Pediatric Safety and Utilization Review: AFLURIA®

Pediatric Advisory Committee Meeting

September 22, 2011

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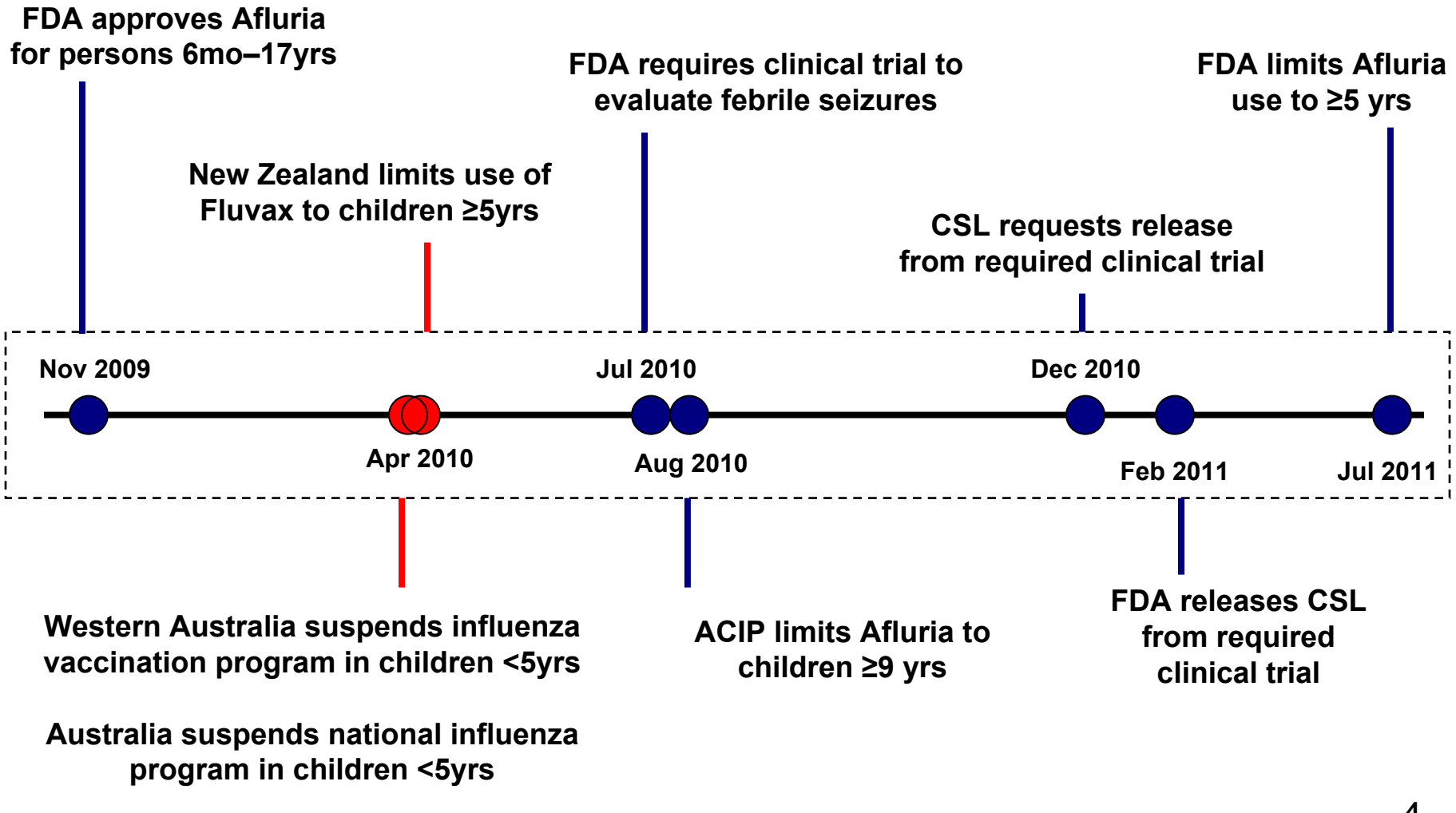
Afluria

