMT	Week 4	196	391	(340.8, 448.6)	195	510.7	(456.1, 571.8)
	GMFR from Prevaccination	Week 4	194	1.9	(1.7, 2.2)	191	2.2	(2.0, 2.5)
60 to 69	GMT	Prevaccination	149	208.1	(174.7, 247.8)	146	248.3	(208.9, 295.2)
	GMT	Week 4	147	398.5	(350.8, 452.7)	141	500.7	(445.3, 562.9)
	GMFR from Prevaccination	Week 4	143	2	(1.7, 2.3)	140	2	(1.8, 2.3)
>70	GMT	Prevaccination	68	237.6	(185.6, 304.1)	64	217.6	(168.3, 281.3)
	GMT	Week 4	66	403.2	(339.8, 478.5)	56	358.3	(290.3, 442.1)
	GMFR from Prevaccination	Week 4	66	1.7	(1.4, 2.0)	56	1.7	(1.4, 2.0)
Combined	GMT	Prevaccination	427	206	(185.6, 228.6)	409	230.5	(208.4, 255)
	GMT	Week 4	409	395.6	(363.7, 430.4)	392	482	(446.4, 520.4)
	GMFR from Prevaccination	Week 4	403	1.9	(1.8, 2.1)	387	2.1	(1.9, 2.2)

The primary immunogenicity analyses demonstrated noninferiority of VZV antibody GMTs (GMT ratio 0.87; 95% CI: 0.80 - 0.95) and strain-specific HAI GMTs (1.02 [95% CI: 0.88-1.18] for the A/H1N1 strain; 1.10 [95% CI: 0.94, 1.29] for the A/H3N2 strain; 1.00 [95% CI: 0.88, 1.14] for the B/Yamagata strain; 0.99 [95% CI: 0.87, 1.13] for the B/Victoria strain) at four weeks postvaccination. Additionally, the analysis of gpELISA GMFR met the pre-specified success criterion (GMFR 1.90; 95% CI 1.76 – 2.05). All primary endpoints met their pre-specified success criteria using the per protocol population for each endpoint.

## Bioresearch Monitoring

CBER Bioresearch Monitoring (BIMO) inspection assignments were issued to three clinical study sites that participated in the conduct of Protocol V211-062-00. The inspections did not reveal 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. A total of 882 healthy adults 50 years of age and older were enrolled into the study reviewed under this supplement (Protocol 062). No pediatric data were submitted in this supplement.

## **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. No special population data were submitted in this supplement.

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

In this Efficacy Supplement to the BLA for ZOSTAVAX, the gpELISA was used to assess immunogenicity of ZOSTAVAX in conjunction with influenza vaccination. The gpELISA were performed by (b) (4). The validation studies for the gpELISA performed at (b) (4) were cross-referenced to the Type V Biologics Master File ((b) (4)), where the sponsor requested to transfer the gpELISA from (b) (4)

The gpELISA was used to measure the IgG antibody to VZV for study Protocol 062 at (b) (4) from January 27, 2016 through April 22, 2016. The assay was originally validated in 2003 at (b) (4) and then transferred to (b) (4). A partial validation report (dated May 27, 2015) and a transfer study report (dated September 3, 2014) were used to support this transfer. The partial validation report and the transfer study report were submitted to (b) (4) on June 15, 2015, and have been reviewed by the Division of Viral Products.

The HAI assay titrates influenza A and B specific antibodies using turkey red blood cells (RBCs). Virus and control sera are obtained from qualified sources such as the National Institute for Biological Standards and Control (NIBSC). The protocol "Hemagglutination Inhibition (HAI) Test for Titrating Influenza A and B Specific Antibodies – Turkey RBCs (b) (4) Serum Dilution) (TSOP.119.00510), Revision D" is located in Master File (b) (4). The protocol describes in detail the HAI test based on the WHO manual on Animal Influenza Diagnosis and Surveillance which is widely regarded as the industry standard.

