

**MEETING AGENDA**

Date and Time:	August 8, 2011 1:00 pm – 2:00 pm
Location:	WOC2 – Room 2201
Call-In Information:	Toll-Free Number: ---b(4)-----
	Passcode: ---b(4)-----
STN #:	125363/0
Sponsor:	GlaxoSmithKline Biologicals
Product:	Menhibrix, Meningococcal Groups C, and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine

CBER/FDA Invitees**COMMITTEE MEMBERS:**

Review Assignment	Committee Member	Supervisor	Attended
Chair	Joseph Temenak	Elizabeth Sutkowski	
RPM	David Staten	Elizabeth Sutkowski	✓
RPM	Kirk Prutzman	Elizabeth Sutkowski	✓
Clinical Reviewer	Meghan Ferris	Lucia Lee	✓
Product CMC/Serology	Mustafa Akkoyunlu	Willie Vann	✓
Product CMC	Willie Vann	Jay Slater	✓
Product CMC	Daron Freedberg	Willie Vann	✓
Product CMC	Drusilla L Burns	Jay Slater	✓
Product CMC	Annisa Cheung		
Product CMC	James E Keller	Drusilla Burns	✓
Product CMC	Majid Laassri	Konstantin Chumakov	
Product CMC	Steven A Rubin	Konstantin Chumakov	✓
Product CMC	Michael Schmitt		
Product CMC	Shuang Tang	Philip Krause	
Product CMC	Iryna Zubkova		
Toxicology	Steven C Kunder	David Green	
Product CMC	Tina Roecklein	Jay Slater	
Facilities/DMPQ	Sean Byrd	Carolyn Renshaw	✓
Advertising/ Promotional Labeling	Maryann Gallagher	Lisa Stockbridge	
Clinical Statistical Reviewer	Barbara Kransnicka	Dale Horne	✓
Assays Statistical Reviewer	Tsai-Lien Lin	Dale Horne	✓
Epidemiology	Manette Niu	Thomas Buttolph	
DPQ/Lot Testing Plan	Rajesh Gupta	Bill McCormick	✓
DPQ/Lot Testing Plan	Karen Campbell	Bill McCormick	✓

Review Assignment	Committee Member	Supervisor	Attended
Lot Release	Joe Quander	Jay Elterman	
BiMo	Soloman Yimam	Patricia Holobaugh	✓
Electronic Integrity Review	David Schwab	Laraine Henschel	

OTHER ATTENDEES:

Elizabeth Sutkowski
Wellington Sun
Marion Gruber
Lucia Lee
Theresa Finn
Jennifer Bridgewater
Cara Fiore
Robert Fischer
Freyja Lynn

1.0 PURPOSE

On April 15, 2011, GlaxoSmithKline Biologicals On (GSK) submitted a complete response to the CR letter and resubmitted a new biologics license application (BLA) for review to support the licensure of MenHibrix for active immunization of infants and toddlers 6 weeks through 15 months of age for the prevention of invasive diseases caused by *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y. The purpose of this August 8, 2011 committee meeting is to discuss issues in the review process that may result in a CR letter being issued. We will also discuss review progress, upcoming review milestones and any issues which may impact the review process or the approval of the BLA.

2.0 BACKGROUND

Original BLA STN #125363 (eCTD Sequence #0000) was submitted by GlaxoSmithKline Biologicals on August 24, 2009 for MenHibrix (Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine). The proposed indication is for active immunization of infants and toddlers 6 weeks through 15 months of age for the prevention of invasive diseases caused by *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y. On June 11, 2011 CBER issued a Complete Response Letter identify 88 separate deficiency items. On April 15, 2011, GSK submitted a complete response to the CR letter and resubmitted this BLA.

2.1 Milestones:

Milestone	Projected Date
▪ Application Received	April 15, 2011
▪ Committee Assignment	May 2, 2011
▪ 1st Committee Meeting	May 9, 2011
▪ Mid-Cycle Review Meeting	July 11, 2011
▪ 1st draft reviews	July 14, 2011
▪ 2nd draft reviews	August 13, 2011
▪ Final Reviews (Signed/Uploaded)	August 28, 2011 (Sunday)
▪ Present to PeRC	August 14, 2011
▪ PMC to FDAAA SWG	August 31, 2011 - Scheduled
▪ Labeling Target	September 28, 2011
▪ PMC Study Target	September 28, 2011
▪ First Action Due	October 15, 2011 (Saturday)