Product	Trivalent inactivated influenza virus vaccine (split-virion)
Formulation	Each 0.5 mL dose contains 15 mcg hemagglutinin of each of the 3 viral strains contained in the vaccine.
Manufacturer	CSL Biotherapies
Indication and use	Active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine for persons ≥ 5 years
US Licensure	28 Sept 2007
Trigger for Review	10 Nov 2009

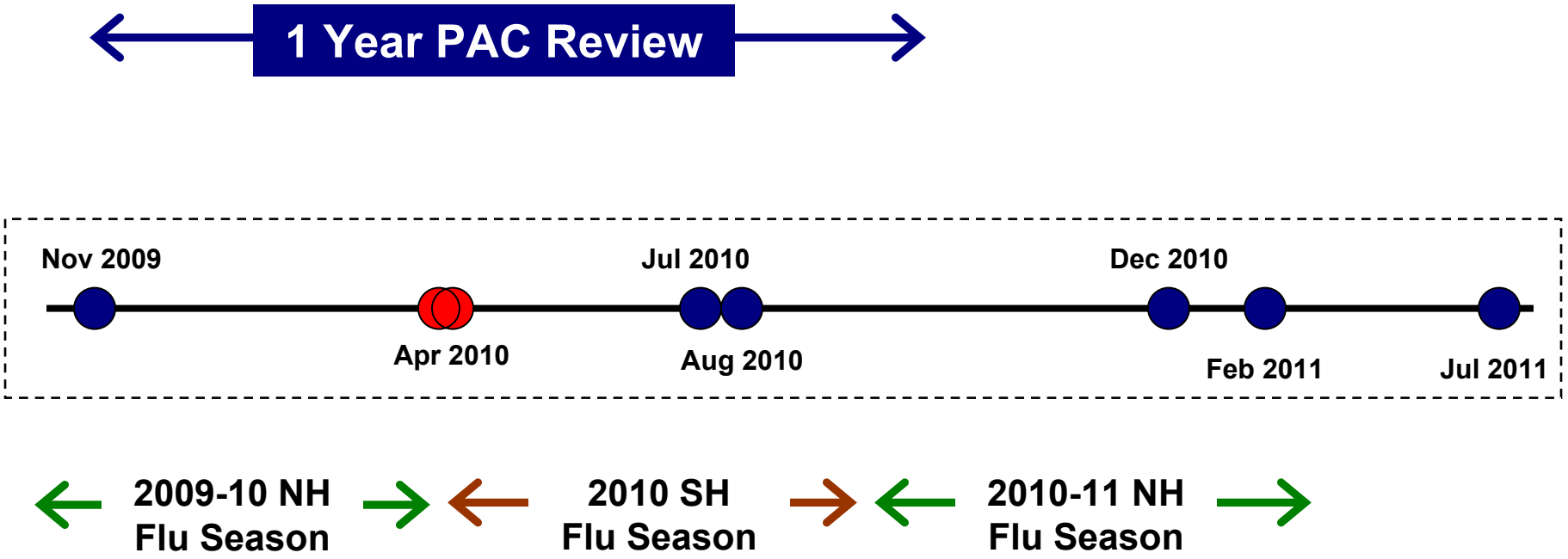
Objectives

- Background
  - Timeline of major regulatory actions and vaccine safety events
  - Vaccine antigens, dose distribution, label changes
- Adverse event review
  - 2009–10 northern hemisphere (NH) flu season
  - 2010 southern hemisphere (SH) flu season
    - Febrile reactions after CSL Fluvax
    - Summary of actions in Australia and United States
  - 2010–2011 NH flu season
- Planned pharmacovigilance studies

