Chair Memo – AFLURIA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
Division of Vaccines and Related Products Applications

DATE: September 27, 2007

FROM: Rakesh Pandey, Ph.D., DVRPA/OVRR

TO: File of STN 125254/0

THROUGH: Loris McVittie, Ph.D., Acting Deputy Director, DVRPA

RE: Approval Recommendation/File Summary

APPLICANT: CSL Limited

PRODUCT: Influenza Virus Vaccine, Afluria®

I. INTRODUCTION:

CSL Limited submitted the BLA for Influenza Virus Vaccine, Afluria® on March 30, 2007. This vaccine was studied under BB-IND -------- and the pivotal safety and immunogenicity study was conducted under this IND by three NIH clinical study sites. This vaccine is going to be the third inactivated influenza vaccines to be approved under the accelerated approval mechanism that has been used to address the shortage of influenza vaccine in the 2004-2005 season, as the number of inactivated influenza vaccine manufactures in US had dropped down to two and with one of them not being able to supply the vaccine due to GMP problems in their facility, the vaccine supply was limited to only one manufacturer. US Govt. and HHS took several steps to boost the vaccine supply in US and encouraged new manufactures to introduce products in US that were licensed in Europe and in other countries. Afluria® has been made by CSL since 1968 and has been licensed in Australia, New Zealand and several other countries around the globe. They market only single dose product that does not contain any preservative in the rest of the world, however due to demand in US for multi-dose vials, decided to introduce both a preserved multi-dose and unpreserved single dose presentation in US. Once they get the license, CSL Limited will be the 6th manufacturer of influenza vaccine for the US market.

Influenza Virus Vaccine, Afluria®, is an inactivated influenza vaccine produced in chicken eggs. It contains hemagglutinin antigen from three influenza strains in circulation during previous influenza seasons and which are those recommended yearly by the WHO, FDA (VRBPAC), and CDC for the Northern Hemisphere. A

summary review of information contained in the BLA is presented in the following sections.

Vaccine Information

Afluria® (Influenza Virus Vaccine) is a sterile, aqueous suspension of inactivated and split influenza virus subtypes A and type B. The virus is purified, inactivated and disrupted to ensure the hemagglutinin (HA) and neuraminidase (NA) antigens remain immunogenic. It is prepared from the allantoic fluid of influenza virus-infected embryonated chicken eggs. The vaccine is supplied in two presentations, a thimerosal-free 0.5 mL single-dose pre-filled syringe and a thimerosal-containing 5 mL multi-dose vial and is administered intramuscularly as a 0.5 mL dose. The proposed indication is for "active immunization to prevent influenza disease caused by influenza virus subtypes A and type B present in the vaccine in adults 18 years and older". Afluria® is formulated to contain the ingredients shown in Table 1. contains thimerosal as preservative. Residual substances that could be present in the vaccine are listed in Table 2. No substances of human origin are used. No adjuvants are used in this product.

DRUG SUBSTANCE:

The Drug Substance, Monovalent Pooled Harvest (MPH), is a sterile, inactivated, aqueous suspension of an influenza virus strain (type A or B). Influenza Virus Vaccine, Afluria® consists of the inactivated, detergent split, monovalent bulks of influenza subtypes A/H1N1 and A/H3N2, and type B. The vaccine produced for 2007-2008 consists of the three strains recommended by the USPHS for the upcoming influenza season. The three strains are grown separately in eggs to produce monovalents that are inactivated by Beta-Propiolactone (BPL) and are split by treatment with sodium taurodeoxycholate (TDOC). For subtype A/H1N1 strain, IVR-145 (A/ Solomon Islands/3/2006 (H1N1)-like virus) was derived from a mixed infection between A/ Solomon Islands/3/2006 and high yielding strain IVR-6 (A/Texas/1/77(H3N2), and contains H1 and N1 from A/ Solomon Islands/3/2006. For subtype A/H3N2 strain, NYMC X-161B (A/Wisconsin/67/2005-like virus) was derived from a mixed infection between A/ A/Wisconsin/67/2005 and high yielding laboratory strain A/PR8 (H1N1), and contains H3 and N2 from A/Wisconsin/67/2005. Similarly, for type B strain, B/Malaysia/2506/2004 reference strain virus was derived from WHO center, and contains HA and NA of B/Malaysia/2506/2004.

