Pediatric Safety Reporting

Drugs, Biologics, Devices and the PAC

Judith U. Cope, MD, MPH
Office of Pediatric Therapeutics
OC, FDA

Outline

- Brief overview of pediatric safety legislation
- Pediatric focused safety review reporting process
- Pediatric Advisory Committee (PAC) meetings
- What we have learned and actions taken
- How will the new legislation change things?

Pediatric Safety Legislation - Overview

1997 FDA Modernization Act (FDAMA)

- No pediatric safety requirement

2002 Best Pharmaceuticals Children Act (BPCA)

- Requires review of all adverse event (AE) reports for 1-year after pediatric exclusivity is granted.

2003 Pediatric Research Equity Act (PREA)

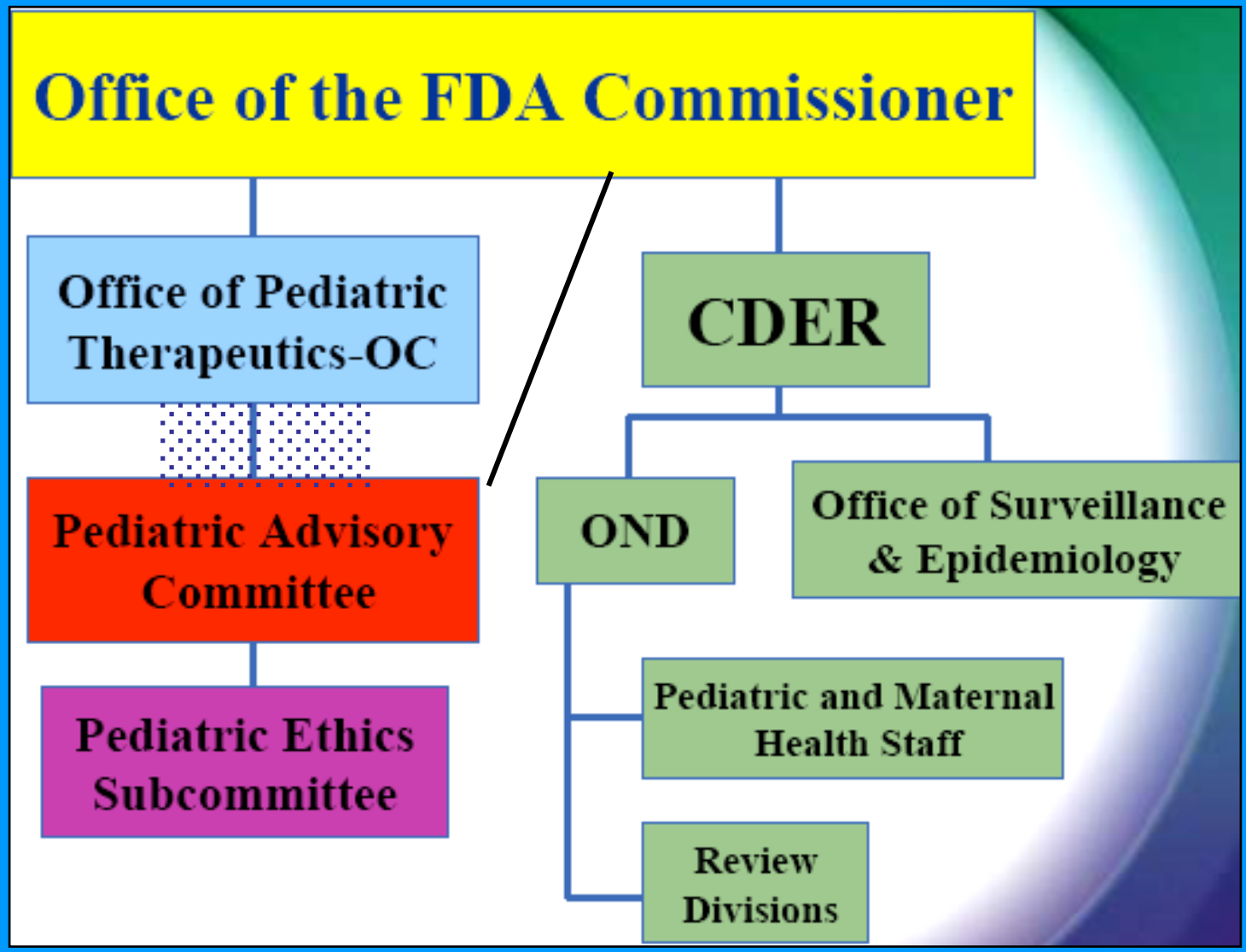
- BPCA is amended to allow the Pediatric Subcommittee of Anti-Infective Drugs AC to become a full PAC

