



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: April 20, 2015

From: Dmitriy V. Volokhov, D.V.M., Ph.D., OVRR/DVP/LMD

IND: BLA 125563-0

Product: (b) (4) Vaccine [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus B Conjugate and Recombinant Hepatitis B]

Sponsor: MCM Vaccine Company (Sanofi Pasteur/Merck)

Subject: Serology Assay Review Memo for Poliovirus Antibody Determination by (b) (4)

To: Rana Chattopadhyay, OMPT/CBER/OVRR/DVRPA/CMC1

Through: Steven Rubin, Ph.D., OVRR/DVP/LMD

Cc: Sara Gagneten, Ph.D., OVRR/DVP
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OVERVIEW:

Sanofi Pasteur submitted a Biologics License Application (BLA) for "Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine (DTaP-IPV-Hib- HepB)," referred to as PR5I or (b) (4) Vaccine. The clinical development of this vaccine in the United States was performed under IND 14496, initially submitted on September 20, 2010.

PR5I is a sterile fully liquid preservative-free suspension presented as a single dose in a vial for intramuscular injection. This hexavalent combination vaccine is being co-developed by Sanofi Pasteur and Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. [Merck]. PR5I is manufactured using modified and/or existing bulk intermediates from vaccines licensed in the U.S. by Sanofi Pasteur and Merck.

The target indication for PR5I is for active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by *Haemophilus influenzae* type b (Hib) and infection caused by all known subtypes of hepatitis B virus in infants at 2, 4, and 6 months of age.

This memo covers my review of the (b) (4)) used to quantitate antibodies against polioviruses types 1, 2, and 3 during the Phase 3 clinical studies.

Poliovirus Antibody Determination By (b) (4))

Anti-poliovirus types 1, 2, and 3 titers were measured in the vaccinees by the neutralization assay. Assays were conducted at the Sanofi Pasteur Inc. GCI platform in Swiftwater, PA.

Validation reports, SOP and assay stability reports for this (b) (4) assay were previously reviewed under INDs 14668 (Quadracel vaccine) and 14496 (PR5I vaccine) in support of the data generated by this assay in the Phase 3 studies for both vaccines. The same (b) (4) assay was used to quantify the level of poliovirus type-specific antibodies in serum of the vaccinees received Quadracel, the recently FDA-approved vaccine, under BLA 125525. The (b) (4) assay was reviewed for BLA 125525 by Dr. Malik, and his review memo dated 10-MAR-2015 is available in EDR.


The documents below are relevant to this BLA.