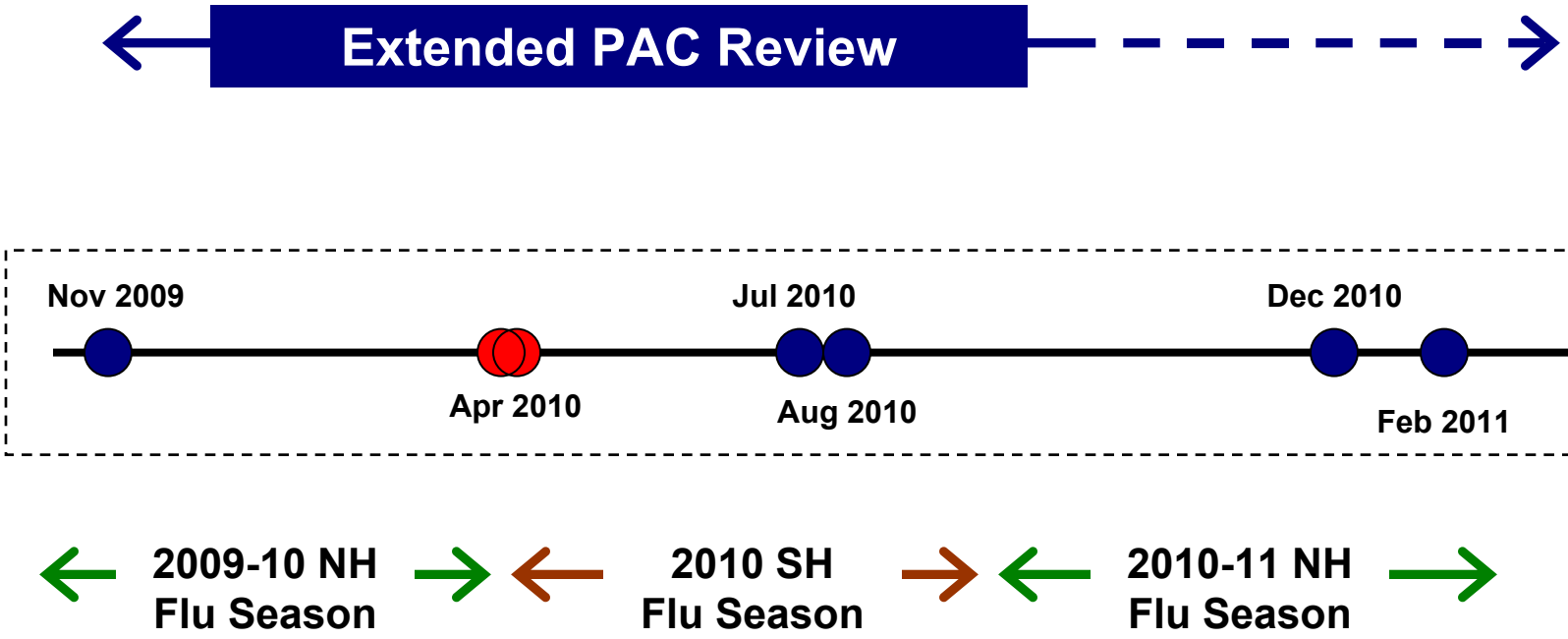
Timeline


FDA approves Afluria for persons 6mo–17yrs
New Zealand limits use of Fluvax to children ≥5yrs
FDA requires clinical trial to evaluate febrile seizures
CSL requests release from required clinical trial
FDA limits Afluria use to ≥5 yrs
Nov 2009
Apr 2010
Jul 2010
Aug 2010
Dec 2010
Feb 2011
Jul 2011
Western Australia suspends influenza vaccination program in children <5yrs
Australia suspends national influenza program in children <5yrs
ACIP limits Afluria to children ≥9 yrs
FDA releases CSL from required clinical trial

Pediatric Advisory Committee Timeline



Pediatric Advisory Committee Timeline



Trivalent Influenza Vaccine Antigens

	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		•	•	•

NH = Northern hemisphere, SH = Southern hemisphere

http://www.who.int/csr/disease/influenza/vaccinerecommendations/en/

US Advisory Committee on Immunization Practices (ACIP) Recommendations

Trade Name	Manufacturer	2009–10*	2010–11†
Afluria	CSL Biotherapies	≥18 yrs	≥6 mo (≥9 yrs) ‡
Fluarix	GlaxoSmithKline	≥18 yrs	≥3 yrs
Agriflu	Novartis	--	≥18 yrs
Flulaval	GlaxoSmithKline	≥18 yrs	≥18 yrs
Flumist	MedImmune	2–49 yrs	2–49 yrs
Fluvirin	Novartis	≥4 yrs	≥4 yrs
Fluzone	Sanofi Pasteur	≥6 mos	≥6 mos

* MMWR 2009 Jul 31;58(RR-8):1-52. and MMWR 2009 Aug 21;58(32):896-7.

