Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Subject: Afluria Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC) Meeting — September 22, 2011

Sponsor: CSL Biotherapies

Product: Afluria, influenza virus vaccine (split virion)

1. INTRODUCTION

On 28 September 2007, Afluria was licensed under FDA's accelerated approval pathway for serious and life-threatening diseases to become the sixth influenza vaccine licensed in the United States.[1] Initially approved for use in persons aged ≥18 years, FDA expanded the use of Afluria to children aged ≥6 months on 10 November 2009. This expansion into the pediatric population is the regulatory trigger for the pediatric safety review and utilization that is the subject of this memorandum.

This Pediatric Advisory Committee (PAC) postlicensure safety review is complicated by several factors:

(a) The timeline of events spans multiple countries and government agencies.
   a. Regulatory agencies:
      i. US FDA
      ii. Australian Therapeutic Goods Administration (TGA)
      iii. New Zealand Medicines and Medical Devices Safety Authority (Medsafe)
   b. Advisory agencies and committees:
      i. US Advisory Committee on Immunization Practices (ACIP)
      ii. Australian Technical Advisory Group on Immunisation (ATAGI)
      iii. New Zealand Ministry of Health

(b) The review involves three influenza seasons that extend beyond the typical one year PAC review.
   a. 2009–2010 northern hemisphere (NH) influenza season
   b. 2010 southern hemisphere (SH) influenza season
   c. 2010–2011 NH influenza season

(c) There are multiple vaccine names and manufacturers.
   a. CSL's trivalent influenza vaccine is named Afluria in the NH, and Fluvax in the SH; the 2010 SH Fluvax was antigenically equivalent to the 2010-2011 NH Afluria vaccine.
   b. CSL's monovalent H1N1 is named Panvax and is an important comparator because it was distributed and administered in the same time period and population as Fluvax
   c. Vaxigrip (Sanofi Pasteur) and Influvac (Solvay Pharmaceuticals) were the only other trivalent influenza vaccines used in the 2010 SH influenza season

(d) Recommendations for use by advisory bodies differ from the product label's indicated use

1.1 Timeline of Major Events Related to Afluria Vaccine Safety, 10 Nov 2009 – 31 July 2011

Date		Decision
28 Sep 2007		FDA approves Afluria for adults aged 18 years of age and older
10 Nov 2009		FDA approves Afluria for children aged 6 months through 17 years
24 Feb 2010		ACIP recommends Afluria for persons aged 6 months and older (becoming effective for the subsequent 2010–11 season)
19 Mar 2010		Official launch of the seasonal influenza vaccination program in Western Australia (WA)
31 Mar 2010		First cluster of reports of febrile convulsions received by Western Australia public health authorities
22 Apr 2010		WA Minister for Health announces suspension of the WA influenza vaccination program for children <5 years of age following advice from an expert group convened by WA Health

23 Apr 2010		Australia's Chief Medical Officer (CMO) announces temporary suspension of national influenza program among children aged <5 years
27 Apr 2010		New Zealand's Ministry of Health recommends against the use of Fluvax in children aged <5 years
30 Jul 2010		• FDA updates the Warnings and Precautions section of the US prescribing information to inform healthcare professionals that the Afluria vaccine has been associated with an increased incidence of fever and febrile seizure among young children reported in the southern hemisphere, mainly among those less than 5 years of age. • FDA also requires CSL to conduct a clinical trial to evaluate febrile reactions among children aged 5 to 9 years. • Australia's CMO announces the resumption of use of the 2010 trivalent seasonal influenza vaccines of either Influvac (Abbott/Solvay) or Vaxigrip (Sanofi Pasteur) in children less than 5 years of age.
5 Aug 2010		ACIP modifies Afluria's recommended use, stating that Afluria should not be used in children aged <9 years, unless the child has a medical condition that increases the child's risk for influenza complications and no alternative vaccine is available
26 Oct 2010		TGA restricts approved use to persons aged ≥5 years and issues boxed warning regarding febrile reactions in SH 2010 in the Fluvax product information
7 Mar 2010		Australia's ATAGI recommends against use of Fluvax in children <5 years. ATAGI also issues a strong preference that Vaxigrip or Influvac be used in children under the age of 10 years, and that Fluvax can be used in children 5 to less than 10 years when no timely alternative vaccine is available[2]
22 Dec 2010		CSL requests to be released from required clinical trial to evaluate febrile reactions among children aged 5 to 9 years
23 Feb 2011		FDA releases CSL from required clinical trial to evaluate febrile reactions among children aged 5 to 9 years
15 Jul 2011		FDA restricts approved use for Afluria to children aged ≥5 years