1. Document RED_00073615 Control Performance of Poliovirus (b) (4) from January 2005 through March 2014.

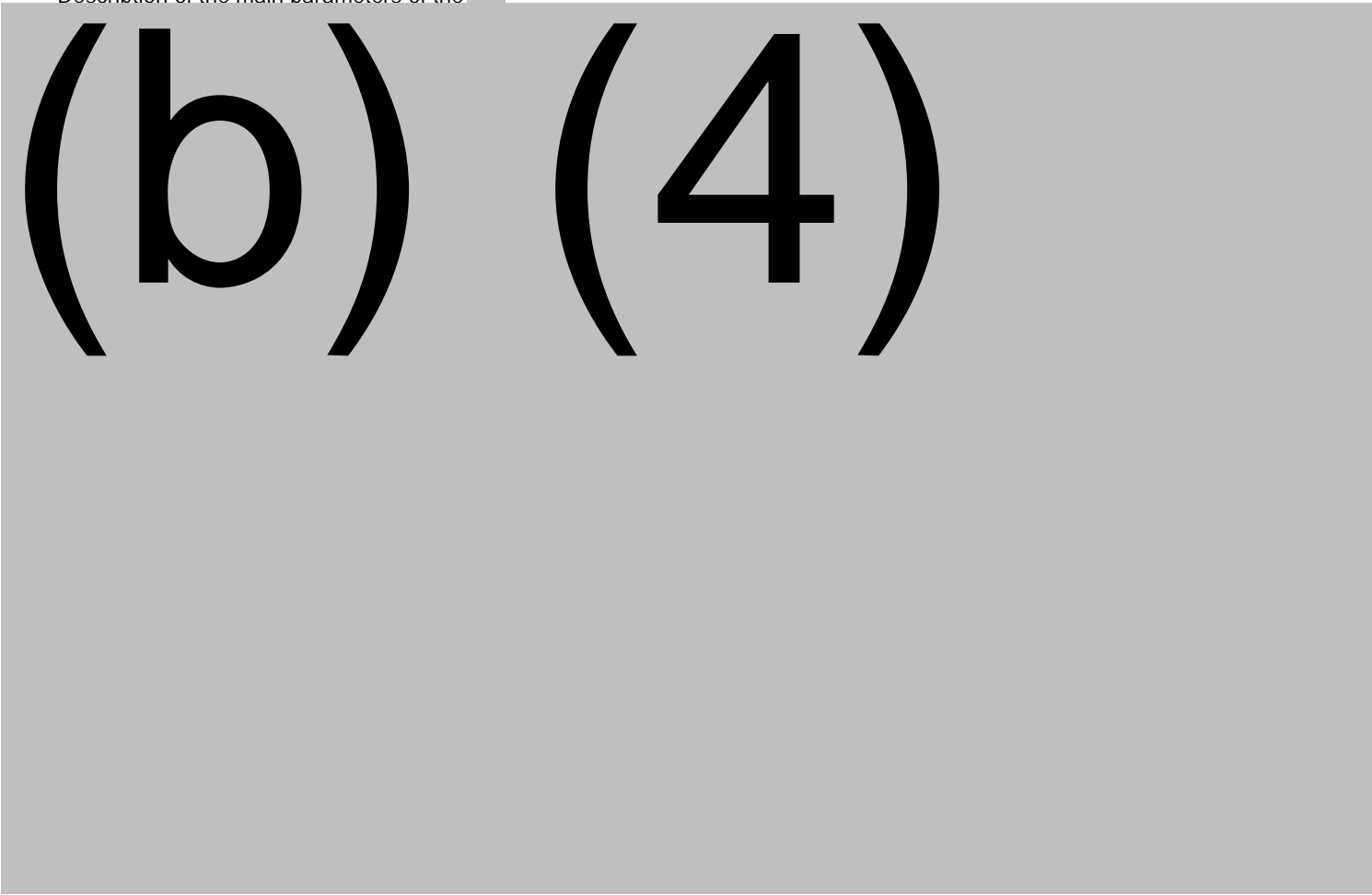
2. Document J001656 Poliovirus Antibody Determination by (b) (4).
3. Document C007956 Validation Report for SWI J001656 [Poliovirus Determination by (b) (4)]
4. Document Q_0236045 Maintenance of the Study Blind during Serological Testing.

The (b) (4) assay and all supporting documents for these assay were previously reviewed under IND 14668 amendments 22 and 24 by Dr. Volokhov, and my review memos are available in EDR.

Document J001656 describes the method used to measure the levels of poliovirus type 1, 2, and 3 neutralizing antibodies, which utilizes (b) (4)



Description of the main parameters of the (b) (4)



(b) (4)

VALIDATION OF THE (b) (4)

The procedure was validated in 2005; the Validation Report SWI J001656 "Poliovirus Determination by (b) (4) was submitted under IND 14668. The validation study was performed in Q1-2 2005 and additional experiments on ruggedness of the assay were performed in Q3-4 2005. The report was written in Q4 2005. The results of this validation demonstrate that the current (b) (4) is precise, accurate, linear, specific, stable, and that the LLOQ of the assay is a titer of (b) (4). This assay is suitable for its intended use to measure level of type-specific neutralizing antibodies to poliovirus in human serum from various stages of clinical trials.

