Food and Drug Administration
Center for Biologics Evaluation and Research
SUMMARY MINUTES
VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE
Meeting # 104: November 16 - 17, 2005
Holiday Inn Select, Bethesda, MD

Committee Members
Dr. Gary D. Overturf, Chair
Dr. Walter Royal III
Dr. Ruth A. Karron
Dr. David Markovitz
Dr. Monica M. Farley
Dr. Philip S. LaRussa
Dr. Steven Self
Dr. Bonnie M. Word
Ms. Cindy Lyn Province, R.N., M.S.N. *

FDA Participants
Dr. Philip Krause
Dr. Andrew Lewis
Dr. Arifa Khan
Dr. Keith Peden
Dr. Douglas Pratt
Dr. Marion Gruber

Acting Industry Representative
Dr. Seth Hetherington

Consultants
Dr. Philip Minor **
Dr. James Cook **
Dr. Lisa Jackson ***
Dr. Steven Piantadosi ***
Dr. Mark Steinhoff ***
Dr. Jeffrey Weiser ***
Dr. Melinda Wharton ***
Dr. Pamela McGuiness
Dr. Robin Robinson

Guest Speakers
Dr. Rino Rappuoli **
Mr. Jeroen Medema **
Dr. Sandra Steiner ***
Dr. Matthew Moore ***
Dr. Jan Poolman ***
Dr. George Siber ***
Dr. Louis Fries ***

Executive Secretary
Christine Walsh, R.N.

Committee Management Specialist
Denise Royster

These summary minutes for the November 16 - 17, 2005 Meeting of the Vaccines and Related Biological products Advisory Committee were approved on _____.

I certify that I participated in the November 16 - 17, 2005 Meeting of the Vaccines and Related Biological Products Advisory Committee and that these minutes accurately reflect what transpired.

_____
Christine Walsh, R.N.
Executive Secretary

_____
Gary D. Overturf, M.D.
Chair

*Consumer Representative **Attended November 16 only ***Attended November 17 only

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) met on November 16 – 17, 2005 at the Holiday Inn Select, 8120 Wisconsin Ave., Bethesda, MD. In open session on November 16, 2005, the committee heard presentations and held discussions on the use of Madin-Darby canine kidney (MDCK) cells for manufacture of Inactivated Influenza Virus Vaccines. In open session on November 17, 2005, the committee heard presentations and held discussions on developing new pneumococcal vaccines for U.S. licensure for adults.

Following is a summary of the discussion. Additional information and specific details may be obtained from the transcript of the meeting. The transcript may be viewed on the World Wide Web at:
http://www.fda.gov/ohrms/dockets/ac/cber05.html#VaccinesandRelatedBiological.

Proceedings were adjourned for the day at approximately 4:48 p.m. EST on November 16, 2005 and approximately 4:45 p.m. on November 17, 2005.

Open Session

The Vaccines and Related Biological Products Advisory Committee meeting was called to order by the Chair, Dr. Gary D. Overturf, at 8:40 a.m. on November 16, 2005. Dr. Philip Krause, FDA, opened the meetings presentations with an introduction and overview to the day's topic: use of MDCK cells for manufacture of inactivated influenza virus vaccines. In his presentation, Dr. Krause addressed the committee on the recent history of OVRR thinking regarding neoplastic cell substrates and presented a summary of scientific concerns on the use of neoplastic cell substrates, and an outline of the plan for the meeting. Dr. Krause also presented the committee with goals for the meeting, which included discussion points for the afternoon panel discussion. Dr. Andrew Lewis, FDA, followed Dr. Krause with a review of regulatory concerns associated with tumorigenic cell substrates, a brief review of tumorigenicity and tumorigenicity testing, as well as a review of mechanisms of neoplastic development and their implications for neoplastic cell substrate evaluation. Following the morning break, Dr. Arifa Khan, FDA, and Dr. Keith Peden, FDA presented talks on adventitious agent issues associated with neoplastic cell substrates and the risks posed by residual neoplastic cell substrate DNA respectively. In her presentation, Dr. Khan spoke to the committee regarding safety concerns and challenges for adventitious agent testing in novel cell substrates, especially tumorigenic cells, described FDA experience with tumorigenic cell substrates, and pointed out adventitious agent testing recommendations for novel and tumorigenic cell substrates including MDCK cells. Dr. Keith Peden, FDA, completed the morning with a presentation that included an overview of the history of cell substrate DNA in biological products, perceived safety issues associated with DNA, and extrapolations from data to assist in the regulatory process. The afternoon session began with an open public hearing. No public comment was offered. Dr. Rino Rappuoli, Chiron Corporation addressed the panel regarding the company's interest in the use of MDCK cells for manufacture of virus vaccines. Mr. Jeroen Medema, Solvay Pharmaceuticals Inc., ended the day's presentations to the panel by providing a background summary on Solvay's

