

Midcycle Meeting_Minutes, July 20 2012 - Q-Pan

Date and Time:

July 20, 2012 1:00 PM – 2:30 PM

Location:

CBER Conf. WOC2-2330

STN #:

125419/0

Applicant:

ID Biomedical Corporation of Quebec (dba GlaxoSmithKline Biologicals)

Product:

Influenza A (H5N1) Virus Monovalent Vaccine

Meeting Chair:

Carmen M. Collazo-Custodio

Meeting Recorder:

Kirk Prutzman

CBER/FDA Invitees

COMMITTEE MEMBERS:

Attended Committee Member Review Assignment

Carmen Collazo-Custodio	Chair
Jeremy Wally	Lead RPM
Kirk Prutzman	Co-RPM
Andrea James	Clinical
Hana Golding	Product CMC
Surender Khurana	Product CMC
Nabil Al-Humadi	Toxicology
Tsai-Lien Lin	Clinical/Assay Stats
Tielin Qin	Assays Stats
Maryann Gallagher	Advertising/Promotional Labeling
Cheryl Hulme	Lot Release
Yandong Qiang	Pharmacovigilance
Hector Izurieta	Epidemiology (Effectiveness)
Anthony Hawkins	BIMO
Randa Melhem	Facilities/DMPQ
Jei He	Facilities/DMPQ
Manju Joshi	Product Quality
Lokesh Bhattacharyya	Product Quality
Karen Campbell	Product Quality

Supervisor

Elizabeth Sutkowski
Elizabeth Sutkowski
Elizabeth Sutkowski
Lewis Schrager
Jerry Weir
Hana Golding
David Green
Dale Horne
Dale Horne
Lisa Stockbridge
Joseph Quander III
Wei Hua
Richard Forshee
Patricia Holobaugh
Chiang Syin
Chiang Syin
William McCormick
William McCormick
William McCormick

Attended Committee Member Review Assignment

David Schwab

Electronic Integrity Review

Supervisor

Laraine Henschal

OTHER ATTENDEES:

Marion Gruber
Theresa Finn
Philip Krause
Maureen Hess
Estelle Russek-Cohen

Elizabeth Sutkowski
Herb Smith
Erik Henschal
Jerry Weir

Wellington Sun
Annisa Cheung
Robert Ball
Brenda Baldwin

Douglas Pratt
Dale Horne
Richard Forshee
Chiang Syin

1.0**PURPOSE**

The objectives of this meeting were:

- To brief management on the status of reviews.
- To describe any issues identified with the file.

2.0**BACKGROUND**

The proposed indication of BLA STN 125419 is for active immunization for the prevention of disease in persons 18 years of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine. Influenza A (H5N1) Virus Monovalent Vaccine is also denoted Q-Pan H5N1 in the context of this meeting summary.

3.0

DISCUSSION TOPICS

3.1

MILESTONES AND MEETINGS

Milestone	Projected Date
Application Received	February 22, 2012
Committee Assignment	March 7, 2012 (FDA Tracked Milestone)
1st Committee Meeting	March 12, 2012
Filing Meeting	April 9, 2012
Filing Letter Issued	April 22, 2012
1st Draft Reviews	June 21, 2012
Mid-Cycle Review Meeting	July 20, 2012(FDA Tracked Milestone)
2nd Draft Reviews	August 30, 2012
Final Reviews (Signed/Uploaded)	October 14, 2012
Present to PeRC	October 20, 2012 (Target Date, Saturday)
Labeling Comments to Sponsor)	November 9, 2012 (FDA Tracked Milestone)
Notify GSK of PMC/PMR	November 12, 2012
Labeling Complete	December 4, 2012
First Action Due	December 22, 2012 (Saturday)