Table 1. Composition of Influenza Virus Vaccine - Thimerosal Containing

Names of Ingredient	***Nominal Amount per Dose (0.5 mL)***	***Function***	***Compendial Reference***
Active Ingredients			
Influenza virus type A and B, inactivated and disrupted	≥ 15 mcg HA per strain	Immunogen	Complies with USP monograph *Influenza Virus Vaccine*
Excipients			
Sodium chloride [b]	4100 mcg	Maintains tonicity	Complies with USP
Dibasic sodium phosphate [b]	300 mcg	Buffer	Complies with USP
Monobasic sodium phosphate [c]	80 mcg	Buffer	Complies with USP
Potassium chloride [d]	20 mcg	Buffer	Complies with USP
Monobasic Potassium	20 mcg	Buffer	Complies with *Ph. Eur*.

Names of Ingredient	*Nominal Amount per Dose (0.5 mL)*	*Function*	*Compendial Reference*
Phosphate [d]			
Calcium chloride [d]	1.5 mcg	Buffer	Complies with USP
Water for Injection	To 0.5 mL	Solvent	Complies with USP
Thimerosal	0.01% w/v	Preservative	21CFR § 610.15(a)

[a] Based on target fill volume.

[b] ----------

[c] The salt concentration of the Vaccine Diluent is diluted when combined with MPH.

[d] This component is not a true excipient, but is present in the drug product as a component of the drug substance (MPH). ----------

Physicochemical Properties

Physical State

Appearance

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pH

Biological Activity

Quantity/Potency

Sedimentation (HA Ag) Profile

Strain identity

Purity

Sterility

Residual infectious virus

Consistent with expected strain

Complies with USP <71> for sterility

Substances of Animal Origin

CSL has indicated that no substance of human and animal origin have been used for either of the two (Thimerosal-free or Thimerosal containing) formulations. Only NaTODC is derived from cholic acid which is of bovine origin. TDOC is manufactured from cholic acid derived from bovine bile and is sourced from a CSL approved supplier (Australian origin). Each lot is supplied with a Certificate of Analysis, which must comply with CSL specifications and confirm that the lot meets the requirements of the European TSE (Transmissible Spongiform Encephalopathies) Certificate of Suitability.

Product development

The most significant change in manufacturing of this product in the last several years, except for the annual updates of the strain composition, has been---------- For the current 2007-2008 season they have introduced a preserved formulation for the US market, which requires addition of thimerosal as a preservative in the final formulation. They have also included data in the submission to demonstrate the effectiveness of thimerosal as a preservative and demonstrated that up to 28 days since the first dose has been withdrawn, the product remains sterile and usable.

II. SUBMISSIONS AND REVIEW ACTIVITIES

Afluria® BLA (STN 125254) was submitted March 30, 2007 as a paper submission in CTD format. Clinical data was provided as ---------- on CD-ROM and labeling was provided in electronic format as well, to facilitate CBER review. This vaccine BLA was not discussed at any VRBPAC meeting as this accelerated approval was on the similar lines as to two other influenza vaccine BLAs and the clinical decision is based on immunogenicity endpoint as a surrogate for vaccine effectiveness. Under the provisions of accelerated approval regulations, the sponsor will be conducting clinical studies with culture confirmed influenza as the clinical endpoint to demonstrate efficacy. Such data will be used to support a clinical efficacy supplement for traditional approval.

Attachment 1 provides a listing of the amendments submitted to the BLA and a listing of selected submissions and meetings that took place before BLA submission.

