Public Communication Activities Under FDA's Safety Authority

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Application of Pharmacovigilance to U.S. FDA Regulatory Decisions for Vaccines

June 3, 2012

Objectives

- Discuss Vaccine safety communication principles
- Understand types of FDA product risk communications
- Describe legal requirements for FDA to post drug and vaccine safety risks

Principles of Vaccine Safety Communication

- **Goal of Transparency**
  - FDA Transparency Initiative: part of Open Govt.
  - Transparency promotes accountability by providing information to the public about what the Government is doing

- **Balance Vaccine Risks and Benefits for Individuals, Populations:**
  - Individual: Risk of vaccine adverse event (AE) versus benefit of protection from disease
  - Populations: Risk of Perception of harm (i.e., lower vaccine coverage) versus benefit of open communication

http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/default.htm

http://www.whitehouse.gov/open

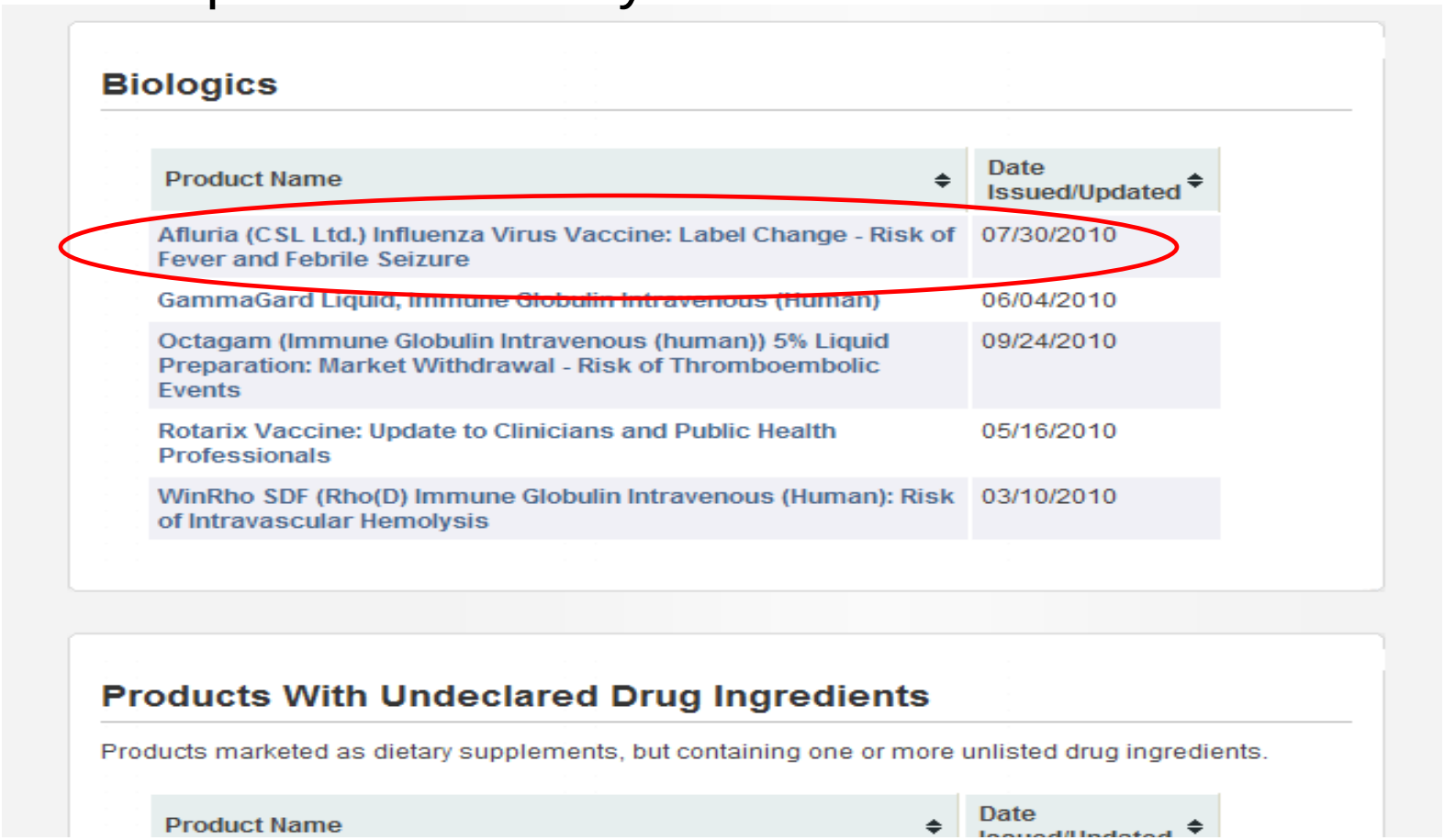
Medical Product Safety Communications

- **MedWatch Safety Alerts**
  - Timely new safety information on drugs, devices, vaccines and other biologics
  - Contain actionable information that may impact treatment and diagnostic choices
  - Archived by year

http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm
http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/DrugSafetyInformation/default.htm

MedWatch Safety Alerts

- Example: 2010 Safety Alerts



Biologics

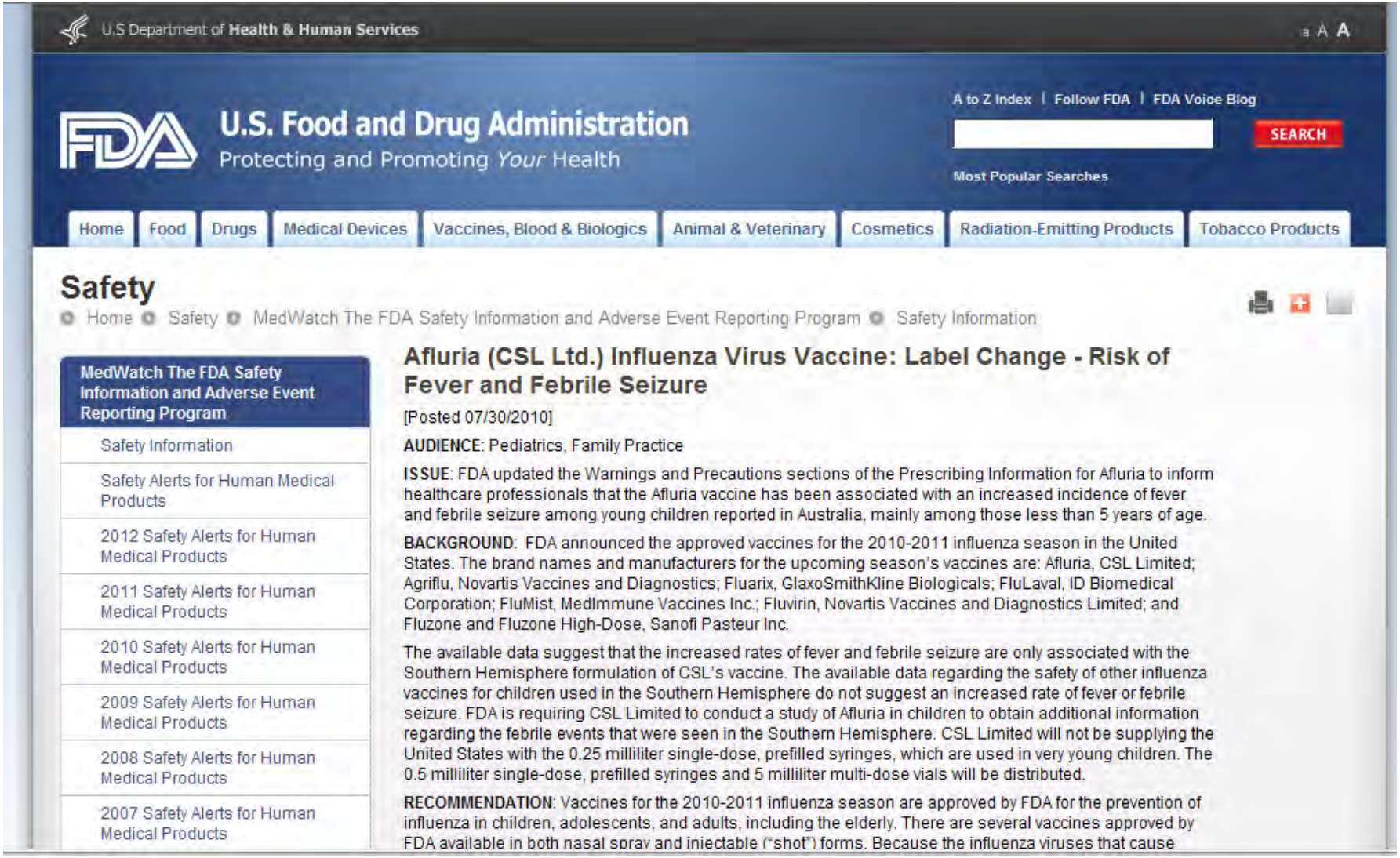
Product Name	Date Issued/Updated
Afluria (CSL Ltd.) Influenza Virus Vaccine: Label Change - Risk of Fever and Febrile Seizure	07/30/2010
GammaGard Liquid, Immune Globulin Intravenous (Human)	06/04/2010
Octagam (Immune Globulin Intravenous (human)) 5% Liquid Preparation: Market Withdrawal - Risk of Thromboembolic Events	09/24/2010
Rotarix Vaccine: Update to Clinicians and Public Health Professionals	05/16/2010
WinRho SDF (Rho(D) Immune Globulin Intravenous (Human): Risk of Intravascular Hemolysis	03/10/2010