The Assay Parameters That Were Validated

(b) (4)

(b) (4)

LONG-TERM PERFORMANCE FOR THE (b) (4)

The report (submitted Document RED_00073615; under IND 14668) was created to demonstrate the long-term performance of the (b) (4) by analysis of historical results of (b) (4) and positive IQC reference (Internal Quality Control) ratio obtained from the previously validated method. These results were generated as part of clinical and non-clinical testing that began January 2005 (the method was validated in December 2005) and continued through March 2014, a period of time spanning approximately (b) (4) of continuous production. In order to demonstrate the stability of the long-term performance of the Poliovirus (b) (4) trending charts for the serotype-specific (b) (4) positive IQC reference ratio, positive IQC reference rolling average GMT (for information only) and positive IQC titer (for information only) were plotted. Finally, the data provided for the poliovirus (b) (4) serotype-specific (b) (4) IQC reference ratio and IQC rolling GMT and IQC titer are consistent with an assay in control over the period from January 2005 to March 2014.

Summary of Critical Reagents Used for the Poliovirus (b) (4)

(b) (4)

(b) (4)

Reviewer's Note: The (b) (4) performance characteristics and the statistical analysis for the (b) (4) assay were reviewed by Tsai-Lien Lin, OMPT/CBER/OBE/DB/VEB (Statistical Reviewer). Her review memo dated 08-Apr-2015 is available in EDR under IND 14668 amendments 22. The summary of the statistical review is provided below.

1. The original validation performed in 2005 appears to be inadequate by today's standard. It is recommended that the assay be revalidated for future clinical studies.
2. On the basis that the assay has been approved in the past and has been used for many years, stable and consistent performance of the assay may be considered as the basis for acceptable assay performance. The control charts of (b) (4) however, showed that the assay for poliovirus type 3 was not in control from June 2013 to January 2014, affecting a certain portion of the testing for clinical studies V419-005 and V419-006. During this period of time, the (b) (4) for type 3 poliovirus

not only had larger variability, but also shifted upward. With higher (b) (4) the titers generated would be biased low. For type 2, the (b) (4) generally shifted to a lower level during the testing period for the two pivotal studies. Although they still stay within the acceptable range, titers generated with lower (b) (4) would be biased high, and thus could be a potential concern.

3. The impact of the assay performance consistency issues, identified from the control charts, on the study results of the two pivotal studies may be limited for the following reasons:
 - For each study, the primary samples were tested in the same timeframe and GCI assay operators or contract laboratory testing personnel were blinded with respect to study treatment group assignment. If there is bias in the titers generated from the assay, it is likely to be evenly distributed between the treatment groups. Thus, the between-group comparisons (non-inferiority of PR5I versus control or equivalence between lots) are not likely to be substantially affected. All 95% confidence intervals for the between group differences in % subjects with titer $\geq 1:8$ or GMT ratios are well within the acceptable limits in the two pivotal studies.
 - The only primary IPV immunogenicity endpoint that is not evaluated by comparing with another treatment group is the acceptability of IPV response in study V419-005: the percentage of subjects in the PR5I group with anti-IPV titer $\geq 1:8$ must be $> 90\%$. Only type 2 titers may be potentially biased high based on the control chart. However, the response rate is 100% for all 3 types and the GMT for type 2 is very high (1475.40). Since the type 2 virus (b) (4) generally still stayed above the established lower limit, the magnitude of the bias would be small (possibly less than 2-fold by visual examination). It is highly unlikely that the conclusion would change if there were no bias in assay measurement.

Reviewer's Recommendation

The data supporting the performance of the (b) (4) serologic assay used to quantitate antibodies against polioviruses types 1, 2, and 3 during the Phase 3 clinical studies are sufficient and indicate that the assay performs adequately for its intended use.

I recommend the approval of BLA 125563.