CBER REVIEW:

Regulatory review of the application was provided by Katherine Berkhousen and Rakesh Pandey. Edward Wolfgang also provided assistance with regulatory review towards the end of the review cycle. Pankaj (Pete) Amin and J. McInnis reviewed establishment sections of the BLA. Galina Vodeiko provided the review of the CMC section of the BLA and Carolyn Renshaw provided a consult review of the Mycoplasma testing related sections. Zhiping ye provided feedback on issues related to ------- potency testing and other issues related to testing of the product. Alfred. Del Grosso, Nora Etz, Christine Anderson, and Rajesh Gupta conducted review of the lot release testing methodologies and various analytical procedures used. Cynthia Nolletti and Joseph Toerner reviewed clinical studies with review of the clinical serology assay provided by Galina Vodeiko and Lev Sirota. Tammy Massie conducted statistical review of the data sets. Bhanu Kannan was Bioresearch Monitoring (BiMo) reviewer and coordinated the study site inspections. Catherine Miller reviewed advertising and promotional labeling and the tradename. J. Quander evaluated format and suitability of test reports in the lot release protocols.

Clinical Studies:

The recommendation for accelerated approval of Influenza Virus Vaccine, Afluria® by the clinical reviewers is based on the demonstration of efficacy by a surrogate endpoint: the immune response following administration of Influenza Virus Vaccine, Afluria®. A randomized, placebo-controlled, double-blinded study showed that subjects randomized to receive Influenza Virus Vaccine, Afluria® had immune response criteria that exceeded the pre-defined successful endpoints. While there are no known correlates of immune protection for influenza, these pre-defined immune response criteria have a reasonable likelihood of predicting clinical efficacy. There were no patterns of unusual safety concerns associated with administration of Afluria®.

Therefore, the potential benefits of administration of Influenza Virus Vaccine, Afluria® are balanced against the potential risks. With this accelerated approval, the availability of an additional trivalent influenza vaccine provides meaningful benefit in the setting of potential shortages of influenza vaccine. The license application contained safety and immune response data from three other non-U.S. studies, which included 246 adults greater than or equal to 65 years of age. Post-hoc analyses demonstrated acceptable safety characteristics and favorable immune response data in the geriatric population greater than or equal to 65 years of age.

The applicant has agreed to conduct a clinical endpoint efficacy study in 18-65 year old subjects that will confirm the efficacy of the vaccine as supported by the surrogate endpoint of immune response. As well, the applicant will conduct a study to compare immune responses among adults who receive Influenza Virus Vaccine, Afluria® versus other trivalent inactivated vaccines licensed in the United States. Finally, the applicant plans to pursue development of Influenza Virus Vaccine, Afluria for use in the pediatric population. Although pediatric studies will be deferred, as defined under Pediatric Research Equity Act the applicant will be required to complete clinical development in the pediatric population with due diligence and has already committed to conduct such studies.

The following bullets from the clinical reviewer's executive summary provide a summary description of the clinical data included in this BLA in support of this application:

- *The trivalent inactivated split virion egg-based influenza vaccine Afluria (CSL IVV) should be approved for the active immunization against influenza disease caused by influenza subtypes A and type B contained in the vaccine in adults 18 years of age and older. The recommendation for accelerated approval is based on demonstration of efficacy by a surrogate endpoint: the immune response following administration of CSL IVV. A randomized, placebo-controlled, double-blinded pivotal Phase III study showed that 1077 healthy adults randomized to receive CSL IVV had immune responses that exceeded the pre-specified immunogenicity endpoints. While there are no established correlates of immune protection for influenza, these pre-defined immune response criteria have a reasonable likelihood of predicting clinical efficacy. There were no patterns of unusual safety concerns associated with administration of CSL IVV. Other European studies provided additional immunogenicity and safety data following administration of CSL IVV that support this approval. Therefore, the potential benefits of administration of CSL IVV are well-*

balanced against the potential risks. With this accelerated approval, the availability of an additional trivalent influenza vaccine provides meaningful benefit in the setting of established shortages of influenza vaccine.

