

Internal Mid-Cycle Review Meeting - June 30, 2009 - Prevnar 13

MEMORANDUM

MINUTES OF INTERNAL MID-CYCLE REVIEW MEETING

Meeting Date: June 30, 2009
Meeting Time: 2:00 – 4:00 PM
Meeting Location: Woodmont Office Complex, Conference Room 200S
File: BLA 125324
Product Name: Prevnar 13
Sponsor: Wyeth

Milestones:

First piece of rolling BLA received: 9/22/2008
Last piece of rolling BLA received: 3/31/2009
Action Due: 9/30/2009

Chair

Julienne Vaillancourt, R.Ph., M.P.H.

Committee Members:

| | |
|--|-----------------------------------|
| Clinical Reviewer | Tina Khoie, MD, M.P.H., |
| Biostatistician-clinical | Jingyee Kou, Ph.D., |
| Biostatistician-assays | Lev Sirota, Ph.D., |
| Serological Immune Response Assay Review | Mustafa Akkoyunlu, M.D., Ph.D. |
| Serological Immune Response Assay Review | Drusilla Burns, Ph.D. |
| Serological Immune Response Assay Review | Mike Schmitt, Ph.D. |
| Serological Immune Response Assay Review | Eugenia Dragunsky, Ph.D. |
| CMC Review | John Cipollo, Ph.D. |
| Release Assay Validation | Rajesh Gupta, Ph.D. |
| Pharmacology/Toxicology | Claudia Wrzesinski, DVM, Ph.D. |
| Advertising and Promotional Labeling | Catherine Miller |
| Bioresearch Monitoring | Solomon Yimam |
| Facilities | Nancy Waites |
| Facilities | Martha O'Lone |
| Facilities | Nicole Trudel |
| Facilities | Kim Towns |
| Inspector | Willie Vann, Ph.D. |
| Inspector | Milan Blake, Ph.D. |
| Epidemiology | Marthe Bryant-Genevieve, M.D, MPH |
| Regulatory Project Manager | Colleen Sweeney, M.S. |
| Regulatory Project Manager | Michael Smith, Ph.D. |

Tina Roecklein, M.S.
Karen Campbell
Kim Towns
Deanna Shone

Erik Henchal, Loris McVittie, Wellington Sun, Marion Gruber, Norman Baylor, Tina Khoie, Lucia Lee, Doug Pratt, Mustafa Akkoyunlu, John Cipollo, Drusilla Burns Willie Vann, Jingyee Kou, Lev Sirota, Marthe G. Bryant-Genevier, Andrea Sutherland, Tina Roecklien, Solomon Yimam, Claudia Wrzesinski, Anuja Rastogi, Tammy Massie, Jay Slater, M Rajesh Gupta, Nancy Waites, Martha O'Lone, Nicole Trudel, Colleen Sweeney, Michael Smith, Julianne Vaillancourt.

The purpose of this meeting was to update the entire review team and DVRPA/OVRR management on the review of this original BLA submission.

A brief summary, including product names (proposed proprietary and non-proprietary), proposed indication and chronological regulatory history to date were presented.

Each disciplined reviewer provided a brief summary of data reviewed per assigned BLA section and noted issues, if any, identified to date, as well as whether such issues have been communicated to the sponsor and any subsequent response from the sponsor, as follows:

[illegible]

- [illegible]

3.1.2 Product Testing

- - DPQ is responsible for reviewing analytical methods for drug substance (DS) and drug product (DS), testing in support of the BLA, review of the lot release protocol and development of the testing plan.
 - To date DPQ has been involved in a telecom on June 19, 2009 with the sponsor. During this call the following issues were discussed:
 - The need for an assay for proof of conjugation. In this regard there is no test for the conjugate in DP and there is no stability indicating test on DP (i.e., no test for conjugate).
 - With regard to DS (monovalent bulk conjugate), CBER has questions on the test for -----(b)(4)---, specifically concerning the -----(b)(4)-----.
 - Other issues identified to date:
 - Methods Validations – not performed according to ICH, A number of examples on accuracy, precision and linearity have been identified.
 - Testing in support of BLA – all samples have been received and testing will start in a week with a target to end testing at the end of August. Also, there are issues concerning the lack of a test for conjugate in DP and concerning -----(b)(4)---in DS.
 - Lot release protocol – target for completion is the end of July.
 - Development of testing plan/overview of product testing – drafted and to be completed by mid-August.

3.2 Inspection of Manufacturing Facilities

The four Wyeth facilities will be inspected. The (b)(4) contract facility inspection will be waived. The inspection schedule was presented. The inspection teams for three of the scheduled inspections will include DBPAP review team members. The Schedule is as follows:

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- ---(b)(4)--- 24-28 August DMPQ and Product Office Inspectors
- Pear River 20-24 July DMPQ Inspectors only
- ---(b)(4)--- 03-07 August DMPQ and Product Office Inspectors
- ---(b)(4)--- 10-20 August DMPQ and Product Office Inspectors

DMPQ inspectors: Nancy Waites, Nicole Trudel, Martha O'Lone, Jennifer Schmidt, Sarah Tanksley (training).