LEGEND

FDA action **ACIP action**

2. OBJECTIVES

This targeted postlicensure safety review for Afluria covers the time period from 10 November 2009 – 31 March 2011. There are three main objectives:

(a) Review the major safety issue that has arisen during this PAC review period: the association between febrile seizures and CSL Fluvax identified in the southern hemisphere 2010 influenza season

(b) Review the postmarketing safety data for two northern hemisphere influenza seasons (2009–2010 and 2010–2011) to:

   a. Determine whether any new safety concerns have emerged as a result of extending Afluria's approved use into the pediatric population

   b. Determine whether febrile seizures was also associated with Afluria during the 2010–2011 influenza season

(c) Ensure that the prescribing information accurately reflects the current safety data

(d) Review the current safety monitoring plans for Afluria

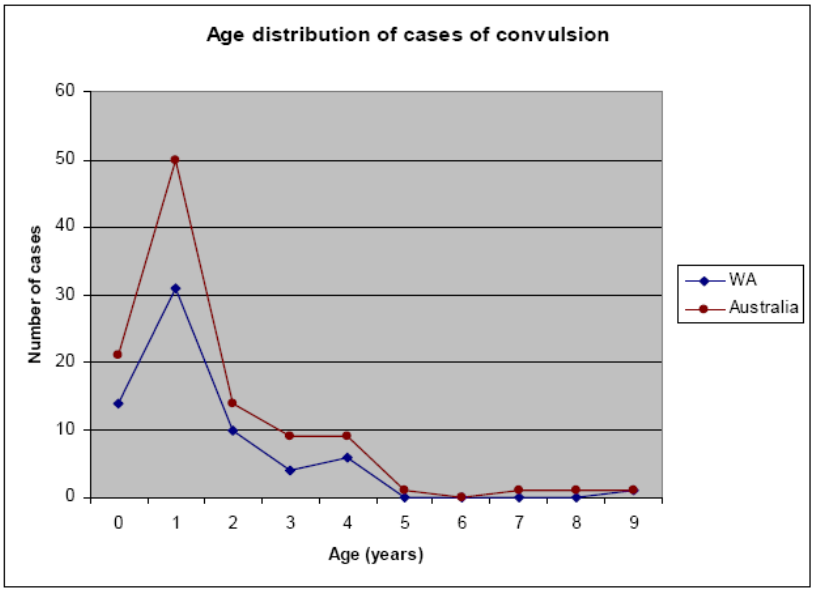
3. FEBRILE SEIZURES AFTER THE 2010 SOUTHERN HEMISPHERE CSL FLUVAX VACCINE

3.1 Overview: CSL Fluvax, Panvax and Afluria

During the 2010 southern hemisphere influenza season, CSL's Fluvax vaccine was associated with an elevated rate of febrile seizures and febrile reactions within the first 24 hours after vaccination among children aged 6 months to <5 years.[3,4] Using a variety of methods, postmarketing surveillance from the TGA estimated that the overall rate of febrile seizures was up to 9 per 1,000 doses (up to 1 in every 110 doses), significantly higher than historical passive surveillance rates.[5] No safety concerns were identified for the other trivalent and monovalent influenza vaccines distributed in the southern hemisphere, including CSL's H1N1 vaccine (Panvax). This safety concern was relevant to the United States because the 2010 SH CSL Fluvax vaccine was antigenically equivalent to the 2010-2011 NH CSL Afluria vaccine.

The figure below shows the age distribution of passive surveillance reports of febrile convulsion after Fluvax vaccination to the TGA from Western Australia and nationally.

Figure 2 Age distribution for reports of convulsion on database at 7 May 2010



Source: Overview of vaccine regulation and safety monitoring and investigation into adverse events following 2010 seasonal influenza vaccination in young children. http://www.tga.gov.au/safety/alerts-medicine-seasonal-flu-101008.htm (Accessed July 21, 2011)

3.2 Epidemiologic studies for fever and febrile convulsions after Fluvax

Several epidemiologic analyses were undertaken by TGA and ATAGI to investigate the excess rates of fever and febrile convulsions after Fluvax.[3,4,6]

Fever

- Uncontrolled cohort study, Western Australia:
  - Children aged <3 years: 40–50 per 1,000 doses of Fluvax, compared to 5 per 1,000 doses of Influvac
  - Children aged 3 to <5 years: Rates after Fluvax were 10 – 20 fold higher compared to Influvac

- Retrospective cohort study from three hospitals in New South Wales found that fever was reported in 46% of children who received Fluvax, compared to 16% after Panvax and 7% after Influvac. Parents did not know the brand of influenza vaccine administered when reporting fever in this study.