Meetings	Scheduled Date
First Committee Meeting	March 6, 2012
Filing Meeting	April 9, 2012
Monthly Team Meeting	April 30, 2012 (revised date - May Meeting)
Monthly Team Meeting	June 11, 2012
Monthly Team Meeting	July 9, 2012
Monthly Team Meeting	August 3, 2012 (revised date)
Monthly Team Meeting	August 31, 2012 (revised date – Sept. Meeting)
Monthly Team Meeting	October 5, 2012 (revised date)
Monthly Team Meeting	November 6, 2012 (revised date)
Monthly Team Meeting	December 10, 2012
Mid-Cycle Review Meeting	July 20, 2012
PeRC	September 26, 2012
VRBPAC	November 14, 2012
SWG	Not Yet Scheduled
Labeling Meetings	Not Yet Scheduled

3.3

DISCUSSION TOPICS:REVIEW STATUS AND ISSUES

3.3.1

Introduction– ChairReport

The Chair gave a short background of the BLA and updated management on the progress of the review.All reviewers reported that they had completed their first draft

reviews. GSK submitted their responses on June 20, 2012, July 18, 2012, and July 19, 2012, to CBER's Information Request provided on April 30, 2012. GSK submitted a pediatric plan on July 19, 2012. PeRC and VRBPAC meetings were scheduled (see above).

3.3.2

Facilities/DMPQ Review Report

The Facilities/DMPQ reviewer reported that she drafted a memo recommending waiving the pre-license inspection for Influenza A (H5N1) Monovalent Vaccine at the Ste Foy Facility in Quebec, Canada. In addition, the manufacturing facilities of Adjuvant AS03 (Rixensart/Wavre, Belgium) will not be inspected because the site is US licensed with an acceptable compliance history.

3.3.3

Clinical Review Report

The Clinical reviewer discussed the preliminary evaluation of the safety and immunogenicity studies. Immunogenicity: Studies Q-Pan-001 and Q-Pan-002 met their immunogenicity endpoints.

Safety: The Clinical reviewer discussed that both studies Q-Pan-001 and Q-Pan-002 reported more Grade 1, 2, and 3 injection site pain reactions in the adjuvanted vaccine treatment groups when compared with unadjuvanted vaccine controls or placebo. Studies Q-Pan-001 and Q-Pan-002 reported more systemic symptoms (for example: fatigue, headache, muscle aches, joint aches, and shivering) in the adjuvanted vaccine groups vs. unadjuvanted vaccine. The ISS confirmed findings of studies Q-Pan-001 and Q-Pan-002 with respect to reactogenicity events. An increased relative risk (RR) of adverse events associated with Q-Pan H5N1 over control was observed for:

- solicited reactogenicity events – nausea, malaise, injection site pruritus, injection site reaction, injection site warmth, RR 2- 10 (1.1,38).
- cystitis RR – 7 (1.1,277)
- dizziness RR- 2 (1,2.5)
- insomnia RR – 4 (1.3,21)

There were no differences in SAEs or deaths between the treatment groups and control.

3.3.4

Statistical Review Report

The Statistics reviewer discussed the preliminary review of the Van Buynder clinical study report, submitted to the application as a pivotal study to support the traditional approval of the Q-Pan H5N1 vaccine. The Van Buynder study was a case-control test negative retrospective, observational study. The reviewer identified multiple issues with the Van Buynder study, including:

- Small sample size: 91 participants completed the study. There are wide confidence intervals in any analysis of the data. Additionally, all analyses of the data are sensitive to how missing data values are handled.
- Design methodology issues: Many sources of bias/confounders were discussed. For example, selection bias may have been introduced because ordering H1N1 tests was done at the decision of the patient's physician and not as part of a pre-written protocol for testing patients. The study does not account for health care seeking behavior. There

were no data collected for previous H1N1 infection. The number of days between sample collection and ILI onset were not considered.

- Missing data: 20/111 (18%) tested subjects should have been eligible but were not included in the study.