OVR/DBPAP inspectors: Milan Blake, Willie Vann, John Cipollo, Jennifer Bridgewater

3.3 Pharmacology/Toxicology Data

Data provided and under review includes:

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- subcutaneous toxicity study in juvenile rats (5 doses, dosing every 2 weeks)
- subcutaneous toxicity study in monkeys (7 doses, dosing every 2 weeks)
- intramuscular toxicity study in rabbits (5 doses, dosing every 3 weeks)
- subcutaneous toxicity study in rats (7 doses, dosing every 2 weeks)
- subcutaneous toxicity study in rats (7 doses, dosing every 2 weeks)
- single dose intramuscular irritation study in male rabbits.

3.4 Clinical Data

The clinical studies provided in the BLA were reviewed briefly with emphasis on studies 004 (US pivotal non-inferiority immunogenicity study) and 3005 (US lot consistency study). The immunogenicity and safety results from study 004 were presented. Issues noted include the failure of three serotypes to meet the co-primary endpoint of proportion of responders to 0.35 µg/mL, particularly serotype 3, and the clinical relevance of these results. Evaluation of concomitant vaccine administration in these two studies and results were summarized. Concerns about the lack of data to support an otitis media indication and the proposed catch-up and transition schedules were noted by the clinical reviewer. The sponsor's proposed plans for PREA were summarized. The sponsor's plans for post marketing studies based on interactions with the review team to date were discussed.

3.5 Statistical Analysis of Clinical Safety and Immunogenicity Data

The statistical evaluation of the file to date was covered, to include issues surrounding studies 004, 005 and 009. Further discussion will be required on these issues.

3.6 Serological Assay Validation & Response Data

3.6.1 Pertussis Antigens:

The pertussis PT, FHA, and PRN ELISAs performed at ---(b)(4) and used for the pivotal concomitant vaccination study, 6096A1-004, are adequate and appropriate when considered in the context of the endpoints of that study. The pertussis immunogenicity endpoints used for the pivotal study 6096A1-004 (proportion of subjects in the 13vPnC group with ELISA values at least as great as the observed value achieved by 95% of the subjects in the 7vPnC group; GMCs) provide a meaningful comparison between the group that received 7vPnC and the group that received 13vPnC. Several supportive concomitant vaccination studies were conducted, however issues exist that limit the usefulness of pertussis immunogenicity data generated from these studies. Vaccines used in a number of the studies were either not licensed in the U.S. or were not given on the U.S. schedule. Two “supportive” clinical studies used pertussis vaccines containing FIM in addition to PT, FHA, and PRN. FIM antibody responses were evaluated using a FIM ELISA. The FIM ELISA was not demonstrated to be adequately validated and therefore results from that assay cannot be interpreted.

3.7 Bioresearch Monitoring (BiMo)

1. BIMO issued high-priority inspection assignments for clinical investigators at the following study sites:

| | |
|------------------------|----------|
| Nampa, Idaho | Site 013 |
| Fayetteville, Arkansas | Site 018 |
| Murray, Utah | Site 044 |
| Little Rock, Arkansas | Site 001 |
| Park Ridge, Illinois | Site 021 |

In addition, inspection assignment was issued for the sponsor’s laboratory that performed the immunogenicity assays; pneumococcal immunoglobulin G (IgG) and pneumococcal opsonophagocytic (OPAs) immunological assays:

3.8 Labeling

3.10.1 The first draft of the proposed draft labeling has been reviewed and discussed in the first round of labeling meetings. Labeling comments will be communicated to the sponsor this week. Issues of note include the limited data to support the proposed schedule for transitioning from Prevnar to Prevnar 13 and inclusion of immunogenicity data from study 008 in the Clinical Studies section of the label. Study 008 is primarily supportive for safety. In addition, significant revisions will be needed to section 6.0 to improve presentation of the

safety data; at this time, the sponsor will be referred to CBER guidance. In the near future, internal discussion regarding the otitis media indication and the lack of effectiveness data with Prevnar 13 will be needed.

3.9 Promotional labeling and Advertising

3.9.1 APLB reviewed the proposed name of Prevnar 13 and recommended that it be found unacceptable. However, after looking at the review, OVRD determined that the proposed name is acceptable. Since “Prevnar” is already on the market, a re-evaluation of the proposed name within 90 days of approval of the application is unnecessary.

Regarding the carton and container labels, APLB commented that the font style of “Prevnar 13” makes it appear as “Prevnar B.” Also, the oval line around “13” in the name is intervening graphic matter and should be deleted. We also recommended that the labels prominently state “For pediatric use only.”

APLB provided comments on the PI recommending that promotional claims be

No promotional materials have been received at this time.

3.10 Pharmacovigilance Plan

The following items were discussed regarding the pharmacovigilance plan (PVP)

- - Overview of components of proposed PVP
 - Status of plan & identified issues pending resolution
 - Potential PMRs or PMCs

Post Marketing Vaccine Effectiveness Plan

- - Overview of components of proposed vaccine effectiveness studies
- Status of plan & identified issues pending resolution

4.0 Action Items

- Continue review process of all disciplines.
- Further discussions pending related to discussions on consistency of manufacture, to include issues surrounding serotype 5.

Contact FDA

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