

Food and Drug Administration
Center for Biologics Evaluation and Review

SUMMARY MINUTES
VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

November 14-15, 2012
FDA White Oak Campus, Bldg. 31, Great Room
Silver Spring, MD

Committee Members

Dr. Robert Daum, Chair
Dr. Ambrose Cheung
Dr. Anna Durbin +
Dr. Gregory Gray
Dr. Gary Schoolnik +
Dr. Carol Tacket
Dr. Gillian Air
Dr. Edgar Marcuse
Dr. Kent Kester +
Dr. Michael Hudgens
Dr. Pedro Piedra
Dr. Nathanael Brady *

Temporary Voting Members

Dr. Pamela McInnes
Dr. Melinda Wharton
Dr. Jack Bennink
Dr. Trudy Murphy ##
Dr. Roland Levandowski # +

Industry Representative

Dr. Felip Dubovsky **

Designated Federal Official

Donald Jehn, M.S.

FDA Participants

Dr. Marion Gruber
Dr. Jerry Weir
Dr. Wellington Sun
Dr. Carmen Collazo-Custodio
Dr. Andrea James
Dr. Hana Golding
Dr. Alexandra Worobec
Dr. Lorie Smith
Dr. Marion Major
Dr. Jesse Goodman

Speakers

Ms. Donna Boyce (GSK)
Dr. Bruce Innis (GSK)
Dr. Felix Arellano (GSK)
Dr. Joseph Bresee (CDC)
Dr. Robin Robinson (HHS)
Dr. J. Tyler (Dynavax)
Dr. Robert Janssen (Dynavax)
Dr. Gregory Poland
Dr. William Schaffner
Dr. Stanley Plotkin +

Committee Management Specialist

Denise Royster

* Consumer Representative
** Alternate Industry Representative
+ Did not attend

Topic 1 only
Topic 2 only

These summary minutes for the November 14-15, 2012 Meeting of the Vaccines and Related Biological Products Advisory Committee were approved on December 18, 2012.

I certify that I participated in the November 14-15, 2012 Meeting of the Vaccines and Related Biological Products Advisory Committee and that these minutes accurately reflect what transpired.

///original signed///
Donald Jehn, M.S.
Designated Federal Official

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Robert Daum, M.D.
Chair

The Chair, Dr. Robert Daum, called the Meeting of the Vaccines and Related Biological Products Advisory Committee to order at 8:30 a.m. EST on November 14, 2012. Following administrative remarks and reading of the conflict of interest statement, Topic I, the Safety and Immunogenicity of an Influenza A (H5N1) Virus Monovalent Vaccine Manufactured by GlaxoSmithKline began. Topic I was introduced by Dr. Jesse Goodman, Chief Scientist and Deputy Commissioner for Science and Public Health, FDA. This introduction was followed by speakers from the Office of Vaccines Research and Review (FDA), BARDA (HHS) and CDC. The sponsor GSK then gave their presentation, followed by a presentation and concluding remarks from FDA. There were no Open Public Hearing remarks. The questions were then presented to the Committee for discussion and voting. The meeting adjourned at 4:00 p.m.

On November 15, 2012 at 8:30 a.m. EST, the Chair called Day 2 of the Vaccines and Related Biological Products Advisory Committee to order. Following administrative remarks and reading of the conflict of interest statement, Topic II, the Safety and Efficacy of a Hepatitis B Vaccine manufactured by Dynavax began. An introduction was conducted by FDA, followed by the sponsor presentations. The FDA then concluded their presentations. An Open Public Hearing was called and Ms. Maureen Kamischke of the Hepatitis B Foundation spoke to the Committee. The questions were then presented to the Committee for discussion and voting. The meeting was adjourned at 2:00 p.m.

Following is a summary of the discussion. Additional information and specific details may be obtained for the transcript and the webcast of the meeting. The transcript may be viewed on the World Wide Web at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm288695.htm>.

Open Session

The committee was briefed on the expected conditions for distribution of the Q-Pan H5N1 vaccine in the event of an influenza H5N1 pandemic, FDA's accelerated approval regulations, and the safety and effectiveness data that have been submitted to the FDA in support of licensure of the Q-Pan H5N1 vaccine. GSK developed the Q-Pan H5N1 vaccine to fulfill a contract with BARDA. The Q-Pan H5N1 vaccine will be owned by the US Government, which will control its distribution and use. GSK is seeking licensure of the Q-Pan H5N1 vaccine under FDA's accelerated approval regulations, based, in part, on immunogenicity data on a surrogate endpoint that is accepted by FDA as reasonably likely to predict clinical benefit. Under these regulations, GSK would be required to further verify and describe the clinical benefit of the Q-Pan H5N1 vaccine post-licensure.