The current version of the assay differs from the first version in MF (b) (4) the initial serum dilution is changed from (b) (4), and the neutralization temperature is changed from (b) (4) at (b) (4) to (b) (4). The changes were in response to our review of the assay for another product submitted by a different company (IND (b) (4)). However, that company and the sponsor of this supplement contracted the same company to perform the HAI assays. The new initial dilution aligns

with the industry standard. The change in incubation time and temperature realigns the current version with the original version of the assay; the original version of the assay resulted in titers near the mean of a (b) (4) laboratory study attempting to establish an international standard. Revision D of protocol TSOP.119.00510 was found satisfactory by the Division of Viral Products.

#### **a) Product Quality**

ZOSTAVAX® is a lyophilized preparation containing phosphate, gelatin, and sucrose (PGS) as stabilizers. To maintain potency, the frozen formulation of ZOSTAVAX® must be stored between -58°F and +5°F (-50°C and -15°C) with a shelf life of 18 months. Use of dry ice may subject ZOSTAVAX® to temperatures colder than -58°F (-50°C). The refrigerator-stable formulation of ZOSTAVAX®, licensed in the U.S. and used in the clinical trial summarized within this document (Protocol 062), allows the vaccine to be stored refrigerated at 2°C to 8°C or colder over the entire shelf-life of 18 months. When reconstituted, each 0.65-mL dose of either formulation contains a minimum of 19,400 plaque-forming units (PFU) of the Oka/Merck strain of VZV.

ZOSTAVAX® is a single-dose, sterile, preservative-free, live virus vaccine. The VZV strain (parental Oka strain) from which the attenuated vaccine was derived was initially obtained from a Japanese child infected with naturally occurring varicella. The isolate from this child was then introduced into (b) (4)

Further passage of the virus for use in a vaccine was performed at Merck Research Laboratories (MRL) in human diploid cell cultures (MRC-5) that were free of adventitious agents. No new product information was included in the supplement.

#### **b) Environmental Assessment**

The exclusion from the Environmental Assessment was granted under the original BLA and since no change in the manufacture of the product was indicated in this supplement, the Review Committee concurs with the exclusion.

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

No nonclinical pharmacology or toxicology studies were conducted in support of this application.

##### **6. Clinical Pharmacology**

No clinical pharmacology studies were conducted in support of this application.

##### **7. Safety**

All enrolled subjects were followed for safety through Day 28 following each vaccination. This interval is the same as that used in Protocol 011, based on findings

from previous trials that there was no difference in AEs reported from Days 28 through 42 following vaccination with ZOSTAVAX® and with placebo. Safety data were collected following each vaccination via an electronic Vaccination Report Card (eVRC) that was completed by the subject on a daily basis. The eVRC prompted subjects for injection-site adverse experiences (AEs) and temperature: (1) systemic AEs through 28 days after each study vaccination, (2) injection-site AEs that were prompted for on the eVRC through 5 days after each study vaccination (erythema, swelling, and pain/tenderness/soreness), (3) all injection-site AEs through 28 days after each study vaccination, (4) elevated temperature ( $\geq 100.4^{\circ}\text{F}$  [ $\geq 38.0^{\circ}\text{C}$ ] oral or equivalent) through 28 days after any study vaccination, and 5) serious AEs throughout the study. All serious AEs that occurred during the follow-up period, regardless of causality, were recorded. In addition, all serious AEs that occurred at any time during the study after completion of the 28-day follow-up period and that were determined by the investigator to be possibly, probably, or definitely vaccine related were also reported. The satisfactory completion and integrity of the eVRC was critical to the assessment of safety; all reasonable steps were taken by the investigators and staff to ensure completion of the eVRC. The clinical study contained in this Application used terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0, when reporting AEs (medical conditions), their associated system organ classification, medical procedures, and social circumstances. The proportions of subjects who reported specific AEs were comparable between the concomitant and nonconcomitant vaccination groups for both ZOSTAVAX and quadrivalent influenza vaccine.

