Food and Drug Administration
Center for Biologics Evaluation and Research

SUMMARY MINUTES
VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

Meeting # 88 November 28-29, 2001
Holiday Inn, Bethesda
Bethesda, Maryland

Members Present
Dr. Robert Daum, Chair
Dr. Michael Decker
Dr. Walter Faggett
Ms. Barbara Loe Fisher
Dr. Judith Goldberg
Dr. Diane Griffin
Dr. Sam Katz
Dr. Steve Kohl
Dr. Kwang Sik Kim
Dr. Peter Palese
Dr. Dixie Snider
Dr. David Stephens (Nov. 28 only)

Members Absent
Dr. Pamela Diaz
Dr. Audrey Manley
Dr. Julie Parsonnet
Dr. Rich Whitley

Invited Participants
Dr. Juan Felix
Dr. Thomas Fleming
Dr. Ralph Freedman
Dr. Michael Greene
Dr. Pamela McInnes
Dr. Martin Myers
Dr. Dennis O'Connor
Dr. Sonia Pagliusi
Dr. William Reeves
Dr. Ellen Sheets
Dr. Elizabeth Unger
Dr. Edward Wilkinson

Executive Secretary
Ms. Nancy Cherry

These summary minutes for the November 28-29, 2001 meeting of the Vaccines and Related Biological Products Advisory Committee were approved on _____ .

I certify that I attended the November 28-29, 2001 meeting of the Vaccines and Related Biological Products Advisory Committee and that these minutes accurately reflect what transpired.

_____
Nancy Cherry
Executive Secretary

_____
Robert S. Daum, M.D.
Chair

The 88th meeting of the Vaccines and Related Biological Products Advisory Committee was called to order in closed session at 8:30 AM on Thursday, November 28, 2001 by the Chair, Dr. Robert Daum. The first open session, which started at 1:54 PM on Thursday, spanned two days and addressed a single topic: Efficacy trial endpoints for vaccines for the prevention of Human Papilloma Virus (HPV). Open and closed sessions pertaining to review of CBER laboratories were also held.

The Conflict of Interest statement was read. Based on the agenda and on the financial interests reported by meeting participants, the members and consultants may be granted full, limited or restricted waivers, appearance documents permitting full participation, or the opportunity to recuse themselves from the discussions. The following chart summarizes the actions taken for the open session on HPV clinical trials.

SGE	**Action**
Palese	Full Waiver under 208(b)(3)
Fleming	Full Waiver under 208(b)(3)
Freedman	Full Waiver under 208(b)(3)
Daum	Disclosure
Griffin	Disclosure
Stephens	Disclosure
Fleming	Disclosure
Freedman	Disclosure
O'Connor	Disclosure
Sheets	Disclosure
Unger	Disclosure

Although no votes on the HPV session were expected, Drs. Fleming, McInnes, Myers, O'Connor, Reeves, Sheets, Unger and Wilkinson were granted Temporary Voting privileges by the Director of the Office of Vaccines Evaluation and Research for the session on HPV.

An Open Public Hearing session was announced. Three individuals from the audience came forward to address the committee. Ms. Cindy Pearson, Executive Director of the National Women's Health Network, spoke on the choice of endpoints for HPV trials; Ms. Karen Vanderhoof-Forschner from the Lyme Disease Foundation, and Mr. Stephen Sheller of the law firm of Sheller, Ludwig and Beatty, called for the removal of LYMErix vaccine from the market.

Following is a summary of the discussion. A copy of the agenda is attached Additional information and specific details may be obtained from the transcript of the meeting, http://www.fda.gov/ohrms/dockets/ac/cber01.htm.

Proceedings were adjourned at 2:12 p.m. on Thursday, November 29, 2001 at the end of closed session 6.

Session 1, 2, and 3 – Closed Sessions

In closed sessions, the committee considered issues related to products under review. Appropriate security checks were performed at the beginning of each closed session.

