Food and Drug Administration
Center for Biologics Evaluation and Research

# SUMMARY MINUTES
# 155th VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

## March 6 – 7, 2019

**Committee Members**
Hana El Sahly, M.D., Acting Chair
David Greenberg, M.D. + (IR)
Holly Janes, Ph.D.
Michael Kurilla, M.D., Ph.D.
Myron Levine, M.D., D.T.P.H., F.A.A.P.
H. Cody Meissner, M.D.
Arnold Monto, M.D.
Paul Offit, M.D.
Andrea Shane, M.D., M.P.H., M.Sc.
Paul Spearman, M.D. +
Geeta K. Swamy, M.D.
Sheldon Toubman, J.D. (CR)
Melinda Wharton, M.D., M.P.H.

**Industry Representative**
Hendrik Nolte, M.D., Ph.D.

**Consumer Representative**
Sheldon Toubman, J.D.

**Designated Federal Officer (DFO)**
CAPT Serina A. Hunter-Thomas, M.S.A., R.N.

**Committee Management Specialist(s)**
Monique Hill, M.H.A.
Joanne Lipkind, M.S.
Natalie Mitchell-Funderburk

**Temporary Voting Members**
Tammy Beckham, D.V.M., Ph.D.
Jack Bennink, Ph.D.
Kathryn Edwards, M.D.
William B. Messer, M.D., Ph.D.
COL Andrew Wiesen, M.D., M.P.H.

**Temporary Non-Voting Members**
Jacqueline Katz, Ph.D.
Jorge Munoz-Jordan, Ph.D.

**Speakers/Guest Speakers**
Anna Durbin, M.D.
CAPT Lisa Grohskopf, M.D., M.P.H.
Jacqueline Katz, Ph.D.
Gabriela Paz-Bailey, M.D., M.Sc., Ph.D.
Leslie Sands, M.S., RAC
CDR Mark Scheckelhoff, Ph.D., M.P.H.

**FDA Speakers**
Anissa Cheung, M.Sc.
Hana Golding, Ph.D.
Manju Joshi, Ph.D.
Ralph LeBlanc, M.D., Ph.D.
Kirk Prutzman, Ph.D.
Carol Weiss, M.D., Ph.D.
Jerry Weir, Ph.D.
Carolyn Wilson, Ph.D.

**FDA Participants**
Marion Gruber, Ph.D.
Philip Krause, M.D.
Konstantin Chumakov, Ph.D.

+ Not in attendance

These summary minutes for the March 6 - 7, 2019 Meeting of the Vaccines and Related Biological Products Advisory Committee were approved on March 29, 2019.

I certify that I participated in the March 6 - 7, 2019 Meeting of the Vaccines and Related Biological Products Advisory Committee and that these minutes accurately reflect what transpired.

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| /s/ | /s/ |
| Serina A. Hunter-Thomas | Hana El Sahly, M.D. |
| Designated Federal Officer | Acting Chair |

On March 6, 2019 at 8:05 a.m. Eastern Standard Time (EST), Dr. Hana El Sahly, Acting VRBPAC Chair, called to order the 155th Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss Topic I "Strain Selection for the Influenza Virus Vaccines for the 2019 – 2020 Influenza Season." The Acting Chair invited everyone around the table to introduce themselves, followed by the DFO's administrative remarks and reading of the Conflict of Interest (COI) statement into the public record. There was one waiver issued for conflicts of interest for this meeting. The waiver was for Dr. William B. Messer for Topic III. The meeting proceeded with Ms. Anissa Cheung who gave the FDA introductory presentation titled "Influenza Virus Vaccine 2019-2020 Strain Selection," followed by CAPT Lisa Grohskopf who gave a presentation titled "U.S. Influenza Surveillance and Interim Vaccine Effectiveness Estimates, 2018-19 Season," followed by a presentation from Dr. Jacqueline Katz titled "Global Surveillance and Virus Characterization." The next presentation was from CDR Mark Scheckelhoff, whose presentation was titled "DoD Influenza Surveillance and Mid-Season Vaccine Effectiveness." CDR Schecklehoff's presentation was followed by Dr. Manju Joshi who presented on "Candidate Vaccine Viruses and Potency Reagents for the 2019-20 Northern Hemisphere Influenza Season." After Dr. Joshi's presentation, the next speaker, Ms. Leslie Sands from GlaxoSmithKline provided the industry perspective and her presentation was titled "Industry Perspective for 2019-20 Northern Hemisphere Influenza Vaccine Supply." After Ms. Sands' presentation, a 45 minute Open Public Hearing session commenced. Dr. Sam Lee from Sanofi Pasteur provided preliminary comments and opted to withdraw from reading his written comment. The Committee then broke for lunch, and then reconvened for a brief "Thank you" and plaque presentation to Dr. Kathryn Edwards, who is the off-going VRBPAC Chair. Afterward, the committee proceeded with discussion followed by a vote for Topic I. There were three voting questions presented to the committee for Topic I:

1. For the composition of the trivalent 2019-2020 influenza virus vaccine in the U.S., does the committee recommend:
    A. Inclusion of an A/Brisbane/02/2018 (H1N1)pdm09-like virus
    B. Inclusion of a B/Colorado/06/2017-like virus (B/Victoria lineage)
2. For quadrivalent 2019-2020 influenza vaccines in the U.S., does the committee recommend:
    A. Inclusion of a B/Phuket/3073/2013-like virus (B/Yamagata lineage) as the 2nd influenza B strain in the vaccine

For Question 1A the committee voted as follows: 14 Yes, 0 No, 0 Abstain
For Question 1B the committee voted as follows: 14 Yes, 0 No, 0 Abstain
For Question 2A the committee voted as follows: 14 Yes, 0 No, 0 Abstain

Following the Committee vote for Topic I, the meeting proceeded to Topic II, Presentation of the Laboratory of Retroviruses (LR) and the Laboratory of Immunoregulation (LIR) Division of Viral Products (DVP) of the Office of Vaccines Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA).

After the COI statement was read by the DFO, the presentations began starting with Dr. Jerry Weir who provided an overview of Division of Viral Products and the Office of Vaccines Research and Review, followed by an overview of the Laboratory of Immunoregulation by Dr. Carol Weis, followed by an overview of the Laboratory of Retroviruses by Dr. Hana Golding, followed by Dr. Carolyn Wilson, who provided an overview of the Research/Site Visit Process in CBER. We then proceeded with Topic II Open Public Hearing (OPH) session. There were no speakers present to comment during this OPH portion of the meeting.

Following the open portion of the meeting on March 6, 2019, the Committee then met in closed session.

The meeting was then adjourned at on March 6, 2019.

March 7, 2019 – Day 2

On March 7, 2019 at 8:35 a.m. Eastern Standard Time (EST), Dr. Hana El Sahly, Acting VRBPAC Chair, called to order the 155th Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss Topic III: Discuss and make recommendations on the safety and effectiveness of Dengue Tetravalent Vaccine (Live, Attenuated)[Dengvaxia] manufactured by Sanofi Pasteur.

The Acting Chair invited everyone around the table to introduce themselves, followed by the DFO's administrative remarks and reading of the Conflict of Interest (COI) statement into the public record. There was one waiver issued for conflicts of interest for this meeting. The waiver was for Dr. William B. Messer for Topic III.

The meeting proceeded with the first speaker, Dr. Kirk Prutzman from FDA, who provided an introduction and presentation of the questions for the committee. Dr. Prutzman's presentation was titled "Dengue Tetravalent Vaccine, Live Dengvaxia – Applicant: Sanofi Pasteur." Dr. Prutzman's presentation was followed by Dr. Anna Durbin from Johns Hopkins Bloomberg School of Public Health, whose presentation was titled "Clinical Consideration of Dengue." The next presenter was Dr. Gabriela Paz-Bailey from CDC-Puerto Rico, whose presentation was titled "Epidemiology of Dengue." Following Dr. Paz-Bailey's presentation, the committee took a 15 minute break which was then followed by the sponsor's combined presentation titled "Dengvaxia for Prevention of Dengue Disease." Following Sanofi Pasteur's presentation, the committee took a break for lunch. Following the lunch break, the meeting proceeded with the Open Public Hearing session. The following individuals provided comments for Topic III portion of this meeting: Dr. Fernando Ysern, Dr. Jose Luis Arredondo Garcia, Dr. Natalia Gomez and Dr. Scott Halstead. Following the open public hearing portion of the meeting, Dr. Ralph LeBlanc from FDA proceeded with his presentation titled "Dengvaxia – Dengue Tetravalent Vaccine, Live – Review of Efficacy and Safety." Following Dr. LeBlanc's presentation, the committee proceeded with the discussion portion of the meeting.

