

Conference Call, August 16, 2012 - Q-Pan

Date and Time: August 16, 2012, 2:30 PM – 3:30 PM
Location: CBER Conf. WOC2-2201; Conference call
STN #: 125419/0
Sponsor: ID Biomedical Corporation of Quebec (dba GlaxoSmithKline Biologicals)
Product: Influenza A (H5N1) Virus Monovalent Vaccine

CBER/FDA Attendees

Carmen Collazo-Custodio
Hana Golding
Rajesh Gupta
Manju Joshi
Surender Khurana
William McCormick
Kirk Prutzman
Jeremy Wally

GSK Attendees

Robert Brobst
Sandra Gilbert
Pierre-Alain Moisset
Michael Schwartz

1.0 PURPOSE

The objective of this conference call was:

- To provide an update on the results of the Single Radial Immunodiffusion (SRID) testing conducted on the H5N1 monovalent bulks and final container lots submitted in support of the BLA. Since 2 out of 3 final container lots did not meet specifications of the potency test, CBER requested a conference call with GSK representatives to discuss this discrepancy.

2.0 BACKGROUND

On August 10, 2012, CBER requested a conference call with GSK to discuss the results of the SRID testing. The testing was performed in the Division of Biological Standards and Quality Control (DBSQC), Office of Compliance and Biologics Quality. DBSQC completed SRID testing on both the monovalent bulks and final container lots submitted in support of the BLA. The results of this testing are shown in Attachment 1. On August 15, 2012, GSK submitted written information in an effort to clarify some of the issues (refer to Attachment 2). The conference call was held on August 16, 2012 (see item 3.0 Discussion Topics).

3.0 DISCUSSION TOPICS

- CBER briefly summarized the SRID potency test results that were provided to GSK via e-mail correspondence on August 10, 2012 (refer to Attachment 1). CBER briefly

described the **standard** methodology used in the SRID assay, in which 3 tests are initially performed and the mean of 3 tests is calculated to report the potency (mg HA/ml). If any lot fails the potency specification from the first 3 tests, 3 additional tests are performed and an average from 6 tests (3 original tests and 3 additional tests) is calculated to report the potency. The specifications are: Average HA content -----(b)(4)-----.

- Based on the initial 3 tests conducted, two final container lots, ---(b)(4)--- and ---(b)(4)---, showed potency values below the specifications of ---(b)(4)--- (12.0 and 13.3 mg/ml, respectively). Additional testing was done for these two lots and the data from 6 tests were pooled to calculate potency results. The potency results were below the specifications of (b)(4) mg HA/mL for these two lots.
- GSK did not conduct the SRID testing potency calculations using the standard SRID method based on CBER's guidelines. GSK briefly described their analysis based statistical calculations using a WHO guidance. GSK indicated that they did not see a difference whether they used 3 gels versus 6 gels. CBER stated that the company would have to submit a data package for our review in order to change the potency specification.
- CBER advised GSK to submit an amendment explaining that the product is beyond the expiration date. This amendment should also explain that CBER and GSK have used different reagents for testing and this could contribute to the inconsistent HA results obtained between CBER and GSK.
- Regarding the stability testing program and the specification for HA potency, GSK asked if it would be possible to have two separate specifications, one for release and another for stability testing. CBER responded that the product should meet release specifications throughout its shelf life.
- Two distinct issues were outlined at the conclusion of the conference call. One was that the proposed HA specification was not acceptable. The other was that the discrepancy in potency results may be explained based on the difference in the reagents used and the expiration of the samples used for testing.

4.0 ACTION ITEMS

GSK will submit a BLA amendment providing additional justification for the discrepancy in HA results between GSK and CBER. Once the BLA amendment is received by CBER, an internal meeting will be arranged to discuss the acceptability of the proposed HA specification and the discrepancy in potency results based on the difference in reagents used and the expiration of the samples tested.

Attachment 1: August 10, 2012, E-mail Communication (CBER to GSK)

From: Collazo, Carmen [mailto:Carmen.Collazo@fda.hhs.gov]
Sent: Friday, August 10, 2012 5:45 PM
To: Michael Schwartz; Kati Abraham
Cc: Prutzman, Kirk C; Campbell, Karen M; Wally, Jeremy; Collazo, Carmen
Subject: STN 125419: Request for a conference call next week-SRID testing
Importance: High

Dear Mike and Kati,

CBER has now completed Single Radial Immunodiffusion (SRID) testing on the monovalent bulks and final container lots submitted in support of your application. The results of this testing are shown below. Please note that 2 out of 3 final container lots did not meet specifications of the potency test. We are requesting the opportunity to have a conference call with you and a representative from GSK-IDB (someone who can discuss SRID testing issues, as appropriate) to discuss this discrepancy.