The Committee was asked the following questions:

1. Do the immunogenicity data support licensure of the Q-Pan H5N1 vaccine for use in adults at increased risk of exposure or during a pandemic?

Please vote yes or no. (The Committee voted a unanimous 14 Yes, 0 Abstentia, and 0 No.)

2. Do the safety data support licensure of the Q-Pan H5N1 vaccine for use in adults at increased risk of exposure or during a pandemic?

Please vote yes or no. (The Committee voted a unanimous 14 Yes, 0 Abstentia, and 0 No.)

The Committee was then asked to please discuss the following two approaches to confirm the effectiveness of Q-Pan H5N1 for "traditional" approval.

1. To confirm the clinical benefit of Q-Pan H5N1 with efficacy data generated with a US-licensed seasonal influenza virus vaccine made according to the same manufacturing process.
2. To confirm the clinical benefit of Q-Pan H5N1 by conducting an effectiveness study (or studies) during an H5N1 influenza virus pandemic.

The Committee expressed different views on the non-voting topic of how the clinical benefit of Q-Pan H5N1 should be confirmed as required under the accelerated approval regulations. Some committee members stated that data derived from a clinical endpoint

efficacy study of a US licensed seasonal influenza vaccine made according to the same manufacturing process is a reasonable and pragmatic approach to confirm the clinical benefit of Q-Pan H5N1. These members noted that it is not reasonable to require GSK to confirm the clinical benefit of Q-Pan H5N1 during a pandemic, and that fulfilling such a requirement is not feasible. Their rationale was based on a number of considerations, including the limitation that results of effectiveness studies conducted during a pandemic would not be available until the pandemic is over, the inability of the current government surveillance system to measure product-specific effectiveness, and GSK's lack of control over vaccine distribution and usage during a pandemic. Other committee members expressed the view that clinical benefit of Q-Pan H5N1 should be confirmed during a pandemic because of uncertainties regarding the relevance of the efficacy of an unadjuvanted seasonal influenza vaccine to clinical benefit of an adjuvanted influenza A H5N1 vaccine. These members questioned the comparability of influenza A H5 subtypes to seasonal vaccine strains in terms of pathogenesis and immunity. Some members discussed that an acceptable approach would be to require GSK to confirm the clinical benefit of Q-Pan H5N1 with clinical endpoint efficacy data accrued for a seasonal unadjuvanted influenza vaccine made by the same process, and to have GSK collaborate with the government to evaluate effectiveness should a pandemic occur.

After opening administrative remarks on November 15, 2012, the Committee was briefed on Topic II, the Safety and Efficacy of a Hepatitis B Vaccine (HEPLISAV) manufactured by Dynavax. The topic was introduced by FDA, followed by presentations by the sponsor and FDA briefing the Committee on the safety and effectiveness data that have been submitted to the FDA in support of licensure of HEPLISAV.

The Committee was asked the following questions:

1. Are the immunogenicity data adequate to support the effectiveness of HEPLISAV for the prevention of hepatitis B virus infection in adults 18 through 70 years of age?

Please vote Yes or No. (The Committee voted 13 Yes, 0 Absentia, and 1 No.)

2. Are the available data adequate to support the safety of HEPLISAV when administered to adults 18 through 70 years of age?

Please vote Yes or No. (The Committee voted 5 Yes, 1 Absentia, and 8 No.)

- If yes, is the proposed pharmacovigilance plan adequate to further evaluate the safety of HEPLISAV post-licensure?
- If no, please discuss what additional studies (pre- & post-licensure) are needed to further evaluate the safety of HEPLISAV.

The majority of the panel voted that the immunogenicity data derived from studies with HEPLISAV support the effectiveness of HEPLISAV for the proposed indication. However, the majority of the committee members considered the pre-licensure safety database inadequate to support the safety of HEPLISAV for use in adults 18-70 years of

age. Committee members stated that there were insufficient numbers of subjects studied to detect relatively infrequently occurring adverse events, especially considering that the adjuvant contained in HEPLISAV is not contained in any other US-licensed vaccine. Some committee members expressed concerns that the available safety data suggested a potential association of thyroid diseases and immune mediated diseases with the vaccine. Other members expressed concerns that the demographic distribution of subjects in the pre-licensure clinical studies did not reflect the demographics of the US population for which the vaccine is intended. Some suggested that Dynavax consider clinical development of HEPLISAV for use in a subpopulation at increased risk for hepatitis B infection and decreased responsiveness to vaccination with currently available vaccines, for whom there may be a greater tolerance of potential vaccine-associated risks. These members noted that usage potentially could be broadened once additional clinical experience is accrued with the vaccine. Committee members stated that the safety database should be increased prior to licensure for the proposed indication and usage, and that study populations should be more ethnically diverse, to reflect the US population. Some committee members recommended evaluation of concomitant administration of HEPLISAV and other relevant vaccines prior to licensure.