



DEPARTMENT OF HEALTH & HUMAN SERVICES

US Food & Drug Administration
Center for Biologics Evaluation & Research
Office of Vaccines Research and Review
Division of Viral Products

MEMORANDUM

Date: April 1, 2024

Sponsor: Merck Sharpe & Dohme LLC

From: Ewan P. Plant, PhD CBER/OVRR/DVP

To: BLA 125814

Through: Zhiping Ye, Laboratory Chief, CBER/OVRR/DVP
Anissa Cheung, CBER/OVRR/DVP
Jerry Weir, CBER/OVRR/DVP

CC: Tatiana ClarodaSilva, CBER/OVRR/ DRMRR/RRB1
Margaret Dayhoff-Brannigan, CBER/OVRR/ DRMRR/RRB1
Hilda Grabczewshi, CBER/OVRR/ DRMRR/RRB1
Diana Oram, CBER/OVRR/DRMRR/RRB1

Subject: **Review of Hemagglutination Inhibition (HI) Assay method and validations:** The HI assay is used to evaluate the immune response of an influenza virus vaccine.

Summary and Recommendation:

The Hemagglutination Inhibition (HI) assay is used by the sponsor to assess the antibody response toward influenza vaccine co-administered with the Pneumococcal 21-valent Conjugate Vaccine (PCV21) vaccine in the Phase 3 clinical study V116-005 in subjects 50 years of age and over. Immune response elicited by the influenza vaccine measured by the HI titer was used to support the hypothesis that coadministration of a seasonal influenza vaccine with the PCV21 vaccine has no impact on hemagglutinin immune response.

The HI assay is performed by the contract organization (b) (4). The standard operating procedures (SOP) is acceptable. The assay is partially revalidated when new viral antigens are included in the updated seasonal influenza vaccine formulations. The HI assay is validated for the four types of influenza antigen recommended for the seasonal quadrivalent vaccines: A/Victoria/2570/2019 (H1N1), A/Darwin/9/2021

(H3N2), B/Austria/1359417/2021 (B Victoria lineage), and B/Phuket/3073/2013 (B Yamagata lineage).

We are not aware of any cross-reacting antibodies that interfere with the assays. The assay is suitable for determining serum antibody titers toward influenza strains included in the 2022-23 Fluzone vaccine used in the coadministration studies.

Submission and Review:

The HI assay is used to measure antibody responses toward influenza antigens. Merck included data from a Phase 3 clinical coadministration study (PCV21 and influenza vaccines) in adults 50 years of age or older in the initial BLA package. The HAI assay is performed by (b) (4) in (b) (4).

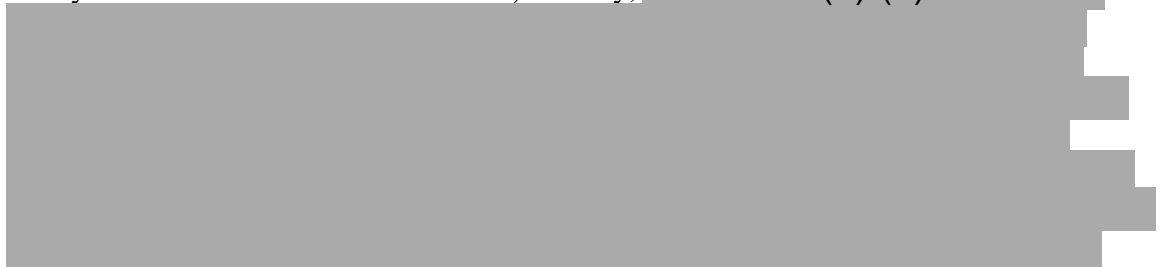
As circulating influenza virus strains evolve, the influenza vaccine formulations will be updated and the protocols will be partially re-validated for the new strains. There were four validation documents with differing acceptance criteria for different virus strains included in the initial BLA. Although the validation results for each virus differ (e.g., the range of the assay), all the data demonstrate that the assay is valid for each strain.

Additional documentation was requested to verify the robustness of the assay. Summaries for the validations are reviewed together for each attribute assessed.

