Midpoint Management Meeting Memorandum - AFLURIA

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
MIDPOINT MANAGEMENT MEETING FOR
CSL Ltd.'s Seasonal Influenza Virus Vaccine, Afluria®
STN 125254
MEETING DATE: July 23, 2007
COMMITTEE MEMBERS:

Name	Position	OPDIV
Rakesh Pandey, Ph.D.*	Committee Chair	OVRR/DVRPA/VVB
Katherine Berkhousen, CDR*	Regulatory Coordinator	OVRR/DVRPA/VVB
Cynthia Nolletti, M.D.*	Medical Officer	OVRR/DVRPA/CTB
Joeseph Toerner, M.D.*	Medical Officer	OVRR/DVRPA/CTB
Galina Vodeiko, Ph.D.*	Product Review	OVRR/DVP/ LPRVD
Tammy Massie, Ph.D. *	Statistical Review	OBE/DB/VEB
Lev Sirota, Ph.D,*	Assay Statistical Review	OBE/DB/VEB
Dale Burwen, M.D.	Medical Officer	OBE/DE/VSB
Bhanu Kannan *	Bioresearch Monitoring	OCBQ/DIS/BMB

Name	Position	OPDIV
Jonathen McInnis	Establishment	OCBQ/DMPQ/BII
Pete Amin *	Establishment	OCBQ/DMPQ/BII
Catherine Miller *	Name Label Review	OCBQ/DCM/APLB
William McCormick	Release Testing Plan	OVRR/DPQ
Rajesh Gupta*	Release Testing Plan	OVRR/DPQ/PQLS
Joe Quander*	Lot Release	OCBQ/DMPQ/PRB

* = members present at committee meeting
OVRR MANAGEMENT PRESENT:

Name	OPDIDV
Norman, Baylor, Ph.D.	Acting Director, Office of Vaccines Research and Review
Florence Houn, MD	OVRR
Eric Henchal, Ph.D.	OVRR
Jerry Weir, Ph. D.	Director, Division of Viral Products
Loris McVittie, Ph.D.	Chief, Viral Vaccine Branch

Name	OPDIDV
Hana Golding, Ph.D.	OVRR, DVP
Anissa Cheung	OVRR/DVP
Laurie Norwood	OCBQ/DMPQ
Chang Syin	OCBQ/DMPQ/BII
Jim Krim	OCBQ/DMPQ/BII

MEETING AGENDA:

1. Identify any issues which would preclude meeting the action due date of 29 September 2007.
2. Bioresearch Monitoring and Facility Inspections

MILESTONE:

Action Due: 29 Sep 2007 (28th September as 29th is a Saturday)

MEETING SUMMARY AND DISCUSSION ITEMS:

CMC ISSUES:

1. ----------
2. ----------
3. ----------

Action Items:

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Product Quality/Lot Release:

4. Rajesh Gupta notified the group that a testing plan draft was under consideration. Joe Quander stated that Product Release Branch had been in touch with CSL to discuss the Lot Release Protocol and what samples need to be submitted.
   Action Items:
   None. Waiting on samples.
   CLINICAL ISSUES:
   Three Main Points from Clinical Review to date:
   - "Pivotal" immune response study met successful endpoints, no safety signals
   - Problems with elderly data: "deep SQ injection", lower immune responses
   - July 17, 2007 BLA amendment: culture confirmation study to begin in Southern Hemisphere in **March 200**9. This does not appear to be due diligence in product development towards full licensure.
5. Introduction
   - CSL manufacturing trivalent inactivated influenza vaccine history:
     - First marketed in 1968 and now authorized in 15 countries.
     - Approximately---------- doses of thimerosal-containing vaccine were distributed globally between 1968 and 2002.
     - thimerosal-free product 2002 registered in 22 countries
     - approximately ---------- doses of thimerosal-free CSL IVV have been distributed globally between 2003 and 2006.
   - approximately one million doses of thimerosal-free pre-filled syringe product and one million doses of thimerosal-containing multidose vial product for launch in the US for the 2007/2008 season.
6. Safety Issues
   - Overall, no significant safety concerns: local and systemic reactogenicity appear similar to other trivalent influenza vaccines.
   - Only 21-day follow-up for pivotal study (our oversight in review of study)
   - There were no deaths or vaccine-associated SAEs in the pivotal study. One case of possible serum sickness, moderate in severity, was attributed to the vaccine in the pivotal study.
   - The post-marketing experience in other countries is approximately ---------- doses distributed since 1968, not very extensive per upper management. We need to confirm these numbers with CSL and request more recent data, e.g., total number of doses distributed over the last 5 years.

