Review Committee Meeting, February 11, 2009 - Menveo

BLA 125300_0
Novartis ACYW-135 Mening Vaccine

February Review Committee Meeting

Date	Time	Location	US Call in	Password	International Call in - Toll
Wednesday Feb. 11 2009	3:00 – 4:00 EST PM	RM 1st Floor WOC 1 WOC- 1 Building	---b(4)---------- ---	Participant Passcode -b(4)------- Leader pass code --b(4)---	----b(4)---------- ---

1. Introductions – please sign in

The following people attended either by phone or in person:

Al-Humadi, Nabil
Bash, Margaret
Blake, Milan
Burns, Drusilla
Campbell, Karen
deVore, Nikki
Fiore, Cara
Freedberg, Darron
George, Joe
Gupta, Rajesh
Krasnicka, Barbara
Lee, Martha
Meysick, Karen
Trudell, Nicole
Sutkowski, Elizabeth
Sun, Wellington
Valenti, Elizabeth
Vann, Willie
White, Janet

2. Amendments (0.4, 0.3, 0.2, 0.1)
    a. Recent: partial DI response (0.4):
        i. Novartis responded to DI questions 15, 16, and 20 *(performance qualification and product stability)*; and provided additional info on 1(e) & 1(f) *(assay precision and accuracy)*, and 9(e) *(diphtheria and tetanus IU/ml)*.
    b. Recent: Response to IRs (0.5):

i. Responses to CBER's questions on the validation of serological assays for diphtheria and tetanus antibodies, transmitted to us by facsimile on 15 January, 2009 (BLA 125300_0 0.3).
ii. Responses to CBER's questions on assay linearity, transmitted to us by secure email on 7 January, 2009.
iii. Final Container Protocol Templates for the drug substance and final product vaccine components, requested by CBER by secure email on 7 January, 2009.
iv. Revised facility floor plan and description of materials flow, to correct an error that we detected in our original BLA.
v. Revised packaging mock-ups to present revised branding – no other changes.
vi. Final information on pregnancies in Study V59P13.
vii. Final immunogenicity data from Study V59P17, submitted after the BLA as agreed at the Pre-BLA meeting.

c. Running list of Amendments
i. optimizing CRM 197 innocula (0.1)
ii. Extractables and Leachables (0.2)
iii. Partial DI response (0.3)
iv. Partial DI response and additional info (0.4)
v. Response to IRs.

d. Clinical 0.2 Dec 5, 2008: SAE reports (11)
e. *Outstanding Issues*
i. *Waiting for submission of the d59P18 final concomitant with pertussis data and the Gardasil concomitant data for P18.*
ii. *Need the IND Amendment number of the 2008 assay revalidation.*

3. Recent communications
a. Email Information Request for Product (hSBA linearity) and Manufacturing (final container)
b. Email Information Request for PVP studies.
c. Email response to Novartis's product and lot testing questions.

4. DI response
a. Concomitant assay validation (TDaP) – sponsor responded (.3)
b. Manufacturing (PQ, stability) – sponsor responded (.4)
c. Statistical – sponsor responded (.3)

5. Review Team Reports - Please bring to the attention any concerns or questions you have on your sections. Please report any outstanding questions or information needed from the sponsor.
a. Clinical – *Review is now through P13. Concern with sera subgroup testing as the older age groups only contained two subgroups. If testing was conducted by age then there would be unblinding to sera subgroups.*

Overall, the primary endpoint was achieved, but not all secondary endpoints. All lots were reviewed by non-inferiority and all lots were as good as or better than Menactra.

One MenW lot had a lower sera response than the other three; the confidence intervals did not overlap. Dr. Bash would like to ensure there are not lot consistency problems that lead to not meeting some secondary endpoints.

The safety data is okay and similar to Menactra. MenACYW is essentially equivalent. There were less than 10 severe local reactions, each with less than 10cm erythema. All of these reactions were in Menveo, none in Menactra. All cases were resolved and constituted a small number overall. It is evidence of capturing study data and proper reporting.

b. Statistical – *Dr. Krasnicka would like additional assay information as she has the same blinding comments and concerns as Dr. Bash. How many different assays were ran by each technician, technician ID, difference in technique?*

If the assays were ran by number (Study 3:1):

2,150 subjects	*A,C, Y, W*	*2:5:1*
5,883	*A, C*	*5:7:1*
600	*C*	*3:1*

We need to determine if the assays were run by age groups. What was written on the tube (i.e., participant #, site, sequence #, sample,…)? Did the lab have a list by age group? Did the lab have a list by participant number? How did the lab run the samples?

The variation with Menactra group was adjusted by assay. There is a difference in the distribution.

c. BIMO – *Investigators are on assignment. One investigator called with a concern: When the study site began group four Menactra was not available for shipment from the sponsor. The site used the Menactra they had in-house. BIMO instructed the investigator to get information on all lots of Menactra that the site used.*

Four inspections were completed by February 9, 2009. No Establishment Inspection Reports (EIRs).