Session 4 – Open Session
Efficacy Trial Endpoints for Vaccines for the Prevention of Human Papilloma Virus

Efficacy endpoints for preventive HPV (human papillomavirus) vaccines were the main topic at the November 28-29, 2001, meeting of the Vaccines and Related Biological Products Advisory Committee held in Bethesda, MD. There were 12 Committee members (including the chairperson) and 12 invited consultants who were also present at the table. Several sponsors and FDA, as well as several guest speakers gave presentations. Most of the discussion centered around the use of persistent HPV infection (only) or CIN (cervical intraepithelial neoplasia) 2/3 with virology as the primary efficacy endpoint.

Most committee members/consultants voiced a preference for use of CIN 2/3 (with virology to determine the associated HPV type) as a primary endpoint, either in the context of "traditional" approval or as a confirmatory endpoint in an accelerated approval. Preference was also expressed for having one large trial that would assess both CIN 2/3 and virology in a definitive manner. It was recognized that CIN 2/3 itself is a "surrogate" for cervical cancer, but the data were thought to be adequate to accept CIN 2/3 as a "validated" surrogate for cervical cancer. In addition, it is standard of care in the U.S. to always treat CIN 2/3, e.g., with LEEP (Loop Electrosurgical Excision Procedure). There was agreement that CIN 2/3 histology, rather than HSIL cytology, should be used for any definitive endpoint case definition. Cervical cancer was not viewed as a feasible efficacy trial endpoint, although observational data for cervical cancer rates in a post-licensure setting would be of interest.

With regard to accelerated approval, two endpoints were discussed as possible surrogate endpoints to support the initial approval: 1) an "early" look at CIN 2/3 (with virology), and 2) persistent HPV infection. Incident HPV infection was not considered a useful surrogate due to the transient nature of most infections. There was considerable discussion on possible meaningful definitions for persistent infection; limitations were recognized, with a preference voiced for a duration of $\geq$ 1 year. Concern was expressed that accelerated approval should not be used if this would preclude obtaining a definitive efficacy outcome for CIN 2/3. In this regard, concern was voiced that it would not be feasible to continue any randomized confirmation trial once licensure occurs. Thus, the timing of obtaining adequate data for the "confirmatory" endpoint (CIN 2/3) was viewed as critical. Also, it was viewed as critical that

accelerated approval not preclude having adequate prelicensure safety data, either with regard to number of subjects or quality of data, at the time of initial approval.

One participant indicated that persistent HPV infection alone would be a sufficient efficacy endpoint for an approval without other data. Another participant thought that persistent HPV infection with a spectrum of cytologic and histologic findings (including ones less advanced than CIN 2/3) would be adequate.

The committee members/consultants requested that virological and cytologic data be obtained at frequent intervals during any trial. There was also interest in identifying an immune response correlate(s) of protection for HPV infection (any), persistent HPV infection and CIN 2/3. Assessing durability of protection was viewed as an important clinical development goal.

In a post-licensure setting, it is unlikely that vaccinees will be screened for HPV status prior to vaccination. Thus, the committee members/consultants recommended obtaining some pre-licensure vaccine safety data in people who are HPV seropositive or HPV DNA positive (for vaccine HPV types) at baseline.

This session was called to order at 1:54 PM on Wednesday, was adjourned for the evening at 5:08 PM on Wednesday, reconvened at 8:33 on Thursday, and concluded at 12:24 PM on Thursday. No votes were taken.

Session 5 – Open Session

Briefing on Activities in the Laboratory of Bacterial Toxins

The committee heard short talks on the organizational structure of the laboratory and on the work by Drs. Willie Vann and Michael Schmitt. Dr. Vann described his research activities on the biosynthesis of capsular polysaccharides, specifically polysialic acid and the binding of tetanus toxoid C fragment to gagliosides. He also spoke of the laboratory's work on anthrax. Dr. Schmitt described his research characterizing the iron transport systems in the corneybacterium diphtheria.

Session 6 – Closed Session

The committee met in closed session to review the report prepared by the site visit team which visited the Laboratories of Bacterial Toxins on July 19.

By unanimous vote the committee accepted the report as written. The report, with its recommendations, will be submitted to the Center Director.