2.2 Meetings

First Committee Meeting:	May 9, 2011
Filing Meeting:	May 9, 2011
Monthly Team Meetings:	June 6, 2011 August 8, 2011 August 29, 2011 October 3, 2011
Mid-Cycle Review Meeting:	July 11, 2011
PeRC:	August 31, 2011
VRBPAC:	Not going to VRBPAC
SWG:	Not Scheduled
Labeling Meetings:	Not Scheduled

2.3 Information Requests / Amendments

CBER INFORMATION REQUESTS						
Request Date	CBER Rep(s)	Request	CBER Requester for Info	BLA Amendment Response	Review Pending?	Reviewed by and date reviewed:
5/11/2011	David Staten	Notify sponsor that STN 125363 will not go to VRBPAC	Joe Temenak	None	no	
5/19/2011	Kirk Prutzman, Joseph Temenak, Willie Vann, Jennifer Bridgewater, Rajesh Gupta, Karen Campbell, William McCormick	CBER request for updated product manufacturing status. Request for Samples and Reagents	Willie Vann, Jennifer Bridgewater, Rajesh Gupta, Karen Campbell, William McCormick	None	Yes	Willie Vann, Rajesh Gupta, Karen Campbell
6/23/2011	Kirk Prutzman, Joseph Temenak, David Staten	Concerns Regarding GSK's response to Item 86 of CR Letter	Sean Byrd, Carolyn Renshaw, Deborah Trout	125363.13	Yes	Sean Byrd, Carolyn Renshaw
6/30/2011	Kirk Prutzman, Joseph Temenak, Sean Byrd, Deborah Trout	Tcon meeting with GSK to discuss Item 86 issues	Sean Byrd, Carolyn Renshaw, Deborah Trout	None	No	
7/15/2011	Kirk Prutzman, Joseph Temenak, David Staten	CBER concurrence with quarantined lots and diluent inspection protocol		None	No	

2.4 Amendments

Date

Summary

7/29/2011

Responses to the June 23, 2011 information requests for Item 86 of the CR Letter.

3.0 DISCUSSION TOPICS: STATUS AND ISSUES

Q1: Is there agreement that these issues are CR issues?

IOD (Marion Gruber and Theresa Finn) agreed that the MenY hSBA Assay was not performing adequately and that the review team was not able to judge the efficacy of the MenY vaccine component. This was demonstrated by both the CMC review team and the statistics review team. **IOD agreed that the poor performance of the MenY hSBA assay rose to the level of a CR letter being issued.** IOD also agreed that many of the other CMC/product issues discussed also rose to the level of a CR Letter. There was not enough time to discuss all of the CMC/product issues.

Q2: Is the poor performance of the hSBA Assay a fatal flaw?

IOD expressed concern at the poor performance of the MenY hSBA assay but decided that there was NOT sufficient data at the present time to determine if it was a fatal flaw.

Q3: How should we proceed with the review process?

IOD made multiple decisions on how to proceed with the review process.

1. The review team should continue to identify all CR Letter items that are not sufficient (and therefore a CR item), adequate, or items that can be worked out with the sponsor as an IR request.
2. The review team should communicate **all information requests** to GSK before the CR Letter is sent.
3. The Clinical reviewers are still going to present MenHibrix to PeRC.

3.1 CR Letter Issues

☑ A. Serology hSBA Assay (CR items 1 and 2)

Mustafa Akkoyunlu discussed that the Men Y hSBA assay showed decreased titer results over time and is therefore not reliable. According to his review, CR Letter items 1 and 3 remain CR issues while CR Letter item 2 was adequately addressed. He discussed that GSK had at least 3 explanations for the drop in titer.

1. The human sera was “out of date” (collected in 2005)
2. The -----b(4)-----.
3. The test sera for study 005 was ---b(4)-----

However, the decrease in titer in the MenY hSBA assay was observed in across the studies. Additionally, GSK submitted -b(4)----- test results from -b(4)----- cycles that indicated -b(4)----- would not significantly reduce SBA titer levels in their hSBA assay.

The possible explanations from GSK were considered inadequate and the MenY hSBA assay was considered unreliable. The review team and IOD agreed.

✓ B. Statistical Items relating to hSBA Assay (CR items 1 through 12)

Tsai-Lien Lin discussed the statistical analysis with the MenY hSBA Assay. She agreed that CR Letter items 1 and 3 remained as CR items. The statistical review indicated that the titer of SBA in the MenY hSBA assay decreased over time and that serum storage seemed to be an issue. It was unclear why this occurred and GSK offered no explanation. Tsai-Lien indicated that it was not clear how the samples were randomized and that there is a lot of missing data in this submission making her review difficult.