Products With Undeclared Drug Ingredients

Products marketed as dietary supplements, but containing one or more unlisted drug ingredients.

Product Name	Date

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm196258.htm



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- 2007 Safety Alerts for Human Medical Products

Afluria (CSL Ltd.) Influenza Virus Vaccine: Label Change - Risk of Fever and Febrile Seizure

[Posted 07/30/2010]

AUDIENCE: Pediatrics, Family Practice

ISSUE: FDA updated the Warnings and Precautions sections of the Prescribing Information for Afluria 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 Australia, mainly among those less than 5 years of age.

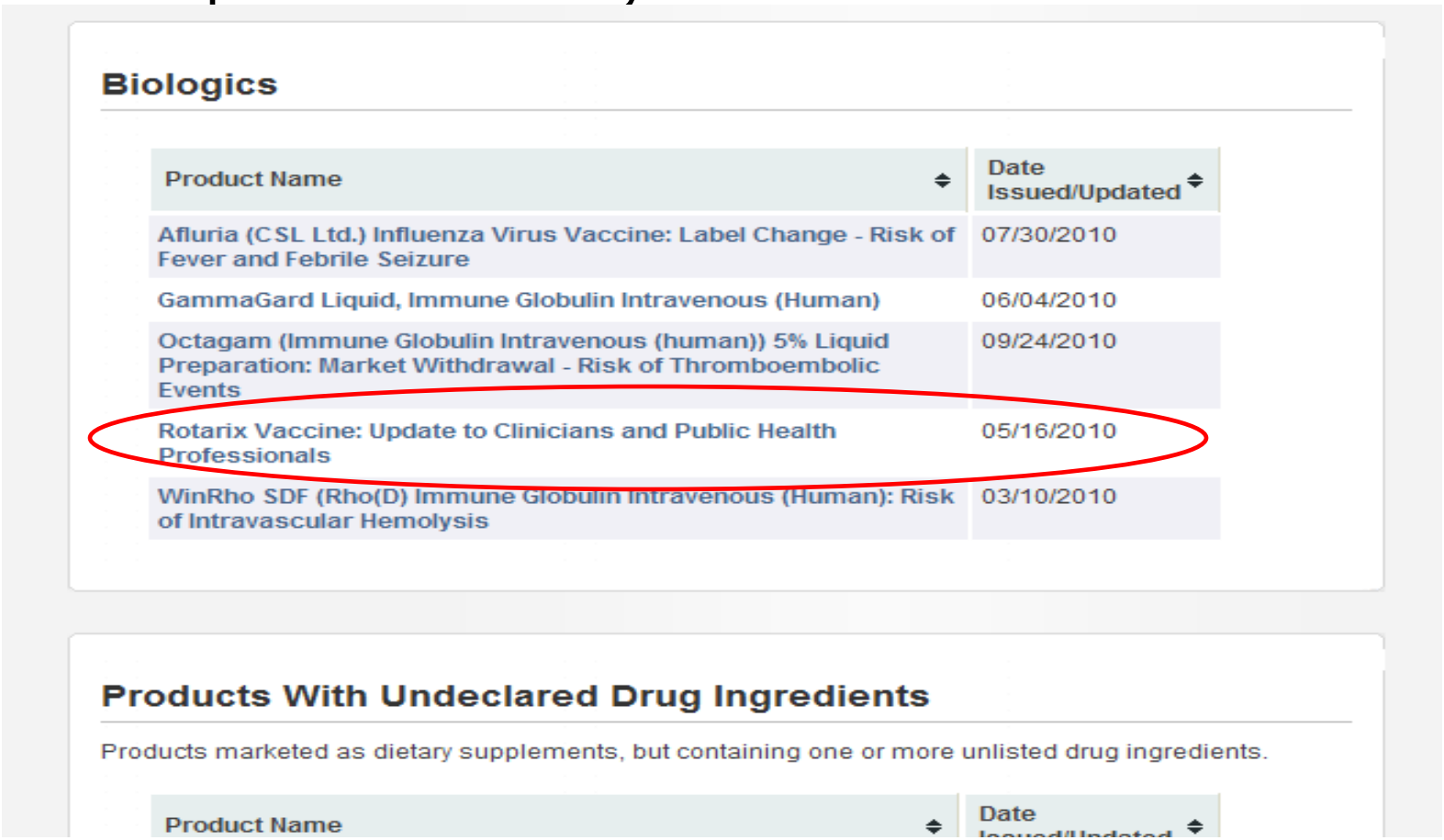
BACKGROUND: FDA announced the approved vaccines for the 2010-2011 influenza season in the United States. The brand names and manufacturers for the upcoming season's vaccines are: Afluria, CSL Limited; Agriflu, Novartis Vaccines and Diagnostics; Fluarix, GlaxoSmithKline Biologicals; FluLaval, ID Biomedical Corporation; FluMist, MedImmune Vaccines Inc.; Fluvirin, Novartis Vaccines and Diagnostics Limited; and Fluzone and Fluzone High-Dose, Sanofi Pasteur Inc.

The available data suggest that the increased rates of fever and febrile seizure are only associated with the Southern Hemisphere formulation of CSL's vaccine. The available data regarding the safety of other influenza vaccines for children used in the Southern Hemisphere do not suggest an increased rate of fever or febrile seizure. FDA is requiring CSL Limited to conduct a study of Afluria in children to obtain additional information regarding the febrile events that were seen in the Southern Hemisphere. CSL Limited will not be supplying the United States with the 0.25 milliliter single-dose, prefilled syringes, which are used in very young children. The 0.5 milliliter single-dose, prefilled syringes and 5 milliliter multi-dose vials will be distributed.