The most commonly reported AEs for both groups and vaccines were pain, erythema/swelling, and pruritus.

The most common solicited injection site AEs experienced were pain (33.3% versus 35.6%, concomitant vs non-concomitant), erythema (30.1% versus 28.5%), and swelling (85% versus 92%) after ZOSTAVAX administration. When ZOSTAVAX was administered four weeks after injection with Fluzone Quadrivalent, the most common reactions were again pain (30.6% versus 27.9%), erythema (7.8% versus 2.5%) and swelling (7.1% versus 3.7%). The overwhelming majority of these were mild-moderate in severity with only two severe solicited AEs after ZOSTAVAX administration (severe injection site pain in 2 subjects in the non-concomitant group) and one severe instance of injection site pain in a single subject after Influenza vaccination.

Infections (predominantly URIs) comprised the largest category of unsolicited AEs with 41 subjects in the concomitant group and 47 subjects in the non-concomitant group. This is followed by musculoskeletal disorders (predominantly arthralgia) with 26 subjects in the concomitant group and 23 in the non-concomitant group.

Unsolicited AEs are presented as a composite following “any vaccination” and separated between treatment arms making identification of AEs after ZOSTAVAX versus Fluzone impossible to distinguish. Still, similar to the solicited AEs, proportions between treatment arms are largely comparable with no concerning safety signals.

A total of 10 subjects (4 in the concomitant group and 6 in the nonconcomitant group) each reported a single SAE during the study period but were not vaccine related.

#### 8. Advisory Committee Meeting

The Application was not referred to the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) because our review of the information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

#### 9. Other Relevant Regulatory Issues

There are no other relevant regulatory issues to discuss.

#### 10. Labeling

Labeling changes to be approved under this supplement consist of the revision of one paragraph in Section 14 Clinical Studies, Subsection 14.3 Concomitant Use Studies.

The sponsor accepted this change and the proposed revision in the number of subjects randomized to the concomitant and non-concomitant groups per V211-062 CSR, Table 10-1 and 10-5.

The Advertising and Promotional Labeling Branch (APLB) agreed with OVR's proposed revisions.

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

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

The review committee recommends approval.

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

The data from Protocol 062 presented in this Application demonstrate that concomitant administration of ZOSTAVAX® and inactivated quadrivalent influenza vaccine to adults ≥50 years of age is generally well tolerated and immunogenic. The data show that concomitant administration is comparable (noninferior) to the sequential administration of these vaccines with respect to immunogenicity. In addition, the proportions of subjects reporting injection-site AEs, systemic AEs, and serious AEs were comparable between the vaccination groups overall, with significant differences seen for only a few specific AEs. Specifically, injection-site bruising, following administration of ZOSTAVAX®, and injection-site erythema and swelling, following administration of quadrivalent influenza vaccine, were significantly higher in the Concomitant Group than in the Nonconcomitant Group, though absolute numbers of subjects reporting these AEs were low in both groups: <8% for each. These data suggest that ZOSTAVAX® can be

administered concomitantly with inactivated influenza vaccines, including quadrivalent influenza vaccine, for the prevention of HZ and influenza. The concomitant administration of these vaccines is expected to have comparable immunogenicity and safety profiles as their sequential administration in the older adult population for whom both vaccines are indicated. The option to provide concomitant administration of these vaccines is essential in this older population, and is expected to contribute to an increase in vaccine coverage for both ZOSTAVAX® and quadrivalent influenza vaccine. Given the noninferior immunogenicity and safety profiles of concomitant vs. nonconcomitant administration, the clinical study presented in this Application demonstrates a favorable benefit/risk profile for concomitant administration.

**c) Recommendation for Postmarketing Activities**

No new postmarketing activities are requested.