Current and Future Inspections:

At one site there were no 483 items, but there were potential blinding issues that were addressed in the EIR.

One site had a Voluntary Action Indicated (VAI) and one 483 issue of record keeping. The rest of the data is being reviewed.

At another site the visit is ongoing and should be completed by Friday. There were record keeping and drug

accountability problems that have been resolved.
Another site will be visited in the next two weeks.

d. DPQ – *The draft plan contains multiple problems, including data organization and translation errors; however a quality check was performed on the entire application and it is consistent with the IND.*

Product Quality issues include the use of limit tests instead of quantitative tests in the analytical methods (for example the --b(4)--- test), studies without complete validation, and compendium methods not properly followed or deviations from those methods not adequately justified. At a minimum, the tests for release must be similar to Menactra.

e. DMPQ – *DPQ and DMPQ will meet and decide which comments to forward to the sponsor. The testing plan requires revision and will be best reviewed after inspection. The lot release protocol must have specifications.*
f. Product – *The application does not contain validation or linearity data and the review team is not yet satisfied with some assays. The review should be completed by early March.*
g. Labeling – Review Completed
h. Toxicology – Review Completed
i.Reproductive Toxicology
j.Assay Validation (concomitant and hSBA)
k. OBE/PMC – Review Completed

6. Upcoming events
   a. *February OVRR Action Update: Drs. Vann and Fiore and LT Valenti will not be available. Dr. Vann asked Dr. Bash to present an update on the clinical data and Dr. Gupta to report the product problems in the application.*
   b. PeRC/PREA –April 22, 2009
   c. BIMO inspection - on assignment
   d. Pre-Licensure Inspection - February 16 – 28, 2009. *Dr. Vann asked that if anyone has a particular aspect they would like reviewed during the inspection to email it to him by COB, Thursday, February 12, 2009. Joe George reported that they needed to look at the deviation from the MenW process validation.*
7. Documents/Communications – Reviews, memos, telecons, emails, meetings summaries, etc.
   a. All deadlines include uploading **s**igned, certified pdf with attached Word doc into EDR. If you have problems, please email david.schwab@fda.hhs.gov and cc me (cara.fiore@fda.hhs.gov).
   b. Send all original reviews, telecons, memos, etc to DVRPA (Cara Fiore)
   c. Communication with sponsor – please capture all communications with the sponsor and email them to the regulatory coordinators and Chair. They will have to be listed on the documentation review spread sheet for the Division Director.
8. Committee assignments, Roles and Responsibilities (SOPP 8401)

Al-Humadi, Nabil- Tox
Austin-Hansberry, Lori- OBE - reg coor
Bash, Margaret- Clin
Blake, Milan- hSBA Product
Burns, Drusilla- Assay Validation
Campbell, Karen- DPQ
Devore, Nicole- Prod coord trainee
Fiore, Cara- RPM
Freedberg, Daron- Product
George, Joseph- Facilities
Green, Dave Tox Chief (cc)
Gruber, Marion- Repro tox
Krasnicka, Barbara- Stat
Lee, Martha- Stat – assay
Lee, Robert- Product
McVittie, Loris- Dep Dir DVRPA (cc)
Meysick, Karen- Assay Validation
Miller, Catherine- APLB
Pratt, Doug- Clin Chief (cc)
Richman, Paul- Branch Chief (cc)
Roecklein, Tina- Product Coord
Schraeger, Lewis- Clin Chief, (cc)
Schwab, David- Elect. Integ
Sun, Div Dir DVRPA (cc)
Trudel, Nicole- Facilities
Vann, Willie- CHAIR
White, Janet- BIMO
Wise, Robert- OBE
Menschik, David- PMS
Valenti, Elizabeth- Back up RPM

9. Major Due Dates are on Table below

Milestones	**Date**
STN Assignment	11Sept08
Committee Assignment	11Sept08
1st Committee Meeting	17Sept08
VRBPAC Determination	12Oct08
Filing Meeting	>13Oct08
PeRC – schedule pres.	27Oct08
Filing Action	>28Oct08
Deficiencies identified	>11Nov08
Draft Reviews Due/Mid Cycle review	**25Jan09**
PREA determination	25Jan08
Final Reviews Due	**26Mar09**
PMC to FDAAA Safety WG	06May08
Package to Branch Chief	27May09

Milestones	Date
Final Action Due Date	**29Jun09**
Action Package Posting	**01Jul09**
Monthly Meetings (Team report)	Every Month
IOD Monthly Update	Every Month

10. Next Meetings –
    a. March 11, 2009 (Wednesday), 3:00 – 4:00
    b. April 8, 2009 (Wednesday), 3:00 – 4:00
11. Questions/Comments/Concerns?
    a. Please continue to include Cara and Betsy on emails.