The Committee discussed the safety and efficacy data derived from the clinical disease endpoint efficacy studies conducted in subjects 2 – 16 years of age in the Asian Pacific Region and Latin America including Puerto Rico. The Committee was reminded to focus its discussion on subjects 9-16 years of age as this age range is included in the broader age range (9 through 45 years of age) for which the applicant is seeking an indication. In its deliberations the Committee considered the epidemiology of dengue disease in Puerto Rico. Committee members noted that data support the efficacy of Dengvaxia in pediatric subjects with prior exposure to dengue virus and living in endemic areas. Committee members expressed concern about the safety signal identified in the efficacy studies, namely an increased risk of hospitalization and severe dengue in individuals with no prior exposure to dengue who were vaccinated with Dengvaxia and subsequently infected with dengue, and considered ability of establishing laboratory-confirmed previous dengue infection to mitigate this concern, if the vaccine were to be licensed and recommended for use. Concern was expressed that currently available serological tests to establish previous dengue infection may lead to false positive results because of cross-reactivity with other flaviviruses. Committee members also noted the operational/logistical and infrastructure concerns of serotesting prior to vaccination. There was broad recognition of the need for an FDA cleared rapid diagnostic assay to establish prior exposure to dengue in individuals to be vaccinated.

Committee members also expressed concern about inferring vaccine efficacy in the adult population based on antibody titers in the pediatric efficacy trial population because available data were derived from small immunogenicity studies that were conducted in adults living in countries with high dengue endemicity, i.e., Vietnam and India. There was concern that these data may not reflect immune responses in adults living in Puerto Rico, and that in the absence of immunogenicity data derived from adults living in Puerto Rico or regions with dengue epidemiology similar to Puerto Rico, it was difficult to infer efficacy from the pediatric to the adult population.

Following the discussion portion of the meeting, the committee proceeded with a review of the voting questions and then on to vote. Initially there were two voting questions:

1. Are the available data adequate to support the effectiveness of Dengvaxia for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in persons 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?

   Please vote Yes or No.

2. Are the available data adequate to support the safety of Dengvaxia when administered to persons 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?

   Please vote Yes or No.

For Question 1 the committee voted as follows: 6 Yes, 7 No, 1 Abstain
For Question 2 the committee voted as follows: 7 Yes, 7 No, 0 Abstain

Following the first two questions, the committee was presented with two additional questions:

3. Are the available data adequate to support the effectiveness of Dengvaxia for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in persons 9 to <17 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?

   Please vote Yes or No.

4. Are the available data adequate to support the safety of Dengvaxia when administered to persons 9 through <17 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?

   Please vote Yes or No.

For Question 3 the committee voted as follows: 13 Yes, 1 No, 0 Abstain
For Question 4 the committee voted as follows: 10 Yes, 4 No, 0 Abstain

Additional information and details may be obtained from the transcript and the recording of the webcast of the meeting that may be viewed at:

March 6, 2019
Part 1: https://collaboration.fda.gov/p6b0gsxyemif/
Part 2: https://collaboration.fda.gov/p4rbq6un5814/
Part 3: https://collaboration.fda.gov/p7ii28rbghvr/

March 7, 2019
Part 1: https://collaboration.fda.gov/p6s6aitlhdra/
Part 2: https://collaboration.fda.gov/pnt4exlj1nci/
Part 3: https://collaboration.fda.gov/pahhotrewkk5/