RECOMMENDATION: Vaccines for the 2010-2011 influenza season are approved by FDA for the prevention of influenza in children, adolescents, and adults, including the elderly. There are several vaccines approved by FDA available in both nasal spray and injectable ("shot") forms. Because the influenza viruses that cause

MedWatch Safety Alerts

- Example: 2010 Safety Alerts



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Rotarix Vaccine: Update to Clinicians and Public Health Professionals

Audience: Pediatric and family practice healthcare professionals, public health professionals

[UPDATED 05/16/2010] FDA has determined it is appropriate for clinicians and health care professionals to resume the use of Rotarix and to continue the use of RotaTeq. Based on a careful evaluation of laboratory results from the manufacturers and its own laboratories, a thorough review of the scientific literature, and input from scientific and public health experts, the agency is revising its recommendation to temporarily suspend use of the Rotarix vaccine. FDA has also determined that RotaTeq vaccine should remain in use.

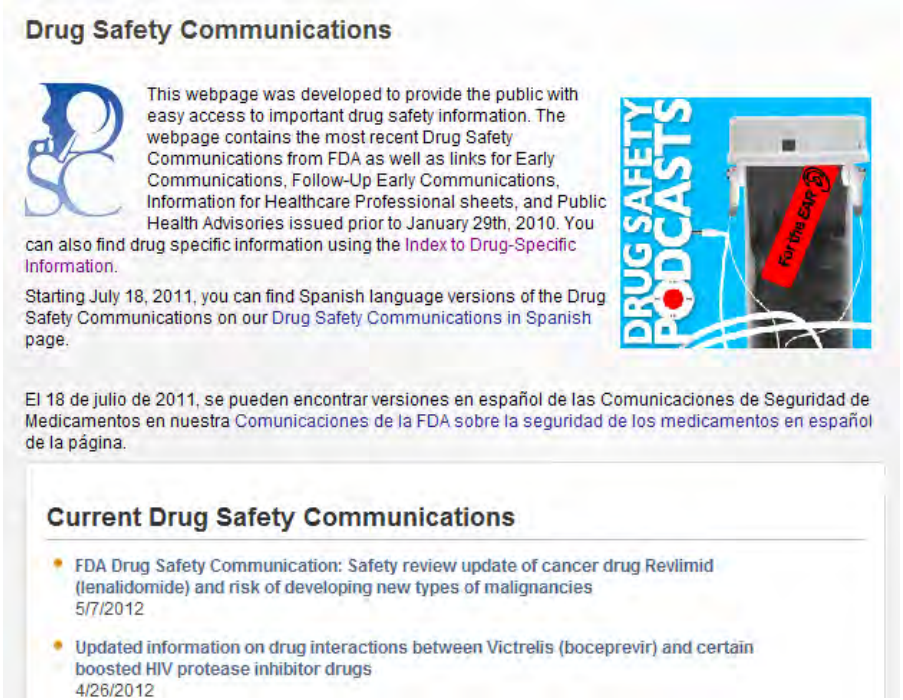
In its decision, FDA considered that both vaccines have strong safety records, including clinical trials involving tens of thousands of patients as well as clinical experience with millions of recipients. FDA has no evidence that either porcine circovirus (PCV1 or PCV2) poses a safety risk in humans, and notes that neither is known to cause infection or illness in humans. The benefits of the vaccines are substantial, and include prevention of hospitalization for severe rotavirus disease in the United States and of death in other parts of the world. he benefits outweigh the risk, which is theoretical. FDA and the manufacturers will continue to investigate the findings of PCV in rotavirus vaccines and will evaluate information from ongoing testing by FDA and the manufacturers.

[Posted 03/22/2010] FDA is recommending that healthcare professionals temporarily suspend the use of Rotarix, a vaccine used to prevent rotavirus disease. FDA's recommendation is a precaution taken while the agency learns more about the situation.