7. Immune Response Issues:
- No concerns with immune response results of pivotal study conducted under U.S. IND: appears to have met all Guidance Document criteria for success.
- Lower immune response results among elderly subjects in the supportive studies.
- Studies in elderly administered vaccine "either IM or deep subcutaneous" route
- Tables of immune response results were presented in summary format at the meeting.

8. Preliminary Immune response Conclusions
- Afluria met all six surrogate efficacy endpoints in Adults ≥18 to <65 years of age in the pivotal Phase III study CSLCT-FLU-05-09 conducted under BB-IND---------.
- With the exception of H1N1 in CSLCT-NHF-05-13 in Older Adults, the four supporting non-IND studies conducted in the UK met CPMP endpoints required for licensure in the EU.
- A post hoc analysis of the four supporting non-IND studies examining subjects ≥65 years of age and applying FDA criteria for immunogenicity revealed lower immune responses to both the H1N1 and B strains. These analyses are limited by the small sample sizes of the studies which did not have sufficient power to assess criteria based on confidence intervals rather than point estimates. Nearly identical results were found for the US and EU licensed comparator controls.
- We have a precedent for approval of Flulaval despite failure to meet immunogenicity endpoints in the H1N1 and B strains.
- Other factors which limit our ability to interpret the results of the non-IND studies include the deep subcutaneous route of administration in an uncertain percentage of subjects and the HI assay itself which was not validated for the non-IND studies and which was performed at two different laboratories.
- Another potential factor influencing immune response in the elderly and raised during the meeting was the role of potency calculations. It was suggested that, due to differences in calculating antigen content, less antigen may be used in the EU versus the US manufacturing process. Lower vaccine antigen content could potentially partially account for weaker immune response in the elderly. If this vaccine is approved in the elderly, it would need to be manufactured according to FDA approved specifications and according to our potency calculations.
- Despite the lower immune responses found in the elderly in the non-IND studies, Afluria is a trivalent inactivated influenza vaccine which has been marketed under different trade names by CSL worldwide since 1968 and which the applicant states has a long tradition of efficacy against natural infection. The antibody responses induced by Afluria in the Phase III pivotal trial appear sufficient to reasonably predict clinical benefit in adults ≥18 to <65 years of age with lower responses in the elderly.

9. Postmarketing
- On July 17, 2007 the Clinical Review team received a response from CSL outlining their plans for postmarketing studies which do not represent due diligence:
- October 2008 safety and immunogenicity non-inferiority study to a US-licensed comparator in at risk adults ≥65 years of age to be conducted in the US.

- Feb/March 2009 (Southern Hemisphere flu season) placebo-controlled culture confirmation clinical endpoint study in healthy adults 18 to < 65 years of age to be conducted in Australia and New Zealand.
- Request to defer the pediatric immunogenicity and safety study until after results of the clinical endpoint study are reviewed by CBER and judged to be supportive of vaccine efficacy.
  - These plans were felt to be inconsistent with 21CFR 601.41 regulations for accelerated approval for biological products. CSL was made aware of these regulations in June of 2006 after submitting IND-------- for the pivotal study to the BLA. The group felt that CSL must be encouraged to conduct the culture confirmation study expeditiously.

Action Items:

- CSL to clarify what groups are recommended to receive annual influenza vaccine in Australia.
- CSL to clarify the total number of doses of vaccine distributed since 1968, since 2002, and the countries in which the vaccine is distributed.
- CSL to provide additional immune response data in the elderly if available from older studies conducted for the purpose of annual registration in the EU.
- CSL to clarify differences in methods used to calculate antigen content or potency between the US and the EU which might partially account for lower immune responses elicited by the CSL vaccine. Consider designing a study which uses a higher antigen content or a second booster dose in the elderly.
- Arrange a telecon to discuss the immune response and postmarketing study concerns and in particular to strongly encourage the culture confirmation study to be conducted in the influenza season following approval.

BIMO ISSUES:

Bhanu Kannan reported that two of the BIMO sites have been inspected thus far. As many of the clinical sites were recently inspected due to other BLA licensing processes, the following sites were selected for this BLA.

New Orleans, Duke University and Stanford University.

Action Item: Continue reviewing inspection reports as they arrive.

STATISTICAL ISSUES:

The statistical review is ongoing. There were no outstanding issues of note.