The Statistics reviewer was not able to draw any meaningful conclusions from the Van Buynder study. She expressed concern of using the information from this study in a label for the Q-Pan H5N1 vaccine, such as extrapolation of vaccine efficacy (100%) and the definition of a statistical criterion for vaccine effectiveness.

3.3.5

Epidemiology (Effectiveness Study)

A preliminary review of the ensemble of three published studies (Van Buynder et al. - Influenza Other Respi Viruses. 2010;4(4):171-178; Mahmud et al. – Vaccine 29 (2011) 7975-7981; Skowronski et al. – BMJ 342 (2011) c7297) led to the conclusion that the monovalent H1N1 adjuvanted vaccine is effective against the pandemic H1N1 Influenza virus. The effectiveness of the adjuvanted H1N1 vaccine was higher for younger age groups. The Epidemiology reviewer also noted the limitations of the Van Buynder study as described by the Statistics and Clinical reviewers and concurred with their recommendation that the Van Buynder study alone should not be considered as a pivotal study for traditional approval of the Q-Pan H5N1 vaccine.

3.3.6

Conclusions and Recommendations

There was discussion among the review team and management about using the Van Buynder study and the path forward for approval. Both the review team and management agreed that the Van Buynder study was not sufficient to serve as a pivotal study for traditional approval of the Q-Pan H5N1 vaccine. There was also agreement that the preliminary reviews of the safety and immunogenicity data submitted in the BLA support licensure of the Q-Pan H5N1 vaccine in individuals ≥ 18 years of age via the accelerated approval regulations. Several scenarios were considered as possible confirmatory studies.

One path discussed was accelerated approval of the Q-Pan H5N1 vaccine using the results from the *FluLaval* efficacy study FLU Q-QIV-006 [A phase III, observer blind, randomized, non-influenza vaccine comparator-controlled, multi-country and multi-centre study of the efficacy of GSK Biologicals' quadrivalent, inactivated, split virion, seasonal influenza vaccine candidate, GSK2282512A (FLU Q-QIV), administered intramuscularly in healthy children 3 to 8 years of age] as a confirmatory study. The other path was accelerated approval using the results of a post-marketing study conducted during an H5N1 outbreak used as a confirmatory study.

Post-Meeting Update: On August 7, 2012, Management informed the review committee that the VRBPAC would be solicited for advice regarding the licensure pathway for the Q-Pan H5N1 vaccine at the November 2012, meeting.

4.0

Information Requests Conclusions and Recommendations

Request Date	CBER Rep(s)	Request	CBER Requester for Info	BLA Amendment Response	Review Pending?	Reviewed by and Date Reviewed
4/30/2012a	Carmen Collazo-Custodio	IR for Pediatric Plan, stability data, clinical assay validation, HA content by SRID validation, other assay validation, facilities information, pharmacovigilance	Andrea James, Hana Golding, Surrender Khurana, Tsai-Lien Lin, Tielin Qin, Manju Joshi Lokesh Bhattacharyya, Yandong Qiang, Randa Melhem	125419.2	Yes	
4/30/2012b	Carmen Collazo-Custodio	Revised 356h form, SRID testing reagents and results	Carmen Collazo, Karen Campbell	125419.1	Yes	
6/21/2012	Carmen Collazo-Custodio	Adjuvant lots and SRID calculation spreadsheet	Karen Campbell	-	-	

Date/STN Summary

May 3, 2012 (125419.1) Partial response to 4/30/2012b IR. Revised 356h form.

May 25, 2012 (125419.2) Partial response to 4/30/2012b IR. Answers to Item 2.

June 20, 2012 (125419.3) Partial response to 4/30/2012a IR. Answers to Items 24-34.

July 18, 2012 (125419.4) Partial response to 4/30/2012a IR. Answers to Items 2-23 and 35-36.

July 19, 2012 (125419.5) Partial response to 4/30/2012a IR. Answer to Item 1. All responses to IR now submitted.