FDA has learned that DNA from porcine circovirus type 1 (PCV1) is present in Rotarix. PCV1 is not known to cause disease in humans. There is no evidence at this time that this finding poses a safety risk. Because

Other Medical Product Safety Communications

- **Drug Safety Communications Page**
  - **Label Changes**
  - **Epidemiologic Reviews of drug safety**



Drug Safety Communications

This webpage was developed to provide the public with easy access to important drug safety information. The webpage contains the most recent Drug Safety Communications from FDA as well as links for Early Communications, Follow-Up Early Communications, Information for Healthcare Professional sheets, and Public Health Advisories issued prior to January 29th, 2010. You can also find drug specific information using the Index to Drug-Specific Information.

Starting July 18, 2011, you can find Spanish language versions of the Drug Safety Communications on our Drug Safety Communications in Spanish page.

El 18 de julio de 2011, se pueden encontrar versiones en español de las Comunicaciones de Seguridad de Medicamentos en nuestra Comunicaciones de la FDA sobre la seguridad de los medicamentos en español de la página.

Current Drug Safety Communications

- FDA Drug Safety Communication: Safety review update of cancer drug Revlimid (lenalidomide) and risk of developing new types of malignancies
  5/7/2012
- Updated information on drug interactions between Victrelis (boceprevir) and certain boosted HIV protease inhibitor drugs
  4/26/2012

http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm

Biologics Safety and Availability Information

- **FDA/CBER posts notices about important adverse event reporting, recalls, shortages, and biological product deviations.**

http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/default.htm

Biologics Safety and Availability Information

2011

- Information for Health Care Professionals: Anticipated Short Supply of Coral Snake Antivenom (Pfizer Inc.)
- Fluzone Vaccine Safety
- Important Safety Information: Risk of Thrombotic Adverse Events with Subcutaneous or Inappropriate Intravenous Use of Vivaglobin (Immune Globulin Subcutaneous)

http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/default.htm

Vaccine Safety Communication Example

Fluzone Vaccine Safety

FDA and CDC Update on Fluzone Influenza Vaccine and VAERS Reports of Febrile Seizures in Children

January 20, 2011

The Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) routinely monitor the safety of all U.S. vaccines by using several vaccine safety surveillance systems, including the Vaccine Adverse Event Reporting System (VAERS). VAERS collects and analyzes information from reported adverse events (health problems or possible side effects) that occur after vaccination.

FDA and CDC have recently detected an increase in the number of reports to VAERS of febrile seizures following vaccination with Fluzone (trivalent inactivated influenza vaccine or TIV, manufactured by Sanofi Pasteur, Inc.). Fluzone is the only influenza vaccine recommended for use for the 2010-2011 flu season in infants and children 6-23 months of age. These reported febrile seizures have primarily been seen in children younger than 2 years of age. Data from VAERS are preliminary and serve as a sign or indication that further investigation is warranted. Further investigations are under way to assess whether there could be an association between influenza vaccination and febrile seizures, or if other factors could be involved. FDA and CDC have seen no increase in VAERS reports of febrile seizures in people older than 2 years of age following vaccination with TIV, and no increase after live attenuated influenza vaccine (FluMist, the nasal spray vaccine). In the cases reported, all children recovered and no lasting effects have been seen. Recommendations for the use of flu vaccine in children have **not** changed.

FDA and CDC will continue to conduct studies and provide additional information to the public and health care providers as it becomes available.

http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm240037.htm

Safety Communications Required by FDA Amendment Act (FDAAA)

- **Potential Signals of a Serious Risk from the Adverse Event Reporting System (AERS) (aka Section 921)**
- **Comprehensive 18-month safety review (aka Section 915)**
- **Post-approval Pediatric Safety Reviews for Pediatric Advisory Committee (PAC)**

Potential Signals of a Serious Risk from the Adverse Event Reporting System (AERS)

- **FDAAA requires FDA to post *potential* signals of serious risks identified from AERS data each Quarter**

- **Early communication; before evaluation**
  - Does not mean that FDA has determined that the drug has the risk
  - Does not mean that FDA has determined that there is a causal relationship

Potential Signals of a Serious Risk from the Adverse Event Reporting System (AERS)

- **Includes signals identified**
  - From AERS only, or
  - From other sources and AERS data contributed