2007 Food & Drug Administration Amendments Act

- Expands the focused pediatric safety reviews to PREA products and certain devices (HDEs)

Pediatric Focused Safety Review Reporting Process

Players: Drug Product Safety Review



Pediatric Safety Review Team and Process

Safety Review Team

OSE: Safety evaluators, epidemiologists (if needed), conduct review of adverse event reports from AERS database and additional data from drug utilization reviewers.

Review Division: Medical officer, pharmacologist, statistician familiar with the pre-market history and trials

PMHS: Medical officers with pediatric expertise

OPT: Manages PAC and coordinates the review by PAC of adverse event reports for drugs granted pediatric exclusivity.

Process

- Initially identifies known concerns
- Safety review is generated. It originally focused on the 1-year AEs, however, upon request by the PAC, it has developed to provide a broader context
- Focused consult and review to address the issues
- Team assesses results, whether any new pediatric safety signals and evaluates need for additional data or analyses

Review Team and Process (continued)

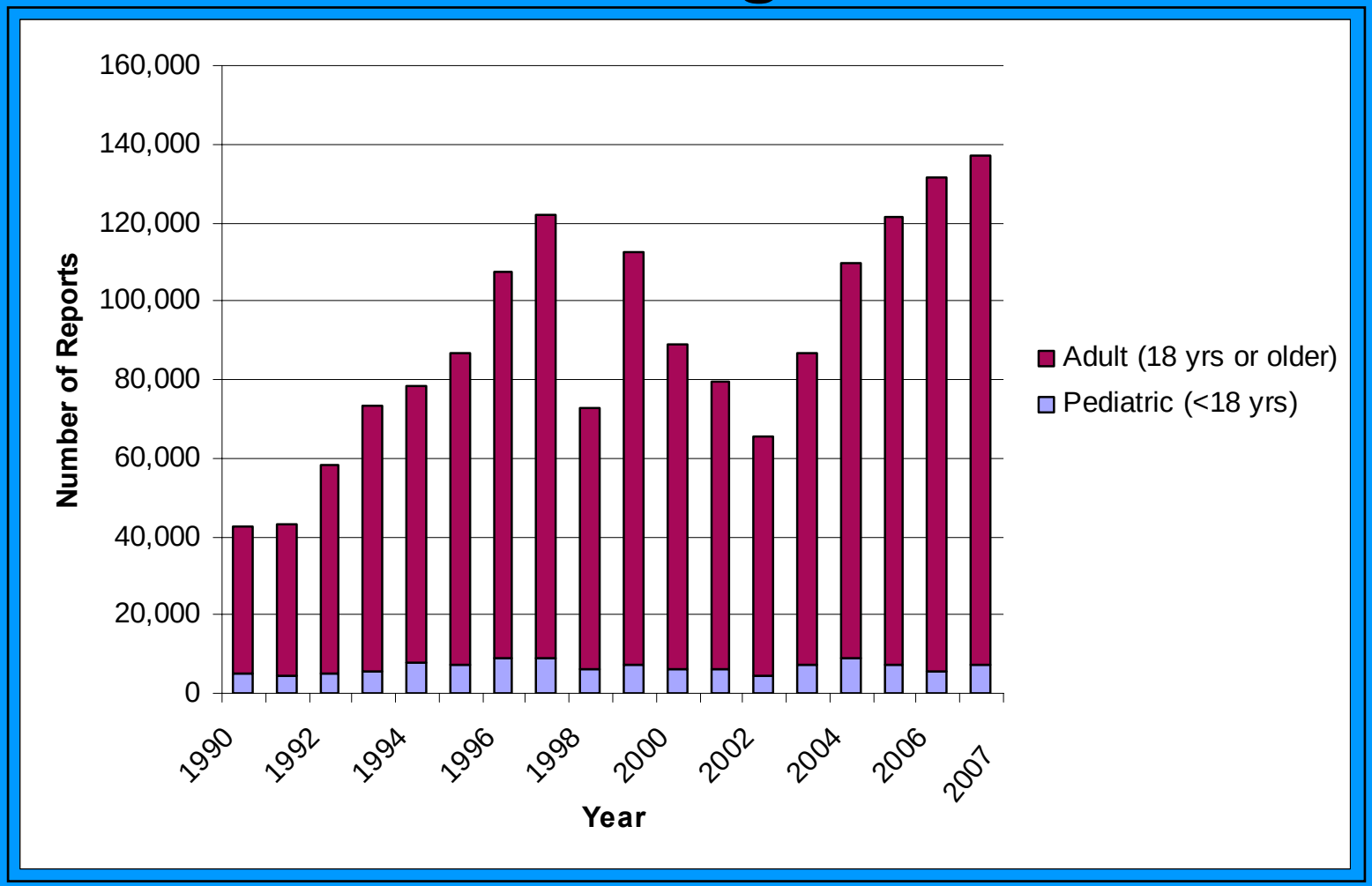
- PAC's role
  - Assess reviews, presentations and PAC questions
  - Advise and make recommendations for action.
- FDA takes these recommendations into consideration and may
  - Recommend return to routine monitoring
  - Recommend product labeling changes
  - Recommend additional safety studies
  - Recommend continued monitoring
  - Use risk minimization (e.g., revise Medication Guides or issue a Public Healthcare Notification or Public Health Advisory)