- *The license application also included safety and immune response source data from four adult studies conducted in the United Kingdom. These studies enrolled 652 subjects that received CSL IVV, 343 of which were 65 years of age or older. Post hoc analyses from active controlled studies demonstrated that immune responses to CSL IVV were acceptable in the geriatric age group. Two small uncontrolled open-label studies revealed lower immunogeniciy in the geriatric population. However, two active controlled studies showed similar immune responses between CSL IVV and the comparator influenza vaccine among subjects 65 years of age or older, and immune response data from studies of three other U.S. licensed trivalent influenza vaccines have also demonstrated lower immune responses in the elderly. Therefore, additional immune response data support an extension of the approved indication to adults 65 years of age and older.*
- *The application's overall safety database included source data from 1089 healthy adults in the pivotal study and 652 older adults, 343 of whom were 65 years of age or older, from the UK studies. To enhance the safety database, the applicant provided a small uncontrolled open-label pediatric study as well as an integrated analysis of safety data from 23 older studies in adults conducted in Australia, for a total safety database of 4156 CSL IVV recipients. There were no new safety concerns identified on review of these data or in the review of more recent post-marketing spontaneous adverse event reports. A post hoc analysis of the 65 years and older population from the four supporting non-IND studies did not reveal safety issues unique to this age group.*
- *There were no apparent differences in safety or immunogenicity between the thimerosal-free and preservative-containing formulations.*
- *The proposed dosing regimen is a single 0.5mL dose, containing 15µg of influenza antigen for each of the three vaccine strains, administered intramuscularly in the region of the deltoid muscle of the upper arm.*
- *Overall, the methodology, integrity of the data, and results of the safety and immunogenicity assessments support approval of the license application.*
- *The applicant has committed to conduct postmarketing studies in healthy adults to demonstrate efficacy against culture-confirmed influenza illness as supported by the surrogate endpoint of immune response. The applicant will also conduct a non-inferiority study of Afluria against a U.S. licensed trivalent influenza vaccine in the geriatric population. Finally, the application included source data from an uncontrolled study of 298 children which revealed satisfactory immune response and safety parameters. The applicant will pursue its pediatric development plan as required under the Pediatric Research Equity Act with two postmarketing pediatric studies, one open-label and one non-inferiority, to be conducted with due diligence.*

The *summary* above was copied from the clinical reviewer's executive summary.

Statistical Review:

Dr. Tammy Massie reviewed the statistical part of the BLA provided as --------- datasets. Her analyses of the electronic datasets revealed results and trends similar

to those of CSL. The Statistical Review supports approval of Afluria in adults 18-65 years of age, but has concerns relating to lower immune responses in the elderly. The Clinical Review has addressed these concerns as the indication agreed is in persons 18 years of age and above.

Hemagglutination Inhibition (HI) Assay:

The evaluation of pre- and post-immunization anti-hemagglutinin titers in sera was measured in a HI assay. The HI assay measures the neutralizing antibodies that interfere with attachment of viruses to chicken red blood cells. The SOP and validation report for the HI assay were provided for our review. The validation of the study met the descriptive acceptance criteria and was supportive of a robust reproducible assay. The assay was also found to be well controlled and reproducible. Detailed review memos from Drs. Lev Sirota and Galina Vodeiko have been included in the approval package.

Pharm-Tox:

The BLA did not contain a pre-clinical pharm-tox data or nonclinical study reports on the components of the trivalent influenza vaccine. CSL has supplied the vaccine since 1968, before the introduction of nonclinical safety/toxicology requirements. At the pre-IND meeting between CBER and CSL held on February 22, 2005, it was agreed that no specific pre-clinical studies were required for this vaccine licensure.

Bioresearch Monitoring:

Review of the conduct of the clinical studies and the inspection of three clinical study sites were performed. Inspection close-out letters were issued for two of these sites. Results of these investigations confirmed that all three sites were acceptable. Details can be found in BiMo reviewer Bhanu Kannan's memo.

Labeling:

Tradename Afluria was found to be acceptable and there is a memo from Ms. Catherine Miller on this topic. Labeling including carton and container labels and the package insert were reviewed and a series of revisions were submitted to the BLA. The current versions are acceptable for the approval of the BLA. Final drafts of the labels have been submitted to the BLA and the approval package.