† MMWR 2010 Aug 6;59(RR-8):1-62

‡ Changed to ≥9 years, MMWR 2010 Aug 13;59(31):989-992.

Afluria Dose Distribution, United States

	Aug 2009 – June 2010
0.25 mL pediatric PFS	0
0.5 mL PFS	5,601,806
Multi-dose vials	2,295,160
Total Doses	7,897,020

PFS = Pre-filled syringe

0.25 mL dose is indicated in children 6 months to <3 years

Afluria Label Changes

- 30 July 2010
- ***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."

- 15 July 2011
- ***Usage***: Persons aged 5 years and older

Modified Vaccine Information Statement

5 What are the risks from inactivated influenza vaccine?

A vaccine, like any medicine, could possibly cause serious problems, such as severe allergic reactions. The risk of a vaccine causing serious harm, or death, is extremely small.

Serious problems from inactivated influenza vaccine are very rare. The viruses in inactivated influenza vaccine have been killed, so you cannot get influenza from the vaccine.

Mild problems:

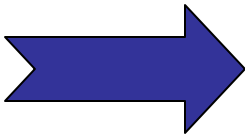
- soreness, redness, or swelling where the shot was given
- hoarseness; sore, red or itchy eyes; cough
- fever • aches

If these problems occur, they usually begin soon after the shot and last 1-2 days.

Severe problems:

- Life-threatening allergic reactions from vaccines are very rare. If they do occur, it is usually within a few minutes to a few hours after the shot.
- In 1976, a type of inactivated influenza (swine flu) vaccine was associated with Guillain-Barré Syndrome (GBS). Since then, flu vaccines have not been clearly linked to GBS. However, if there is a risk of GBS from current flu vaccines, it would be no more than 1 or 2 cases per million people vaccinated. This is much lower than the risk of severe influenza, which can be prevented by vaccination.

One brand of inactivated flu vaccine, called Afluria, **should not be given** to children 8 years of age or younger, except in special circumstances. A related vaccine was associated with fevers and fever-related seizures in young children in Australia. Ask your healthcare provider for more information.



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v. 8.10.2010

Afluria Reports in VAERS

10 Nov 2009 – 30 June 2010

	Serious*		Deaths		Non-Serious		TOTAL	
	US	Global	US	Global	US	Global	US	Global
All Ages	8	8	0	0	38	40	46	48
0–16 Years	0	0	0	0	2	3	2	3

- ACIP recommended use only for ages ≥18 years
- All pediatric reports were non-serious
- No febrile convulsions
- No safety signals identified during the 2009–10 influenza season

* Death, life-threatening experiences, inpatient hospitalization or prolongation of hospitalization, or persistent disability.

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Fever after CSL SH Fluvax

	CSL SH 2010 Vaccine	Other 2010 SH
Uncontrolled cohort study in Western Australia (<3 yrs)	40–50 per 1,000	5 per 1,000
Retrospective cohort, New South Wales (<5 yrs)	46%	7–16%
New Zealand telephone survey (<5 yrs) (Vaxigrip vs. Fluvax)	27%	7%

SH = Southern Hemisphere

http://www.tga.gov.au/safety/alerts-medicine-seasonal-flu-101008.htm
Petousis-Harris H et al. Vaccine. 2011 Apr 5;29(16):2933-7.

