Summary Basis for Regulatory Action

Date: March 27, 2015

From: Luba Vujcic, Chair of the Review Committee

BLA/ STN#: 125108/774

Applicant Name: Merck Sharp & Dohme Corp.

Date of Submission: May 28, 2014

PDUFA Goal Date: March 28, 2015

Proprietary Name/ Established Name: ProQuad®/ Measles, Mumps, Rubella and Varicella Virus Vaccine Live

Indication: ProQuad® is indicated for active immunization for the prevention of measles, mumps, rubella, and varicella disease in children 12 months through 12 years of age. The first dose is usually administered at 12-15 months of age, with a second dose, if needed, administered at 4-6 years of age.

Reason for the Submission: To include clinical data that support the safety and immunogenicity of refrigerator-stable and frozen formulations of ProQuad with (b) (4) (b) (4) per dose. These formulations are produced (b) (4) (b) (4)

Recommended Action: Approval

Signatory Authorities Action: Approval

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

X 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	
Material Reviewed/ Consulted	**Reviewer Name – Document(s) Date**
Clinical Review	Ann Schwartz, M.D. – January 30, 2015
Statistical Review	Tielin Qin, Ph.D. – February 11, 2015
CMC Review	Ana Sierra-Honigmann, Ph.D. – December 18, 2015
Bioresearch Monitoring Review	Carla Jordan, C.S.O. – February 19, 2015

1. Introduction

On September 6, 2005, FDA approved a biologics license application for Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live. ProQuad is the trade name of this combined attenuated live virus vaccine containing measles, mumps, rubella and varicella viruses.
ProQuad is a sterile lyophilized preparation that consists of the components of two previously licensed vaccines, combined:

- M-M-R™II (Measles, Mumps and Rubella Virus Vaccine Live):
  - Measles Virus Vaccine Live, a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain;
  - Mumps Virus Vaccine Live, the Jeryl Lynn™ (B level) strain of mumps virus;
  - Rubella Virus Vaccine Live, the Wistar RA 27/3 strain of live attenuated rubella virus

- Varicella Virus Vaccine Live, the Oka/Merck strain of varicella-zoster virus (VZV).

When reconstituted as directed, each 0.5-mL dose contains not less than 3.00 log10 TCID50 (50% tissue culture infectious dose) of measles virus; 4.30 log10 TCID50 of mumps virus; 3.00 log10 TCID50 of rubella virus; and a minimum of 3.99 log10 PFU (plaque-forming units) of Oka/Merck varicella virus.

ProQuad is for subcutaneous injection and it exists as frozen and refrigerator-stable formulations. The quadrivalent vaccine is manufactured at their West Point, PA facility and distributed by Merck of Whitehouse Station, N.J., and it is currently indicated for active immunization for the prevention of measles, mumps, rubella, and varicella disease in children 12 months through 12 years of age. The first dose is usually administered at 12-15 months of age, with a second dose, if needed, administered at 4-6 years of age.

2. Background

ProQuad (measles, mumps, rubella, and varicella virus vaccine [MMRV]) was developed to improve vaccine coverage for measles, mumps, rubella and varicella diseases by the administration of a single combination vaccine rather than separate injections at a single healthcare visit, thereby preventing delayed or missed vaccinations.

In this BLA supplement, the applicant submitted a clinical study report for a single Phase 3 study, Protocol 027, which was conducted to evaluate the immunogenicity, safety, and tolerability of a formulation of ProQuad [referred to as MMRV Vaccine (AMP)] manufactured by the Alternative Manufacturing Process (AMP) with

3. Chemistry Manufacturing and Controls (CMC)

This efficacy supplement was submitted to (b) (4) in the ProQuad final product. The current specification was implemented with CBER approval of the (b) (4) The proposed for the refrigerated and frozen ProQuad formulations would (b) (4) lots that could be used to manufacture ProQuad and consequently would reduce the risk of market supply shortages. This supplement includes clinical data from Protocol 027, which supports the safety, tolerability, and immunogenicity of ProQuad™ containing the (b) (4) specification. No changes to the product labeling are proposed as a result of this submission.

a. Product Quality

Under this supplement, the maximum (b) (4) in ProQuad can be at a level above the current maximum specification. The previous specification (b) (4) was implemented with the (b) (4) The new specification to be implemented under this supplement is (b) (4). This change could (b) (4) lots used to manufacture ProQuad™ and therefore help maintain adequate product on the market. No changes to any other specifications for lot release were necessary or requested under this supplement. The only CMC information contained in the current supplement consists of the proposed specification for the (b) (4) in ProQuad and a rationale for the proposed new specification to be able to (b) (4) lots that could be used in the manufacture of refrigerator-stable and frozen formulations of ProQuad.

b. CBER Lot Release

A review of Product Release Branch records indicates that there are no pending lots or issues that would affect approval of this submission.

c. Facilities Review/Inspection

A facilities inspection was not conducted.

d. Environmental Assessment

There was no Environmental Assessment, Finding of No Significant Impact (FONSI) or categorical exclusion submitted to the file.