- **Limited to AERS data (i.e., signals for drugs and therapeutic biologics), but general principles apply to FDA communications about vaccines**

Sample 921 posting

Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) January - March 2010

Product Name: Active Ingredient (Trade) *or* Product Class	**Potential Signal of a Serious Risk / New Safety Information**	**Additional Information (as of July 31, 2010)**
Azacitidine (Vidaza)	Acute febrile neutrophilic dermatosis (Sweet's syndrome)	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Azithromycin (Zithromax)	Liver failure	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Azithromycin extended release 2 g (Zmax)	Pyloric stenosis	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
C1 esterase inhibitors (Cinryze, Berinert)	Thromboembolic events in patients with certain thrombogenic risk factors	FDA is evaluating this issue to determine whether current labeling is adequate.

Postmarketing Drug and Biologics Safety Evaluations (18-month Reviews)

- **FDAAA requires FDA to conduct a comprehensive safety evaluation of all new products after 18 months since approval and use in 10,000 patients**

- **FDAAA requires FDA to post results of the reviews on the web**

Guidance, Compliance & Regulatory Information

Surveillance

- Postmarketing Surveillance Programs
- Regulations and Policies and Procedures for Postmarketing Surveillance Programs
- Staff Manual Guide: Chapter 53; Postmarketing Surveillance and Epidemiology: Human Drugs
- Postmarketing Drug Safety Evaluations
- Adverse Events Reporting System (AERS)
- Drug Marketing, Advertising, and Communications

Resources for You

- Questions and Answers on FDA's Postmarketing Safety Summaries of Recently Approved Drugs and Biologics

Postmarketing Drug Safety Evaluations

- What is FDA Posting?
- Why is FDA posting this summary information?
- What information is provided on this web site?
- What information does FDA consider for these postmarketing safety evaluations?
- How is the information analyzed?
- Postmarketing Drug Safety Evaluation Summaries

What is FDA posting?

This web site provides summary information about ongoing and completed postmarketing safety evaluations of adverse drug experience reports made to FDA for New Drug Applications (NDAs) and Biologic License Applications (BLAs) approved since September 27, 2007. The evaluations are done to determine if there are any new serious adverse events not previously identified during product development, known side effects reported in unusual number, or potential new safety concerns now that the products are being used in the general population. In accordance with Title IX, section 915 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) which created a new section 505(r) of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 355(r)), these postmarketing evaluations are performed 18 months after approval of the drug or after its use by 10,000 individuals, whichever is later.

Why is FDA posting this summary information?

FDA is posting this information in accordance with section 505(r) of the FDCA. This section of the statute directs FDA to improve the transparency of information about drugs and to provide patients and health care providers better access to information about drugs by developing a web site with specified types of drug safety information.

In response to the statutory requirement, FDA developed the Postmarket Drug Safety Information for Patients and Providers web site, which has links to a wide variety of drug safety information, including this web page.

Sources of Safety information for 18-month Safety Reviews

FDA assesses several data sources including:

- The product's pre-approval safety profile
- The product's current FDA-approved label
- Reports made to FDA's Adverse Event Reporting System (AERS)
- Reports made to the Vaccine Adverse Event Reporting System (VAERS)
- Manufacturer-submitted periodic safety reports
- Medical literature
- Drug utilization databases
- Data from post-approval clinical trials and other studies, when applicable

Sample public posting

Postmarketing Drug Safety Evaluation Summaries

Postmarketing Drug Safety Evaluations completed through the fourth quarter of 2009:

Product Name: Trade (Active Ingredient) NDA/BLA Number Approval Date	Major Indication(s)	Summary of Evaluation Findings	Actions Taken and Ongoing Surveillance Activities
Afluria (Influenza Virus Vaccine) BLA 125254 September 28, 2007	For active immunization of persons ages 6 months and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.	No potential safety problems were identified.	No labeling changes required at this time.

Questions?