Febrile Convulsions after CSL SH Fluvax

	CSL SH 2010 Vaccine	Other 2010 SH
Passive surveillance	5–7 per 1,000	0.17 per 1,000 (Panvax)
Uncontrolled cohort study, Western Australia (<3 yrs) (3–4 yrs)	 7–10 per 1,000 1.5–14 per 1,000	 0 after 1,450 doses 0 after 1,800 doses (Influvac)
Controlled cohort study, <5 yrs	Risk ratio = 5 (vaccinated vs. unvaccinated)	

MMWR 2010 Aug 13;59(31):989-992.
http://www.tga.gov.au/safety/alerts-medicine-seasonal-flu-101008.htm

Therapeutic Goods Administration (TGA) Conclusions

- "No available clinical or epidemiologic factors offers a plausible explanation"
- CSL vaccine administered in all cases with known brand name
  - 21 batches implicated, 2 batches accounted for >50% cases
- Rapid onset not consistent with infectious etiology (mean, 7.2 hrs)
  - Respiratory symptoms less common in postvaccination cases than non-vaccine related febrile seizures ($p < 0.001$)
- 75% cases previously healthy
- No evidence of "priming effect"
  - Baseline seropositivity to H1N1 in clinical trials associated with lower rates of febrile responses
- TGA laboratory investigation found excess neuraminidase activity

Summary of Actions, Australia

- Regulatory (TGA)
  - Nov 2010 limited approved use to persons >5 years
  - Issued boxed warning regarding febrile reactions in SH 2011
  - Audits of CSL facilities: "To date, no underlying cause for the adverse reactions has been identified. Work is ongoing."
- Changes to recommended use
  - Mar 2010 Australian Technical Advisory Group on Immunisation (ATAGI) limited use to ≥10 yrs, unless no alternative vaccine available*

* "*Fluvax may be used in children aged 5 years to less than 10 years when no timely alternative vaccine is available. If Fluvax is administered, parents should be informed of the potential increased risk of fever but that febrile convulsions are rare in this age group.*"

http://www.immunise.health.gov.au/internet/immunise/Publishing.nsf/content/immunise-atagi-vaccine-advice

http://www.tga.gov.au/newsroom/btn-csl-tga-statement-110708.htm

FDA Required Clinical Trial

- FDA originally required CSL to conduct a study to evaluate febrile reactions in children aged 5–9 years

- FDA released CSL from required clinical trial under the "good cause" clause due to study feasibility, ethical concerns, relevance of results to the true population of interest (<5 year olds)

Status of CSL Investigations

- CSL is conducting *in vitro* and *in vivo* studies to evaluate cytokine and temperature responses to various formulations of trivalent influenza vaccine and individual vaccine strains

- Extensive investigations conducted to date have yet to identify a root cause for the febrile events

http://www.cslbiotherapies.co.nz/s1/cs/aubn/1255925875541/content/1255925875357/content.htm

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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

- ACIP recommended use only for ages ≥9 years
- No febrile convulsions
- No safety signals identified during the 2010–11 influenza season

* Serious events include death, life-threatening experiences, inpatient hospitalization or prolongation of hospitalization, or persistent disability.

CSL Safety Monitoring SH 2011

- Australia
  - Prospective, observational cohort
  - 600 children aged 5 – 18 years
  - Eligibility: receipt of any influenza vaccine
  - Monitor adverse events for 3 days postvaccination
- New Zealand
  - Prospective, observational cohort (sentinel general practices)
  - 200 children aged <18 years and 200 adults
  - Eligibility: receipt of CSL influenza vaccine
  - Monitor adverse events for 2 days postvaccination

Greenberg. Adverse Events in Children Following 2010 Southern Hemisphere Influenza Vaccination. National Immunization Conference, March 28, 2011. http://cdc.confex.com/cdc/nic2011/webprogram/Paper25435.html

Plans for Vaccine Safety Monitoring in US

- FDA and CDC will continue to conduct routine influenza vaccine surveillance
- VAERS
  - Review serious adverse events
  - Identify disproportional reporting through data mining
- Rapid cycle analyses in CDC's Vaccine Safety Datalink

Conclusions

- No safety signals identified during routine surveillance of NH 2009-10 and NH 2010-11 influenza seasons
- FDA has revised label to mitigate the risk of febrile reactions
- Root cause investigation is ongoing
- CSL is conducting additional epidemiologic studies to evaluate febrile reactions during 2011 SH influenza season
- FDA recommends continuing routine surveillance of Afluria
- Does the advisory committee concur?

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