4. Nonclinical Pharmacology/Toxicology

No pharmacology or toxicology studies were performed in support of the current supplement.

5. Clinical Pharmacology

See Section 6. Clinical/Statistical for a discussion of clinical immunogenicity assessments and analyses conducted under Protocol 027.

6. Clinical/ Statistical

a. Clinical Program

Protocol 027 (V221-027), "A Phase III Double-Blind, Randomized, Multicenter, Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of Measles, Mumps, Rubella, Varicella (MMRV) Vaccine Made with an Alternative Manufacturing Process (AMP)" was developed with input from the Center of Biologics Evaluation and Research (CBER) to compare the safety, tolerability and immunogenicity of a clinical lot of ProQuad manufactured by the currently licensed process (2006 Process) to a clinical lot of MMRV Vaccine (AMP) manufactured using the AMP and resulting in an (b) (4) .

This double-blind, randomized, multicenter , controlled study enrolled approximately 1400 healthy children 12 to 23 months of age, who were randomized in a 1:1 ratio to either 1 of 2 vaccination groups. Group 1 (≈ N=700) received 2 doses of MMRV vaccine (AMP) and Group 2 (≈ N=700) received 2 doses of ProQuad (2006 Process). The two doses of vaccine were separated by 3 months. All subjects were followed for 42 days for safety Postdose 1 and were also followed for serious adverse events from the time of enrollment into the study through 180 days after receiving the second dose of the study vaccine. Blood samples from all subjects were collected for evaluation of immune responses prior to any vaccinations and at Day 42 following the first ProQuad vaccination.

The Objectives of the study were:

1. To demonstrate that MMRV Vaccine (AMP) induces measles, mumps, rubella, and VZV antibody responses 6 weeks Postdose 1 that are non-inferior to those induced by ProQuad™ (2006 Process).

2. To demonstrate that MMRV Vaccine (AMP) induces acceptable measles, mumps, rubella, and VZV antibody responses 6 weeks Postdose 1.

3. To demonstrate that the rate of fever following the first vaccination with MMRV Vaccine (AMP) is non-inferior to that following the first vaccination of ProQuad (2006 Process).

4. A secondary objective was to assess the overall safety and tolerability of MMRV Vaccine (AMP) when administered to children 12 to 23 months of age.

The primary endpoints of the study evaluated the non-inferiority of immune responses (antibody response and GMTs) for measles, mumps, rubella and varicella antigens six weeks following the first dose and the safety in terms of rates of fever (temperature ≥102.2°F [≥39.0°C]) within the five days following the first vaccination.

The results of the study V221-027 demonstrated that the immunogenicity of each of the vaccine components of MMRV Vaccine (AMP) is acceptable and non-inferior to the immunogenicity of ProQuad (2006 Process). Specifically, MMRV Vaccine (AMP) induces measles, mumps, rubella, and VZV-specific antibody responses (as measured by the response rates and by GMTs of antibody titers) that are similar (non-inferior) to those induced by ProQuad (2006 Process) 6 weeks Postdose1. The study also demonstrated that the rate of fever (temperature ≥102.2°F [≥39.0°C] oral equivalent) in the MMRV Vaccine (AMP) group Days 1 to 5 Postdose 1 is non-inferior to the rate of fever in the ProQuad (2006 Process) group meeting the primary safety hypothesis. The MMRV Vaccine (AMP) group experienced statistically significantly more overall vaccine-related injection-site adverse events than the ProQuad (2006 Process) group; however, the rate of these events are still within the range of the incidences observed in other ProQuad studies.

During the time period when ProQuad is known to be associated with an increased risk of febrile seizures, there was no imbalance between the 2 vaccination groups in the occurrence of seizures. Three vaccine related febrile seizures [1 in the MMRV Vaccine (AMP) group and two in the ProQuad (2006 Process) group] were experienced during the 42-day Postdose 1 period and occurred during Day 6-13 when the rate of febrile seizure has historically been shown to be at its highest. However, over the whole course of the study there were more febrile seizures in the MMRV Vaccine (AMP) group compared with the ProQuad (2006 Process) group. For most of these events, subjects had either a risk factor for febrile seizures (family history) or a documented concurrent febrile illness. In addition, the number of febrile seizures observed in subjects who were administered the MMRV Vaccine (AMP) is consistent with what would be expected for this study population based on estimates from incidence rates in the age group and the length of follow up.