Drs. Manju Joshi and Rajesh Gupta are available on the following dates:

Tuesday, August 14, from 11 AM-12 PM

Thursday, August 16, from 2:30 PM-3:30 PM

Friday, August 17, from 2:30 PM-3:30 PM

Please indicate your availability as soon as possible to schedule this conference call.

Regards,

Carmen

Single Radial Immunodiffusion (SRID) Test Results:

1) -----

----- (b)(4) -----
-----:

----- (b)(4) -----

[(b)(4)]

2) Final Container Lots: Testing of 3 lots of final container vaccine was done following the SOP submitted by GSK (9000018734-V08-VR010 Radial Immuno- diffusion for Low HA-Concentration Influenza Vaccine). As per GSK SOP, -----
(b)(4)-----.

As per the standard SRID method, initially 3 tests are performed and mean of 3 tests is calculated to report the potency (mg HA/ml). If any lot fails potency specification from first 3 tests, additional 3 tests are performed and average from 6 tests (3 original tests and 3 additional tests) is calculated to report the potency. The specifications are: Average HA content ---(b)(4)---- (for 3 tests) and ---(b)(4)-- (for 6 tests).

Based on initial 3 tests performed in DBSQC laboratory, two lots: -----(b)(4)-----
 ----- showed potency values less than specifications of ---(b)(4)-----. Additional testing
 was done for these two lots and data from 6 tests were pooled to calculate potency
 results. All the results are summarized in the table below

Reagents Used:

Reference Antigen: H5-Ag-1113

Reference Antisera: H5-Ab-1115

Lot#	HA content (mg/ml) (Average of First set of 3 tests)	HA content (mg/ml) (Average of Second set 3 tests)	HA content (mg/ml) (Average of 6 tests)	Conclusion (within Specification: Yes/No)
---(b)(4)-----	14.7	N/A	N/A	YES
---(b)(4)-----	12.0*	12.5	12.2**	NO
---(b)(4)-----	13.3*	13.8	13.6**	NO

*Potency results below the specifications of --(b)(4)-- HA/ml

** Potency results below the specifications of --(b)(4)-- HA/ml

Attachment 2: August 14, 2012, E-mail Communication (GSK to CBER)

From: Michael Schwartz [mailto:michael.p.schwartz@gsk.com]

Sent: Wednesday, August 15, 2012 4:31 PM

To: Collazo, Carmen

Cc: Prutzman, Kirk C; Wally, Jeremy

Subject: RE: STN 125419: Request for a conference call next week-SRID testing

Dear Carmen,

We held an internal GSK meeting today to prepare for the meeting with Drs. Joshi and Gupta to be held tomorrow to discuss the SRID testing issues described in your email

below. There are several pieces of information that we would like to make CBER aware of prior to the teleconference.

1. The potency release specifications listed in your email below do not pertain to what has been submitted in the Q-Pan BLA, but are specific to what was previously registered in the Q-Pan IND. The release specification in the recent IND update and the BLA is -----(b)(4)----- . A specification of ---(b)(4)--- HA/ml is not applied in either the IND or the BLA for final container DP. For your reference, the release specifications in the BLA are located in 3.2.P.5.1 – Antigens Final Container.

2. The final container batches that CBER recently tested are approximately 41 months old (manufactured March 2009), and thus the release specifications no longer apply due to the age of the material. Rather the stability specification of a LCB –(b)(4)-ug HA/ml is appropriate for these samples. Also, please note that the stability specification is under discussion with CBER (question 4 of the July 30 IR). The stability specifications are best described in 3.2.P.2.2 – Shelf Life Evaluation Antigens (page 19, table 4) and also referenced in 3.2.P.8.2.

3. CBER's results align with GSK's 36 month stability results for these lots. ----(b)(4)----- (mean of 15.2ug HA/ml, LCB of (b)(4)), ---(b)(4)----- (mean of 13.7 ug HA/ml, LCB of (b)(4)), -----(b)(4)---- (mean of 13.9 ug HA/ml, LCB of (b)(4)). These results were most recently provided in the stability responses from the April 30, 2012 IR (responses submitted to CBER on July 18, 2012). We feel that a direct comparison of GSK's 36 month stability results and CBER's recent results is most relevant, rather than comparison to the release specification.

4. CBER and GSK have used different reagents for testing and this could be the reason for slight differences in HA results between CBER and GSK.

This information can be further discussed at the TC tomorrow but we felt that Drs. Joshi and Gupta should be aware of the above information prior to the meeting so we can have a productive discussion. Looking forward to talking to you tomorrow.

Best Regards,

Mike