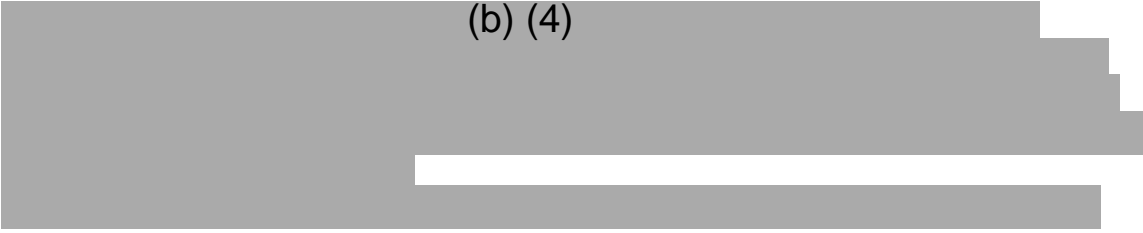
Reviewer comment: Merck included coadministration data of the Phase 3 clinical study V111-005 in the initial BLA package. Non-inferiority testing demonstrated that immune responses after concomitant administration were non-inferior (with a lower confidence interval of (b) (4)) to responses after (b) (4) administration for (b) (4) of the (b) (4) antigens. The result for the (b) (4) antigen was borderline. In a Phase 2 study by Pfizer with ABRYSCO and seasonal influenza vaccine in adults 65 years of age and older, the (b) (4) response also trended lower with concomitant administration. Although the non-inferiority testing criteria are met, it is possible that the immune response toward the influenza antigens is affected by some additional vaccinations in the older adult populations.

Review of Hemagglutination Inhibition Assay Protocol:

The HI assay is performed in many laboratories throughout the world but there are small and sometimes significant variations in the methodology. The assay is described in TSOP.119.00510-rev.g (document 084x88 in section 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies). Briefly, (b) (4)



(b) (4)

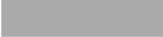


Earlier versions of the  assay (when the company was known as 




Reviewer assessment: This reviewer finds the HI assay protocol suitable for the accurate determination of specific influenza antibody titers.

Review of Hemagglutinin Inhibition Assay Validations:

 assay validation reports were provided for the viruses recommended for the 2022-2023 Northern Hemisphere vaccine season: A/Darwin/9/2021 (H3N2), A/Victoria/2570/2019 IVR-215 (H1N1), for B/Austria/1359417/2021 (Victoria lineage), and B/Phuket/3073/2013 (Yamagata lineage) in section 5.3.1.4 (documents AVAL.119.00406-FDX, AVAL.119.00396-FDX, AVAL.119.00238-13-FDX, and AVAL.119.00238-09-FDX respectively).

Reviewer comment: The validation reports provide data for accuracy, specificity, precision, and linearity as described below. The acceptance criteria are acceptable to this reviewer. Robustness of the assay is not required for validation of new strains but was requested for completeness of the review.



(b) (4)

Reviewer comment: The validation for the Phuket virus was performed in April 2022, and the remaining validations were performed in January and February of 2023. Human sera for the Phuket validation were from (b) (4) employee volunteers. Human sera for the other validations were clinical samples purchased from (b) (4). The antigens were (b) (4) procured from (b) (4), and the reference antiserum were from (b) (4). The strains used for the validation correspond to strains recommended for vaccines by the WHO and FDA VRBPAC committees.

The assay was validated for Precision (repeatability and intermediate precision), Specificity and Limits of Quantification. (b) (4)

. This reviewer finds the data acceptable for all four strains validated.

A summary of the validation results for the four antigens are reproduced in the table below. (b) (4)

(b) (4)

(b) (4)

Reviewer comment: Based on the data submitted, this reviewer agrees that the HI assay is suitable for assessing the immune response after influenza vaccination in clinical study V116-005. The robustness of the assay is not included in this file and a full validation report for the HI assay is requested to ensure the information is easily accessible.

Partial validation of the (b) (4) Hemagglutination Inhibition assay was provided to support the assessment of each influenza antigens used in the 2022-23 season, but a full assay validation report that demonstrates the robustness of the HI assay should be added to the file.

Reviewer comment: The validation report AVAL.119.007-FDX was added to the file on March 29, 2024. Robustness was evaluated by assessing the impact of (b) (4), and having different operators (b) (4). All combinations had effects on the measured titers, but these results were within the set margin of (b) (4). The assays were performed using H1N1 (A/Caledonia/20/1999), H3N2 (A/New York/55/2004), and influenza B/Jiangsu/10/2003 viruses. The HI results were within the set margin of (b) (4).

Reviewer assessment: The validation of the HI assay is acceptable.

Reviewer Recommendation: The HI assay is suitable for determining serum antibody titers toward influenza strains included in the vaccines used in the coadministration study V116-005.