MDCK project and concluding that Solvay will pursue licensing worldwide, including the U.S. Prior to adjourning, the committee held a discussion relating to the presentations and addressed the goals for the meeting in the form of the discussion points presented by Dr. Krause. During the discussion of the issues posed by OVRR, the committee generally agreed that the testing algorithm that OVRR has developed to evaluate highly tumorigenic cell substrates for vaccine manufacture was appropriate and addressed most of the safety issues posed by these types of cell substrates. Concern was expressed by the majority of the Committee over the difficulty of assessing possible oncogenic activity associated with the components of neoplastic cell substrates. The Committee suggested that one way to evaluate possible oncogenic activity in lysates from these types of cells might be to evaluate, in controlled assays, large numbers of animals and follow them over their lifespan. The Committee also noted that the FDA had set high standards for evaluating neoplastic cell substrates that were highly tumorigenic and that the manufacturers were meeting these standards. The Committee members were in general agreement that the MDCK cells could be used for inactivated, subunit, influenza vaccine but needed further discussions for other situations. During the closing comments, the Committee Chairman recommended that the dialogue OVRR had initiated with the Committee in 1998 be continued as the evaluation and application of these types of cell substrates to the manufacture of influenza vaccine progressed in the coming months.

Day 2 of the meeting began with a closed session. The Chair called the open session portion of the meeting to order at 10:18 a.m. Topic for the session was developing new pneumococcal vaccines in adults for U.S. licensure. Dr. Douglas Pratt, FDA, opened the morning's presentation with an overview that included regulatory background of PNEUMOVAX 23, clinical endpoint efficacy/effectiveness study scenarios, and immunologic endpoint and regulatory pathways. Dr. Marion Gruber, FDA, followed Dr. Pratt with a brief presentation listing the discussion points for the day's agenda. Dr. Sandra Romero-Steiner, CDC, addressed the panel on functional antibody activity as measured by opsonophagocytosis, followed by Dr. Matthew R. Moore, CDC, presenting on the epidemiology of Invasive Pneumococcal disease in adults. The afternoon began with an Open Public Hearing. No public comment was offered. The afternoon session was a series of presentations from manufacturers regarding interest in development of a pneumococcal vaccine for adults. Sponsor presentations included GlaxoSmithKline Inc., Wyeth, and ID Biomedical Corporation. Dr. Marion Gruber, FDA, re-presented the discussion points for the panel prior to the afternoon’s discussion. The committee discussed proposals and pathways for licensure of pneumococcal vaccine candidates indicated for the prevention of pneumococcal disease in the adult population. The majority of the committee members expressed concern that non-inferiority studies comparing a new pneumococcal conjugate vaccine with 23-valent polysaccharide vaccine for the common serotypes based on opsonophagocytic antibody (OPA) titer as a surrogate marker may not be sufficient for inferring efficacy against pneumococcal disease for the new product. It was noted that assays measuring OPA are not sufficiently standardized and that OPA, being a laboratory measure, has not been validated as a surrogate for clinical outcome. There was also concern about how to assess benefit of a new pneumococcal conjugate vaccine comprised of fewer serotypes than are covered by the

23-valent polysaccharide vaccine using non-inferiority studies. Committee members acknowledged the difficulty and complexity of performing clinical endpoint efficacy studies using prevention of invasive pneumococcal disease (IPD) as an endpoint. However, the majority of the committee members favored a clinical endpoint efficacy study to support the licensure of a pneumococcal conjugate vaccine to prevent pneumococcal disease in the adults. To make clinical trials more feasible, it was suggested to consider alternatives to standard clinical trial designs, to perform studies in populations where use of pneumoccocal polysaccharide vaccine is not standard of care, as well as to conduct clinical trails at the older end of the spectrum of previously vaccinated persons. Evaluation of non-bacteremic pneumococcal pneumonia as a clinical outcome was also suggested, while noting the need for diagnostic methods specific for pneumococcus. Some committee members suggested that consideration be given to studying new pneumococcal conjugates vaccines in conjunction with current standard of care in order to evaluate duration of protection, induction of hypo-responsiveness, etc. Notably, some committee members felt that non-inferiority immune response studies using OPA as surrogate marker to be sufficient to infer efficacy for new pneumococcal conjugate vaccine against invasive disease in the adult population. It was suggested that accelerated approval could be granted for pneumococcal conjugate vaccines using an immune parameter as an outcome that is reasonably likely to predict clinical benefit combined with post-marketing clinical studies to confirm clinical benefit of the vaccine. The need for Phase IV studies to address questions such as serotype replacement was stressed. For pneumococcal vaccines consisting of noncapsular antigens, the committee unanimously recommended clinical endpoint efficacy studies to support licensure of these products.

The meeting was adjourned by the Chair at approximately 4:45 p.m.