Chemistry, Manufacturing, and Control (CMC)

Since 1968, various modifications to the manufacturing method have been made including:

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2.----------
3.----------
4.----------

5. --

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Facilities:

The table below lists all the facilities and their role. Production of Afluria® up to and including manufacture of MPH and formulation of bulk vaccine (FBV) will be performed at the CSL Limited production site in Parkville, Australia. --------
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Table 2.3.P.3.1-1: Manufacturing Facilities

Manufacturer **Building (if relevant)**	**Production step**
CSL Limited 45 Poplar Road, Parkville 3052, Victoria, Australia	
IVV Manufacturing Facility (dedicated facility)	Manufacture of Drug Substance to FBV, including Formulation of FBV
CSL---------- --- ----------	
----------	Dispensing of FBV to DVB Packaging and labeling of DVB to Finished Vaccine
----------	Dispensing of FBV to DVB Packaging and labeling of DVB to Finished Vaccine
---------- ----------, ---------- ---- ---------- Or ---------- ----------, ---------- ---- ----------	Storage of Finished Vaccine prior to distribution

Jonathan McInnis and Pete Amin reviewed the faculties related part of the BLA and divided the review into upstream processing and downstream processing part. The split was done on the lines of two inspections where the manufacturing of the bulks takes place in Parkville Australia and the filling and packaging operations are conducted in ----------. Both of these reviewers have provided separate review memos for the file that are included in the approval package. No manufacturing issues have come up that have not been resolved at this time.
As part of the review of BLA STN 125254, the facilities at Parkville Australia and ------, ---------- were inspected and all establishment issues, including those noted in Form 483 have been adequately resolved and these inspections have been closed out. There is a separate inspection Tab in the approval package that contains all the details related with inspectional issues.

Environmental Assessment

CSL Ltd. claimed a categorical exclusion to the environmental analysis requirements in accordance with 21 CFR Part 25.31(c). CSL indicated that there are no extraordinary circumstances, as described in 21 CFR Part 25.31, associated with this action. No potential adverse environmental impact is expected from the manufacture and use of Influenza Virus Vaccine, Afluria®. CBER found the request for the categorical exclusion acceptable.

Issues Resolved During the Review:

- ---------- ----- On CBER's request, CSL agreed to test every lot for marketing for BPL using the existing test they had and demonstrated that it could not be detected. ----------
- For the General Safety test, initially they did not meet the CFR 610.11a requirement since they did not use the E2 reference standard for endotoxin testing. CBER pointed this out and provided the necessary reagent. CSL instituted the E2 in their testing and provided the results of testing that was satisfactory and they met the requirement. They have modified the Lot Release protocol to include the E2 standard and are committed to follow the CFR in future and the issue is resolved.
- There were a couple of minor issues related to testing for Thimerosal and TDOC ----------
- CSL was also using a different procedure for ---------testing from what CBER used. They had their own validated procedure and a different version of CBER method that they were using. This issue was brought to the attention of CSL ----------
- ----------

IV. **RECOMMENDATION:**

The BLA committee reviewed all sections of the application and the amendments. All outstanding issues for the BLA have been resolved and agreement has been reached

on specific requirements for post-marketing commitments. The committee recommends approval of Influenza Virus Vaccine, Afluria®.
The final indication is: Afluria® is an inactivated influenza virus vaccine indicated for active immunization of adults 18 years of age and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. This indication is based on the immune response elicited by Afluria®; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with Afluria®.
Afluria is an inactivated seasonal vaccine that is being approved under accelerated approval mechanism and is not adjuvanted. Due to its long history of use in humans, CBER had agreed during the pre-BLA meeting that no pre-clinical toxicity studies will be required, however, like any other influenza vaccine, before its traditional approval the sponsor will have to conduct and provide the data from a repro-tox study in animals. We reviewed CSL's request for a partial waiver for the pediatric age group birth to 6 months of age. We decided to defer pediatric studies until June 30, 2010, as CSL is pursuing with due diligence a pediatric indication for Afluria®. We will re-evaluate the request for a waiver for children less than 6 months of age upon submission of the data from post marketing studies in pediatric populations. Although the pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are deferred, the deferred status of these required postmarketing studies will have to be reported as such annually according to 21 CFR 314.81.