AERS (Adverse Event Reporting System)

AERS is FDA's reporting system of AEs for approved drugs and therapeutic biologics

- A chief tool for FDA post-market drug surveillance
- Maintained by FDA; Both US and foreign reports
- Majority are from manufacturer, mandatory
- <10% are voluntary reports, mainly by healthcare professionals and consumers (MedWatch)
- Accommodates electronic submissions
- Now more than 4 million adverse reports in AERS
- MedDRA (Medical Dictionary for Regulatory Activities), a tool to assist in retrieval of cases using international codes for signs, symptoms, diagnoses.

FDA AERS Reports in U.S., Crude Counts 1990 through 2007



Adapted from FDA report by Johann-Liang, Wyeth, Chen, Cope

•~1 ½ million AEs thru Dec 2007; 5% were < 18 years of age

Limitations of AERS

- Passive surveillance
  - Underreporting (< 10% all events, variable)
  - Multiple reporting biases (e.g., publicity)
- Data
  - Quality of report is variable & often incomplete
  - Duplicates, missing age, problem with confounders
- Analyses
  - Recognition of AE as a possible “signal”?
  - Reporting Rates are NOT incidence rates (do not really know denominator of use)
  - Drug exposure data – can only be projected

Source: Medwatch. The clinical impact of AE reporting. 1996. Available at: http://www.fda.gov/medwatch/articles/medcont/medcont.htm

The Strengths of AERS data

- Includes all U.S. marketed drugs
- Simple, inexpensive reporting system
- Discovery of previously unknown adverse drug events
- Provides “signals” and can trigger further investigation – call for follow-up, review available data, request study
  - AEs too rare to be seen in trials (e.g., liver failure, aplastic anemia, anaphylaxis)
  - AEs in population not exposed in trials (pregnant women)
  - Greater seriousness than AEs seen in trials

Why not just rely on clinical trials?

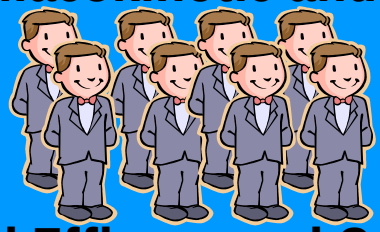
In general:

- **Clinical trials for drug products are limited by**
  - **Size, duration, study population, age group, comorbidity,**
  - **Limited number of trials**

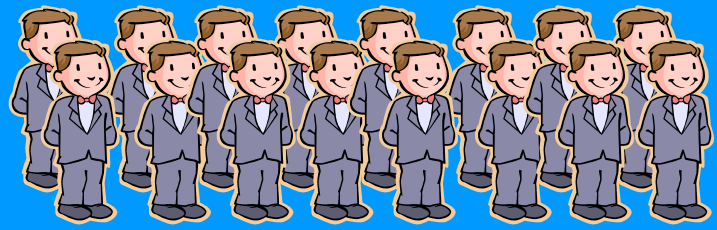
In pediatrics:

  - **Fewer trials**
  - **Fewer patients in trials**
  - **Limited knowledge**

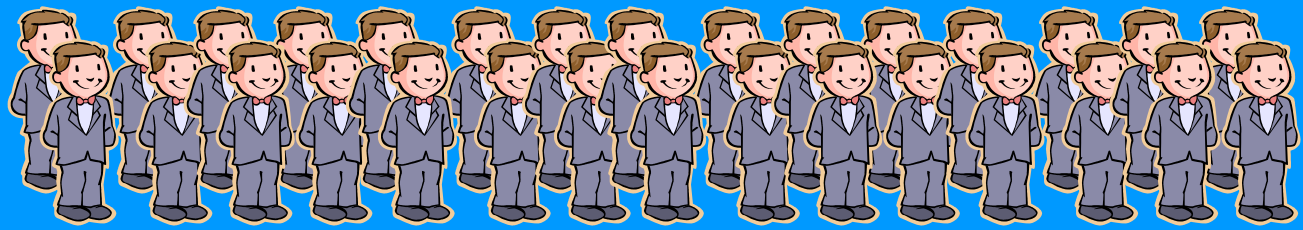
Phase 1 Trials (Pharmacokinetic and Initial Safety Data)



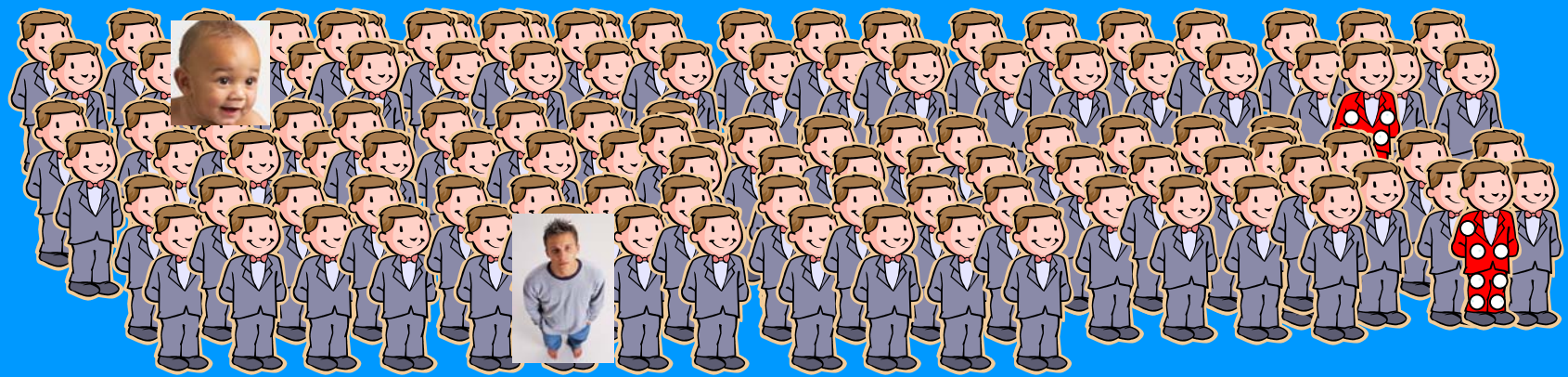
Phase 2 Trials (Initial Efficacy and Continuing Safety Data)



Phase 3 Trials (Pivotal Efficacy and Continuing Safety Data)



Phase 4 Trials (Postmarketing Efficacy and Safety Data)



AERS

AERS may reveal AEs in the "real world" where longer duration of therapy, different use, more vulnerable subgroups of children and greater numbers of children are exposed.

Clinical Evidence Suggestive of Causality

- Temporal relationship
- Positive de-challenge
- Positive re-challenge
- Dose-response relationship
- Biological plausibility
- Absence of alternative etiologies
- Objective confirmation (e.g., toxic blood levels)
- Prior reports of reaction
- Past history of reaction to same or similar drug

From textbook, Principles of Clinical Pharmacology, 2nd Ed. Editors: Abernethy, Atkinson, Daniels, et al. 2007

Pediatric Advisory Committee (PAC) Meetings

How to Improve Safety Reporting to PAC? PAC Recommendations, February, 2005

- Deaths & serious AEs, not the top 10 of 20 AEs!
  - Compare adult and pediatric deaths
- Provide background information on clinical trials
- Request for denominator*
- The PAC agreed to FDA proposal for abbreviated product presentations for safety concerns if PAC still receives complete background materials.
  - FDA to provide reason why they do not think there is a safety signal