Barbara Krasnicka discussed her preliminary statistical review of the clinical trials. Her analysis indicates that there is lot to lot differences in the in the MenY titers. MenC and Hib titers were statistically the same between lots. Barbara also indicated the CR Letter items 4 through 12 were adequately addressed. Barbara also indicated that there is a lot of missing data in this submission making her review difficult.

✓ C. CMC – Out standing Issues that are likely CR items:

Willie Van, Deron Freedburg, Drusilla Burns, and Freyja Lynn discussed the CMC/product review progress.

**CR Letter Item
Item (reviewer):**

NOTE

- 35 (TR,DF): Can be addressed in a IR Letter.
- 36 (DF): Adequately addressed in CR Letter Response
- 37 (DF): Not Adequately Addressed – CR Letter Item
- 38c (DF): Not Adequately Addressed – CR Letter Item
- 38j (DF): Adequately addressed in CR Letter Response
Note: It was discussed that there are many issues outstanding under 38 since this was a multi-part question. Some issues are major. So maybe 38 as a whole is best as a CR
- 39a (TR): Potential CR, Not discussed at meeting.
- 40a (TR): Not Adequately Addressed – CR Letter Item

MA - Mustafa Akkoyunlu
TR - Tina Rocklein
DF - Deron Freedberg
WV - Willie Vann
EK - James E Keller
MS - Mike Schmitt
DPQ - Product Quality
BK - Barbara Krasnicka
TSL - Tsai-Lien Lin
MF - Meghan Ferris
SB - Sean Byrd
ST - Shuang Tang

63(TR,DF): Not Adequately Addressed – CR Letter Item

73b (DF): Not Adequately Addressed – CR Letter Item. Similar issues as 37.

✓ D. CMC – Outstanding Issues that may be able to be addressed:

The following CR Letter items were identified before the meeting as items that possibly could be addressed in an IR letter. These issues were not discussed at the meeting. IOD wanted the review team to come to a final decision as to which items are CR items and which items are IR items.

CR Items that have not yet been adequately addressed:

CR Letter Item
Item (reviewer):

NOTE

- 25c (DF): Talk to firm, test needs to be a release test, and we suggest testing at ---b(4)--- prior to shipping
- 34 (DF): Need to speak to firm clarify if actual tests used are interfered with by (b)(4)
- 38d (DF): Clarification with firm; why is -b(4)- below theoretical value and other assay above it?
- 38e (DF): Clarification with firm, maybe they are doing something wrong in assay
- 38f (DF): Clarification with firm has not evaluated whether evaluated the possibility that there is a signal from ---b(4)----- material that is no longer attached to
-b(4)-----
- 38g (DF): Inadequate, they should not have a baseline correction, a slope, curve; at most a DC offset
- 40d (TR): Discuss with Sean and Rajesh
- 40e (TR): Call firm to clarify other byproducts that may be toxic
- 57(TR,EK): Call firm, they will not get --(b)(4)-- yrs dating, only 2
- 67f (TR): Talk to Rajesh
- 67g (TR): Talk to firm, they must do this
- 68 (TR): Talk to Rajesh
- 69b (TR): Talk to firm, explanation ok but no variability provided
- 69e (TR): Talk to firm, they did not answer the original question at all. Did they misunderstand it?
- 69g (TR): Talk to Rajesh
- 74b(TR,DF):Talk to firm, they need to do this
- 75 (TR,DF): Talk to firm, they still need to provide a plan explaining how they will use both diluent manufacturers in stability studies
- 76 (TR,DF): Talk to firm, we can only give them 24 months for final container expiry dating, not 36

- 77 (TR): Contact firm, sterility and ----(b)(4)----- missing in stability studies; and firm should reconsider PS stability
- 82 (TR): CP; discuss with Rajesh some of these acceptance criteria

E. CMC – Acceptable CR items:

The acceptable CR response items were not discussed at the meeting. The following CR Letter items were determined to be adequately addressed in CR Letter Response:

21-22
23:
24
25 all but c
26 through 33
38 a, b, h, i, k, l
39 b
40 b and c
46 b
56
58 through 62
64 and 65
67:
69 c, d, f
70 through 72
74 a and c
78 through 81
83

Meeting Ended.