Attachment 1. Post-Marketing Commitments

Clinical Studies

CSL Limited commited to the following post marketing studies.

1. **Effectiveness**

1.1 Clinical Endpoint Efficacy Study in a Healthy Adult Population

CSL Limited agrees to conduct Study No. CSLCT-USF-06-28, a placebo-controlled clinical endpoint efficacy study and six-month safety study of CSL Limited's Influenza Virus Vaccine in adults 18 to less than 65 years of age in whom vaccination is not universally recommended. The final protocol for this study will be submitted by October 12, 2007. This study will be conducted during the influenza season following the accelerated approval in the Southern Hemisphere. The study will start by March 31, 2008. If the influenza attack rate is lower than expected, participant enrollment will be extended to a second season. The final study report for the first season will be submitted by June 30, 2009; a final study report for the second season, if the study will be extended to a second season, will be submitted by June 30, 2010.

2. **Additional Studies to Support the Effectiveness of the Vaccine in Populations Not Included in the Clinical Efficacy Study**

2.1 Non-inferiority Study in Adult Population 65 years and older

CSL Limited agrees to conduct Study No. CSLCT-USF-07-41 a non-inferiority immunigenicity and safety study with CSL Limited's Influenza Virus Vaccine and a US Licensed Trivalent Inactivated Split-Virion Influenza Vaccine in an at risk population of adults 18 years and older who have chronic medical conditions placing them at risk for complications of influenza or who otherwise fall into groups for whom yearly influenza vaccination is recommended. The final protocol

for this study will be submitted by April 1, 2008. This study will start by October 1, 2008. The final study report will be submitted by June 30, 2010.

2.2 Safety and Tolerability Study in Pediatric Population

CSL Limited agrees to conduct Study No. CSLCT-USF-06-29, an uncontrolled, open-label, safety and tolerability study of CSL Limited's Influenza Virus vaccine in a pediatric population ages 6 months to less than 18 years. The final protocol for this study will be submitted by August 1, 2008. This study, conducted in the Southern Hemisphere, will start by March 31, 2009. The final study report will be submitted by June 30, 2010.

2.3 Non-inferiority Study in Pediatric Population

CSL Limited agrees to conduct Study No. CSLCT-USF-07-36, a non-inferiority immunogenicity and safety study with CSL Limited's Influenza Virus Vaccine and a US Licensed Trivalent Inactivated Split-Virion Influenza Vaccine in a pediatric population from 6 months to less than 18 years of age. The final protocol for this study will be submitted by April 1, 2009. This study will commence in North America and will start by October 1, 2009. The final study report will be submitted by June 30, 2010.

The clinical protocols for these studies will be submitted to BB-IND --------, with a cross-reference letter to this Biologics License Application (BLA), STN 125254/0.

3. Postmarketing Commitment Annual Report

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, CSL Limited will describe the status in an annual report on postmarketing studies (PMC Annual Report) for this product. The status report for each study will include:

i. *information to identify and describe the postmarketing commitment,*
ii. *the original schedule for the commitment,*
iii. *the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted), and*
iv. *an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment).*

1
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Attachment 2. Submission History