*Not possible with present system

What is a <u>Serious AE?</u> 21 CFR 314.80 - Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- **Death**
- **Life-threatening adverse drug experience**
- **Hospitalization or prolongation of hospitalization**
- **Persistent or significant disability**
- **Congenital anomaly / birth defect**
- **Important medical events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes above**

Safety Reporting to the PAC

June, 2003 - November, 2007

- **12 PAC meetings**
- **73 drug products**

2008 GOAL: Complete all BPCA safety reviews triggered by exclusivity date!

2009 New FDAAA legislation

- **Safety reviews triggered by labeling change includes both drugs (BPCA and PREA) and biologic products.**
- **Negative studies mandated for labeling = more products for safety reviews**
- **Adverse event and update reports to PAC will begin for pediatric HDE devices.**

What we have learned and actions taken

Drug Safety Reviews through Nov 2007; n=73 drugs

N	Specialty	Indication
13	Heme-Onc *	11 cancer,1 anemia, 1 thrombocytopenia
12	Endocrine	5 cholesterol, 4 DM, 2 obesity,1 osteoporosis
9	Infectious	3 HIV, 3 bacterial,1 malaria,1 fungi,1 viral)
8	Psychiatric	5 depression, 3 ADHD
6	Eye *	3 glaucoma, 3 infections
6	Allergy	4 allergic skin or rhinitis, 2 asthma
6	Cardiac	5 hypertension 1 arrhythmia
5	GU	2 bladder, 2 renal disorder, 1 birth control
4	Neurology	2 migraine,1 pain,1 seizure
3	Rheumatic *	3 arthritis
1	Other	1 nausea

*All drug products in this category returned to routine monitoring

PAC Safety Reviews: Results 6/03-11/07; n=73

- 48 Return to routine monitoring
- 14 Led to changes of labeling, Medication Guide or Patient Package Insert (PPI)
- 11 Continued monitoring or further analysis

Recent Labeling Revisions or MedGuides

- **2006 Selective Serotonin Reuptake Inhibitors(SSRIs) boxed warnings & MedGuide. For all ages: (1) suicidality or↑ risk of suicidal thinking & behavior and (2) pregnancy non-teratogenic effects (neonatal withdrawal syndrome). Possible rare risk ↑ for persistent pulmonary hypertension.**
- **Jan-Mar 2008 Tamiflu & other antiviral products (e.g.,Relenza) labeling revised to reflect that influenza can be associated with a variety of neurologic and behavioral symptoms and to advise that neuropsychiatric events have been reported in patients receiving oseltamivir, primarily among pediatric patients.**
- **Rosiglitazone (Avandia): "Data are insufficient to recommend pediatric use of rosiglitazone" placed in the pediatric use section of the labeling.**

How will the new legislation change things?

Overview PAC/OPT and FDAAA 2007

- Labeling
- What's a Biologic and Device?
- New laws related to devices used in children

- Why the workload is doubling

FDAAA 2007

- **Prior to FDAAA: under PREA 2003**
  - **No required pediatric safety reviews**
  - **Information on negative studies was NOT put in the labels**
- **FDAAA (BPCA and PREA)**
  - **Submitted pediatric studies: labeling required**
  - **Pediatric information must be added to labeling**
  - **1-year after labeling, safety review of all AEs is conducted with presentation to the PAC.**
  - **Applicants must submit all AEs for pediatric submissions**
  - **Safety review is expanded to include biologics**

Devices – New Responsibilities

- Safety reporting for HDEs with pediatric indication for which profit making is allowed
- Annual reviews to ensure that the exemption remains appropriate

What's a Device?

FDA Device Definition-1998 US Congress Federal Food, Drug, & Cosmetic Act, Sec. 201.[321].

Definition: Instrument, apparatus, implement, machine contrivance, implant, in vitro reagent, similar articles

- **» Not metabolized in the body**
- **» Not a drug, biologic, or food**

Different AE database: MAUDE

Device applications that meet the criteria for pediatric Humanitarian Device Exemption (HDE)

- < 4000 people a year in the U.S.
- Pediatric age ≤ 21 years
- An HDE is exempt from the effectiveness requirements of a PMA, but is required to meet the same safety threshold. Clinical data relevant to the assessment of the risks and probable benefit is required.
- Profit making is allowed on HDEs with a pediatric indication.