Febrile seizures

- Nationwide passive surveillance (susceptible to stimulated reporting and other limitations): 5–7 per 1,000 doses of CSL Fluvax, compared to 0.08 – 0.017 per 1,000 doses CSL Panvax monovalent H1N1 vaccine
- Uncontrolled cohort study, Western Australia:
    - Children aged <3 years: 7–10 per 1,000 doses of Fluvax, compared to 0 cases after 1,450 doses of Influvac
    - Children aged 3 to <5 years: 1.5–14 per 1,000 doses of Fluvax, compared to 0 cases after 1,800 doses of Influvac
- Controlled cohort study using denominator data inferred from 2009 Australian Childhood Immunisation Register (ACIR) showed 5 times the risk of febrile seizure compared to unvaccinated children 6 months to <3 years.
- Time series data from Western Australia (WA) showed a marked increase in ED visits for febrile convulsions following the start of the WA vaccination program on 8 March 2010, no presentations on Sundays or over the Easter holiday period (when physicians offices are typically shuttered) and a prompt return to baseline following the cessation of the WA vaccination program on 22 April 2010.

3.3 Conclusions from TGA's Epidemiologic and Clinical Investigation

The TGA concluded that no clinical or epidemiologic factors offered a plausible explanation for the observed events for the following reasons.[3]

- The adverse events do not represent a new clinical entity. The clinical pattern of vaccine-associated febrile convulsions was similar to non-vaccine-associated febrile convulsions, and was also consistent with historical experience.
- Fluvax was implicated in all passively reported cases of febrile convulsion with a known brand name. Of these cases, 21 different batches were identified and 2 batches accounted for >50% of the reported cases.
- The presence of respiratory symptoms was less common ($p < 0.001$) in vaccine-associated febrile convulsions compared to non-vaccine convulsions.
- The short interval between onset of febrile reactions postvaccination (mean 7.2 hours, range 5.9–8.4 hours) suggested that infection was not the likely causal factor.
- There was no evidence of a vaccine "priming effect" since only 30% of vaccine-associated febrile convulsions had received influenza vaccine the previous year. Additionally, re-examination of clinical trial data showed that baseline seropositivity to H1N1 was associated with significantly lower likelihood of febrile response to vaccination.

3.4 TGA Inspection of CSL Manufacturing Facilities

As part of the investigation into the excess rates of febrile reactions, TGA conducted extensive and detailed audits of CSL's manufacturing facilities on May 12–13, 2010 and also on June 18, 21 and 23, 2010.[3,7-9] The audit covered the full manufacture of influenza vaccines from seed lot to filling of vials and syringes. Based on findings from these two TGA audits, combined with information from a April 2010 FDA audit, the TGA concluded that no manufacturing deficiency was identified that would explain the higher rates of febrile reactions after CSL Fluvax vaccination.

3.5 TGA and WA Laboratory Investigations

TGA conducted an extensive laboratory investigation and testing of batches of Fluvax vaccine, as described below. The investigation detected excess neuraminidase enzyme activity that may contribute to the increase in febrile reactions. Although the different brands of seasonal influenza all contain antigenically equivalent viral strains, differences in manufacturing may result in different levels of

neuraminidase activity. TGA states that this working hypothesis requires additional studies to confirm whether higher neuraminidase activity is the true cause of the excess rates of febrile reactions observed after the 2010 CSL Fluvax vaccine.[3]

Evaluation	Rationale	Results
Potency	Hemagglutinin is the vaccine's main antigenic determinant and high amounts can contribute to increased pyrogenicity.	Passed
Bacterial contamination	Endotoxin is present during the manufacture of influenza vaccines and maximum levels have been set for residual endotoxin (100 EU/dose).	Passed. Max detected was <6 EU/mL
Contaminants and chemical profile	Residual processing agents are present in trace amounts of the final product. Because the same production methods are used each year, the chromatographic profile of different batches within a given year and between years can be use to detect contamination.	Passed
Protein profile	Protein characterization using size exclusion high performance liquid chromatography was used to assess protein aggregation and detect differences in the vaccine's protein profile.	H1N1 neuraminidase higher than prior years
Viral particles & viable virus	Fluvax is a split virion influenza vaccine and should consist primarily of disrupted viral particles. Electronic microscopy and cell culture assay were carried out to assess for the presence of whole virus particles and live virus in the finished product.	Passed
In vivo pyrogenicity	TGA assessed the capacity of vaccine to produce fever in various animal models.	Ongoing

Additionally, immunologic studies were conducted by Blythe et al. in Western Australia to further investigate possible biologic mechanisms.[6] This exploratory study used an *in vitro* stimulation model where peripheral blood mononuclear cells from 22 donors aged <36 months were stimulated with either Fluvax, Influvac, Vaxigrip, lipopolysaccharide or Staphylococcal enterotoxin B to evaluate cytokine release. Cytokines are chemicals signaling molecules used for communication between cells; stimulation and release of certain cytokines can produce fever.

