

Mid-Cycle Review Meeting - May 14, 2006 - Hiberix

**Hiberix – STN 125347/0
Mid-Cycle Review Meeting
May 14, 2009**

Agenda:

1. Review milestones
2. Discuss status of reviews
3. Develop a list of action items

Milestones:

Application Received:	March 17, 2009
Committee Assignment	March 24, 2009
1st Committee Meeting	March 31, 2009
Filing Meeting	April 1, 2009 (via e-mail)
Filing Action/Deficiencies Identified	April 16, 2009
Target Action Due Date:	July 31, 2009

Committee Assigned:

Chair	Jay Slater, M.D.
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Committee Members

Clinical Reviewer/Labeling	Karen Farizo, M.D.
Product CMC/Serology	Mustafa Akkoyunlu, M.D., Ph.D.
Product CMC	Scott Norris
Product CMC	Tina Roecklein
Facilities/DMPQ	Joseph George
Facilities/DMPQ	Sean Byrd
Advertising/ Promotional Labeling	Maryann Gallagher
Clinical Statistical Reviewer	Ghideon Ghebreorgis, Ph.D.
Epidemiology	David Menschik, M.D., MPH
DPQ/Lot Testing Plan	Rajesh Gupta, Ph.D.
Lot Release	Joe Quander III
BiMo	Christine Drabick, MS
DVRPA Reviewer	Joe Temenak, Ph.D.

RPMs/RC

**DVRPA Regulatory Project
Mgr.
DBPAP Regulatory
Coordinator**

Jason Humbert

Jennifer Bridgewater, MPH

Others present:

Loris McVittie, Ph.D., Deputy Director, DVRPA

Wellington Sun, M.D., Director, DVRPA

Lucia Lee, M.D., Clinical Team Leader

Marion Gruber, Ph.D., Deputy Director, OVRP

Milan Blake, Ph.D., Director, DBPAP

Karen Campbell, Regulatory Coordinator, DPQ

Discussion Items:

Dr. Slater began with a review of regulatory actions taken to this point, including the issuance of the Filing, Deficiencies Identified and Information Request Letters. Dr. Slater reviewed the timelines for this submission: reviews are due June 1 with the goal of July 31, 2009 as the action date.

Dr. Farizo stated that the clinical review is ongoing, and that she anticipates recommending approval. She has come across several items which will be the source of an information request regarding clarification of data submitted, as well as requests for additional analyses. Dr. Farizo stated that some of the proposals made in the PI may be an issue, and the limited data regarding interchangeability with other licensed vaccines will need to be addressed. For concomitantly administered vaccines, some studies used non-U.S. licensed vaccines or off-schedule use of licensed vaccines. Dr. Farizo also discussed the topic of how GSK is attributing AEs to Hiberix in studies with Pediarix and Infanrix (i.e. the incidence of fever with Pediarix as opposed to Infanrix). Dr. Farizo will begin labeling negotiations with GSK in June. GSK is anticipating on submitting a response to the IR letter which contained items pertaining to the concept protocol Study HIB-097 on May 15, 2009.

CMC/Serology was discussed by Dr. Akkoyunlu, Mr. Norris and Ms. Roecklein. The manufacturing process description was discussed. There have been problems finding SOPs and other information. However these questions are being answered during a further examination of the information contained in the BLA. For example, the SOPs do not specify testing limits, but a further review of the translated Batch Records revealed the limits in question.

The committee discussed:

1. asking GSK to provide the information in the Batch Records above in the form of an SOP as a PMC for easier access and review after licensure. Blank Batch Records are serving as the "SOP" for the monitoring of parameters.
2. the requirement for ongoing bulk stability studies. Validations are being examined since information in the BLA is from previously used containers and/or facilities. GSK currently has no plan for ongoing stability measurement of intermediates, but this item will be discussed further in DBPAP.
3. the assessment of assay validation, which has revealed no issues thus far, and the LRP for this product is more robust compared with a similar licensed product. The assays included in the clinical trial data showed that in the German study (020) five

subject samples showed a higher anti-PRP level pre-booster dose compared to post-vaccination. This phenomenon was not observed in review of the other studies; however the assigned case numbers for subjects were close in numerical order, so the possibility of some other contributing factor could not be ruled out.

For the testing in-support, Dr. Rajesh Gupta (DPQ) has not received the reagents and samples from GSK. DPQ has a number of comments on method validation to include in an information request. Comments on the Lot Release Protocol should be ready by the end of May. The Lot Testing Plan should be completed by the end of June. See the record from the May 7, 2009 teleconference. A follow-up discussion with GSK regarding the SOPs included in the BLA will be held on May 19, 2009. The inspection will be conducted June 1-13, 2009.

Joe George and Sean Byrd from DMPQ noted that a supplement submitted under BLA 103239 includes a facility in ---b(4)--- for approval. This facility will be used to help supply theb(4)million doses to the public and private marketplace. However, the action due date for this PAS is August 7, 2009 – a week after the target due date. DMPQ will work to expedite the approval of this facility.

In Amendment 5, GSK submitted a table listing clarifications/corrections to information provided in the original application. The reviewers agreed that GSK should resubmit the corrected documents (to note what was changed).

Dr. Ghebregiorgis noted statistical issues in the review. They include:

1. The sample size calculations are based on a high estimated drop out rate (20%). The sponsor did not provide any rationale for anticipating a high rate of drop out. The protocol doesn't specify how missing data will be handled.
2. The power calculation for the first co-primary objective in the primary vaccine phase is not correct (page 44 of the concept protocol). Based on the information provided and using the software indicated on the protocol (-b(4)- software) the power for sample sizes of 600 from the pooled sub-cohorts Hiberix group and 200 from sub-cohort ActHib is 89.9% not 96.3% as stated on the protocol.
3. In section 11.2.2 the sponsor lists hypothesis to be tested during the study, but the hypotheses, except for the hypothesis given in 'd', are not correctly stated to reflect the objectives the sponsor wants to achieve. The statements on the null and alternative hypothesis should be reversed in order to obtain the stated objectives.

Dr. Ghebregiorgis also commented on the recruitment methods in the concept protocol, i.e. for the 100 centers identified. There appears to be no explanation for how they will select centers.

Dr. Menschik stated that his review is complete. GSK has requested clarifications for items in the Deficiencies Letter, and those clarifications were provided on May 12, 2009. We are awaiting the response from GSK.

Ms. Gallagher from APLB stated that a review of the container and package labeling is complete and the memo has been sent to Dr. Slater. The PNR is ongoing (due date June 29, 2009). The logo appears to be acceptable at this point.

Action Items:

1. Develop a list of methods and CMC items for an IR. This includes what, if anything, can be accepted as a PMC (e.g., information from the Batch Records converted to an

SOP). Items from this list will be from Dr. Akkoyunlu, Dr. Gupta, Mr. Norris, Ms. Roecklein, and Dr. Vann.

2. Request replacement documents for the information that was sent in Amendment 5.
3. Follow-up on the reagents and samples – confirm the appropriate address and contact person for the shipment.
4. Contact GSK about having direct contact numbers for those responsible for clinical and product/facilities content.
5. Follow-up on the status of the response to the IR letter for the concept protocol.