Table 1. Summary of Amendments Submitted to BLA STN 125254

Subm. #	Subm. Date	Contents
0	3/30/07	Original BLA submission in paper CTD format
1	5/2/07	Response to CBER request for electronic copies of the six clinical study reports contained in the BLA
2	5/1007	Response to CBER request for clarification of ------ data sets submitted to the file
3	5/15/07	CSL request for a waiver for using the VAERS-1 Form and instead to use the FDA Form 3500A for adverse event reporting
4	6/29/07	Response to CBER June 13, 2007 telecon/fax requesting additional clinical and chemistry information
5	6/29/0707	Response to CBER June 25, 2007 telecon/fax and requesting CSL to provide the definition table for clinical study CSLCT-FLU-05-09 medical history for the electronic files and xport format
6	7/6/07	Response to CBER June 29, 2007 telecon/fax requesting clarification of clinical concerns and CMC discrepancies and request for reports
7	7/25/07	483 response: Submitted as result of Parkville, Australia facility inspection
8	8/1/07	Response to CBER 7/6/07 telecon/fax request to provide batch records for the new strain A/Solomon Islands and the updated stability data for final product
9	8/707	Response to CBER 7/30/07 telecon/fax request. CSL addresses item #1 of this telecon/fax and provides their post marketing commitment draft plans
10	8/8/07	Response to CBER telecon/fax request dated 7/6/07 to submit ------ each of the first five lots of each strain used in the manufacture of influenza virus vaccine
11	8/8/07	Response to CBER request (telecon dated7/30/07) to items 2, 3 and 4. Item #1 was addressed in 125254/0/9
12	8/10/07	Response to CBER request (telecon dated 8/9/07) to clarify clinical data located in one of the pediatric study tables
13	8/17/07	Response to CBER request (telecon dated 8/15/07) clarification of summary data table in pediatric study CSLCT-FLU-04-05.
14	8/22/07	Response to CBER request (telecon dated 8/3/07) regarding clarification of the----assay used by CSL
15	8/27/07	CSL response to the discussions held during the 8/9/07 telephone conference with CBER. CSL provides a detailed protocol synopsis for their post marketing commitment clinical efficacy study
16	8/27/07	CSL provides the revised package insert based on CBER comments of 8/21/07
17	8/27/07	CSL provides revised container and carton labels for the multi-dose vial and pre-filled syringes based on CBER comments of 8/22/07
18	8/31/07	Response to CBER request (telecon/fax dated 8/20/07) regarding CMC analytical procedure concerns
19	8/30/07	CSL provides a copy of the detailed protocol synopses for the post marketing commitment adults ≥ 65 years and pediatric study populations as discussed in the 8/9/07 telephone conference with CBER
20	9/7/07	Revised PI with response to CBER's 31 Aug 07 comments
21	9/10/07	Consistency data for conformance lots
22	9/11/07	Response to 24 Aug 07 request to amend LRP protocols
23	9/14/07	Revised Package Insert with comments
24	9/14/07	Response to Information Request: Standard Operating Procedure TSOP.119.057

Subm. #	Subm. Date	Contents
		regarding HI assay
25	9/17/07	Response to request for CMC postmarketing commitments
26	9/18/07	Provision of Completed (updated) MPH Results Protocols
27	9/24/07	Revised CMC postmarketing commitments
28	9/24/07	Final draft package insert
29	9/21/07	Revised clinical post marketing commitments (telecon 9/19/07).
30	8/20/07	483 response: Submitted as result of ---------- facility inspection
31	9/26/07	Lot Release Protocol Template
32	9/26/07	Final CMC post marketing commitment in response to IR on 9/26/07

Previous Administrative History (selected dates before submission of STN 125254)
February 22, 2005 Pre-IND meeting with CSL for Afluria
April 10, 2006 IND ---------- submitted to conduct clinical study CSLCT-FLU-05-09
August 3, 2006 Facilities meeting with CSL for Afluria
February 9, 2007 Pre-BLA meeting to discuss accelerated BLA for Afluria.

8
PAGE(S)
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Study CSLCT- FLU-05-09 was a pivotal clinical study evaluating both the thimerosal-free formulation in pre-filled syringes and the thimerosal-containing formulation in multi-dose vials. All lots were manufactured at pilot scale and data was generated for both FBV and DBV.
Study CSLCT- NHF-05-15 was an additional clinical study evaluating only the thimerosal-free formulation in pre-filled syringes. The vaccine was manufactured at commercial scale for supply to the UK and data was generated for both FBV and DBV.

Preserved Lots used for Clinical Study CSLCT-FLU-05-09

Clinical Study Lots	FBV Batch Number	DVB Lot Number
#1	556040N07	556041N13
#2	556040N08	556041N14
#3	556040N09	556041N15

Final Bulk Vaccine Release Testing Results for preserved lots used in the Pivotal Clinical Study (Study No. CSLCT-FLU-05-09)

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11
PAGE(S)
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