Investigators found that multiple pyrogenic cytokines (IFN-α, IL-1β, IL-6, IL-10, IP-10 or CXCL10, and macrophage inflammatory protein 1α) were significantly higher in cultures stimulated with Fluvax compared to Influvac or Vaxigrip. In fact, the cytokine profile of Fluvax resembled that observed during *in vitro* stimulation with inactivated influenza A virus and the early innate immune response to natural influenza infection.

The authors suggested that Fluvax may contain, "innate immune-activating components that resemble, or are derived from influenza virions." However, investigators also found that the 2009 Fluvax vaccine formulation was equally capable of inducing a pyrogenic response *in vitro* and this formulation was not linked with febrile adverse events. This suggests that a vaccine-induced pyrogenic response alone is not sufficient to explain the excess rates in the 2010 southern hemisphere influenza season.

4. ADVERSE EVENT REVIEW

Postlicensure surveillance of trivalent influenza vaccine in the United States has supported the safety of influenza vaccination in young children.[10-13] Prior to the 2010 SH, increased risks of febrile seizure have not been established for recommended childhood vaccines other than whole-cell pertussis and measles-

containing vaccines.[14-17] The estimated background rate for febrile seizures after influenza vaccination is 0.16 per 1,000 doses in children aged 6 months to ≤3 years on days 1 to 7 after trivalent influenza vaccination.[3,18] Simple fevers without convulsions are relatively common adverse events. Published studies of influenza vaccine clinical trials involving children <5 years have noted rates between 8.2–39.5%.[19,20]

4.1 Afluria Doses Distributed, United States 2009–2011

CSL did not distribute any 0.25 mL pediatric doses in the US for either 2009–2010 or 2010–2011 influenza seasons, effectively restricting its use to children 36 months and older. The 0.5 mL doses are approved only for children aged 36 months or older.

	Doses Distributed, Aug 2009 to June 2010
0.25 mL pediatric pre-filled syringe	0
0.5 mL pre-filled syringe	5,601,806
Multi-dose vials	2,295,160
TOTAL DOSES	7,897,020

4.2 Trivalent Influenza Vaccine Antigens and Recommendations for Use

This postlicensure safety review covers 2 influenza seasons in the US. The 2009–10 season is reviewed as part of the traditional one-year PAC review. Due to the safety issue identified in the SH 2010 season, we are also providing a review of the 2010–11 season. This table shows the influenza antigens contained in each seasonal trivalent vaccine by hemisphere.

	SH 2009	NH 2009–10	SH 2010	NH 2010–11
A/Brisbane/59/2007 (H1N1)-like virus	•	•		
A/Brisbane/10/2007 (H3N2)-like virus	•	•		
A/California/7/2009 (H1N1)-like virus			•	•
A/Perth/16/2009 (H3N2)-like virus			•	•
B/Florida/4/2006-like virus	•			
B/Brisbane/60/2008-like virus		•	•	•

FDA approved Afluria for use in children in September 2009. In February 2010, ACIP followed this expanded approved use, by recommending Afluria to children aged 6 months and older (the recommendation did not take effect until the following 2010–11 season).[21] Due to the febrile seizures safety concern identified in southern hemisphere influenza season, ACIP amended this recommendation in August 2010 by restricted use to children aged ≥9 years.[5]

4.3 Label Changes During the PAC Review Period

On 30 July 2010, FDA added the following statement to the warnings and precautions section of the package insert.[22]

- Warnings and Precautions: “Administration of CSL’s 2010 Southern Hemisphere influenza vaccine has been associated with increased postmarketing reports of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years.”

4.4 Afluria Reports in VAERS, 10 Nov 2009 – 30 June 2010

	Serious		Deaths		Non Serious		Total	
	US	Total	US	Total	US	Total	US	Total
All Ages	8	8	0	0	38	40	46	48
0–16 Years	0	0	0	0	2	3	2	3

During this influenza season, ACIP recommended Afluria only for adults aged ≥18 years. Two non-serious events were reported in children:

1. 3 year old with urticaria 1 day after vaccination
2. 1 year old with varicella 3 days after vaccination

No febrile seizures were reported. No safety signals were identified in VAERS.