b. Pediatrics

Studies were only done in pediatric population.

c. Other Special Populations

There were no other populations studied.

d. Overall Comparability Assessment

Non-inferiority was shown for the primary immunogenicity and safety endpoints as pre-specified for the clinical study. The study demonstrated that the immune responses for each of the antigenic vaccine components of MMRV Vaccine (AMP) is acceptable and non-inferior to the immunogenicity demonstrated following receipt of ProQuad (2006 Process). The rate of fever in the MMRV Vaccine (AMP) group is non-inferior to the rate of fever in the ProQuad group. Of note, the incidence of fever102.2° F [39.0°C] (oral equivalent) Days 1 to 5 Postdose 1 was lower than expected during the conduct of this study. Overall, the MMRV Vaccine (AMP) group experienced statistically significantly more vaccine related injection-site adverse events than those observed in the ProQuad group. However the rate of these events is within the range observed in other ProQuad studies, and most events were of mild intensity and of short duration.

e. BIMO Inspection

The BIMO member of the review committee proposed clinical sites to be inspected for this application. The selections were based on the number of subjects who enrolled, previous inspectional history, number and types of adverse events, number and types of protocol deviations, and geographic location. The review committee concurred with the proposed sites. The clinical investigator inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The Contract Research Organization (CRO) inspection was conducted in accordance with FDA's CPGM 7348.810, Sponsors, CROs and Monitors.

The inspections also focused on specific questions concerning the study protocol and the comparison of data submitted in the BLA to source documents.

CBER Bioresearch Monitoring (BIMO) issued five high-priority inspections in support of this Biologics Licensing Application (BLA). The inspections did not reveal significant problems that impacted the data submitted in this marketing application.

7. Safety

Based on study V221-027, MMRV Vaccine (AMP) is generally well tolerated, and has an adverse event profile that is comparable to that of ProQuad (2006 Process) vaccine. The rate of fever (temperature ≥ 39.0°C oral equivalent) with MMRV Vaccine (AMP) is similar (non-inferior) to ProQuad (2006 Process) Days 1 to 5 Postdose 1. Although the rate of injection-site adverse events (erythema, pain/tenderness, and swelling) was higher for MMRVVaccine (AMP) compared to ProQuad (2006 Process), the events were mostly

mild in intensity, similar in distribution by size (mostly ≤ 1 inch), and did not result in hospitalization or discontinuation from the study.

8. Advisory Committee Meeting

A Vaccines and Related Biological Products Advisory Committee meeting for discussion of the data in this submission was not held because review of this supplement did not raise concerns which would have benefited from an advisory committee discussion.

9. Other Relevant Regulatory Issues

There were no additional relevant issues.

10. Labeling

No labeling changes were necessary or submitted in this supplement.

11. Recommendations and Risk/ Benefit Assessment

a. Recommended Regulatory Action

The clinical data from Protocol 027 support the proposed change in the manufacturing process for ProQuad. ProQuad manufactured by the Alternative Manufacturing Process with a (b) (4) dose is comparable with ProQuad (2006 Process) at the currently licensed (b) (4) (b) (4) dose and is generally well tolerated and immunogenic when administered to subjects 12 to 23 months of age.

Overall, there are no critical statistical issues in this submission. For subjects 12 to 23 months of age, non-inferiority in immunogenicity of MMRV Vaccine (AMP) compared to ProQuad (2006 Process) was demonstrated for each of the component antigens (Measles, Mumps, Rubella, and VZV) based on the pre-defined non-inferiority criteria. The acceptability of the response rate for the component antigens in MMRV Vaccine (AMP) met the pre-defined criterion. The rate of fever (temperature ≥ 39.0°C oral equivalent) with MMR(AMP) compared to ProQuad (2006 Process) met the pre-defined non-inferiority criterion. Therefore, there are no statistical reasons for not approving MMRV Vaccine (AMP).

There were no BIMO issues with the 5 sites inspected.

Following the review of all submitted supportive data, the Review Committee and I, as Chair, recommend approval of this BLA supplement.

b. Risk/ Benefit Assessment

The safety profile is comparable between the investigational MMRV Vaccine (AMP) and the currently licensed product, ProQuad (2006 Process). No additional concerns regarding the use of the products have been discovered during the conduct of this clinical trial. The results support the use of MMRV Vaccine (AMP) without modification of the current benefit-risk assessment of the licensed product.

c. Recommendation for Postmarketing Risk Management Activities

No REMS were necessary or proposed for this submission

d. Recommendation for Postmarketing Activities

The Review Committee had no new recommendation for post-marketing commitments or post-marketing requirements.