Additionally, CDC's Vaccine Safety Datalink (VSD) monitored trivalent influenza vaccines among 9 million members in 8 participating managed care organizations. From November 2009 to April 2010, the VSD monitored 2,741,150 doses of trivalent influenza vaccine (no sub-analyses by vaccine brand were conducted, likely due to smalller sample sizes).[23] Using self-controlled analyses and current versus historical comparison methods, VSD detected no safety signals for Guillain-Barre Syndrome, demyelinating disease of the central nervous system, disorders of the peripheral nervous system and neuropathy, seizures, encephalomyelitis, Bell's palsy, other cranial nerve disorders, ataxia, anaphylaxis, and allergic reaction other than anaphylaxis (including angioneurotic edema and urticaria).

4.5 Afluria Reports in VAERS, 1 July 2010 – 31 March 2011

	Serious		Deaths		Non Serious		Total	
	US	Total	US	Total	US	Total	US	Total
All Ages	37	41	0	0	511	515	548	556
0–16 Years	3	3	0	0	38	38	41	41
0–5 Years	2	2	0	0	28	28	30	30

During this influenza season, ACIP recommended Afluria only for children and adults aged ≥9 years. Three serious events were reported:

1. Pregnancy exposure: 15 year old female with unknown medical history who was vaccinated with Gardasil, Recombivax and Afluria approximately 1 week prior to delivery. A male neonate was delivered at 36 weeks and 5 days with laryngomalacia.
2. 4 year old male with history of chronic constipation who developed abdominal pain, vomiting and fever 6 hours after vaccination. Twin sister at home had similar symptoms. Evaluation in the emergency department was remarkable for an elevated C-reactive protein and normal abdominal x-ray: differential diagnosis was appendicitis versus viral gastroenteritis. He was admitted, observed overnight and discharged the next day with a reassuring abdominal exam and tolerating a normal diet.
3. 14 month old male with fever, irritability, red rash and ataxia 1 week after receiving MMR, Afluria, VAQTA, Prevnar, and Varivax. Diagnosed with acute cerebellar ataxia by a neurologist.

No febrile seizures were reported. No safety signals were identified.

5. VACCINE SAFETY MONITORING FOR AFLURIA

5.1 US Safety Monitoring

FDA and CDC will continue to conduct routine influenza surveillance for Afluria. This consists of review of all serious adverse events reported in VAERS and signal detection using data mining methods to identify disproportional reporting. Additionally, CDC's Vaccine Safety Datalink, a population-based active surveillance system will monitor high priority adverse events.

5.2 CSL Ongoing Safety Studies

To date, CSL has not identified an explanation for the febrile events, but the root cause investigation is ongoing. CSL is conducting further *in vitro* and *in vivo* studies to evaluate cytokine and temperature responses to various formulations of trivalent influenza vaccine and individual vaccine strains.[24]

Meanwhile, CSL is conducting the following 2 epidemiologic studies to assess the safety of Fluvax in Australia and New Zealand during the current 2011 southern hemisphere influenza season.[25]

Australia
- Prospective, observational cohort study
- 600 children aged 5–18 years
- Eligibility: receipt of any influenza vaccine
- Monitor adverse events for 3 days postvaccination

New Zealand
- Prospective, observational cohort study (using sentinel general practices)
- 200 children aged <18 years and 200 adults ≥18 years
- Eligibility: receipt of CSL influenza vaccine
- Monitor adverse events for 2 days postvaccination

6. CONCLUSIONS

No safety signals were identified during routine surveillance of the 2009–10 and 2010–11 influenza seasons in the United States. ACIP's recommendations to restrict the use of Afluria to children aged ≥9 years was a key policy decision and virtually eliminated the potential risk of febrile seizures in young children. FDA and TGA have subsequently revised the approved use of Afluria for only children aged ≥5 years.

No causal factor has been identified for the excess febrile events and CSL's root cause investigation is ongoing. Both FDA and TGA have independently audited CSL's manufacturing facilities and have not uncovered an underlying cause for the adverse reactions.[7] CSL will also conduct additional postlicensure epidemiologic studies in Australia and New Zealand to evaluate the safety of Fluvax as it is administered to children 5 years and older.

For the upcoming 2011–2012 northern hemisphere influenza season, ACIP has continued to recommend Afluria only for children aged ≥9 years. Given this policy, the revised pediatric labeling, and the results of this postlicensure review, FDA recommends continued routine postmarketing surveillance of Afluria.

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