Example of Pediatric HDE: Vertical Expandable Prosthetic Titanium Rib (VEPTR)

www.fda.gov/cdrh/devadvice/pma/app_methods.html

What is a Biological Product?

Section 351 PHS Act, as amended by FDAMA

Regulatory definition:

"virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product applicable to the prevention, treatment or cure of diseases or condition of human beings."

Examples:

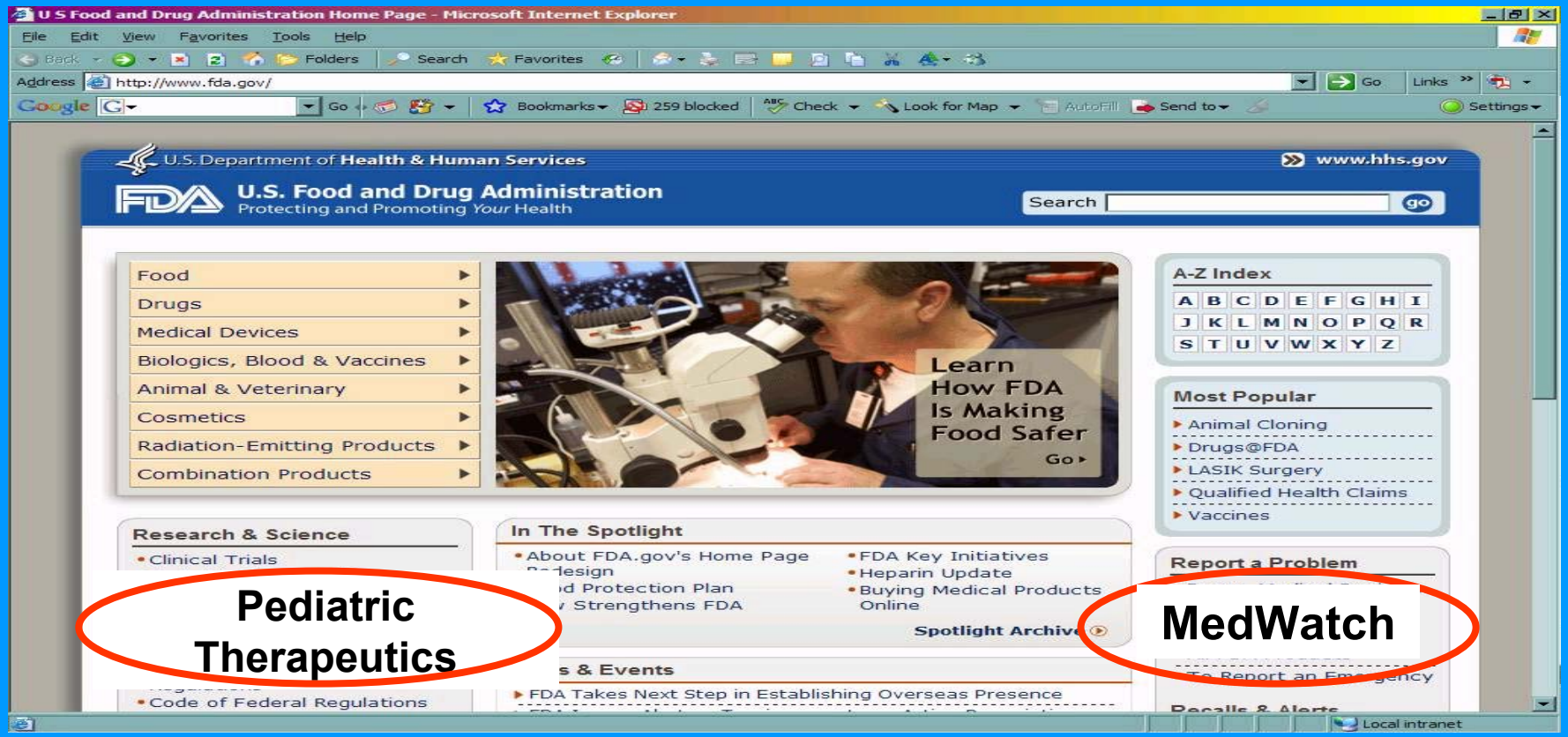
Plasma derived products, vaccines, blood test kits, growth factors, cellular products, antitoxins, monoclonal antibodies, proteins (e.g., cytokines)

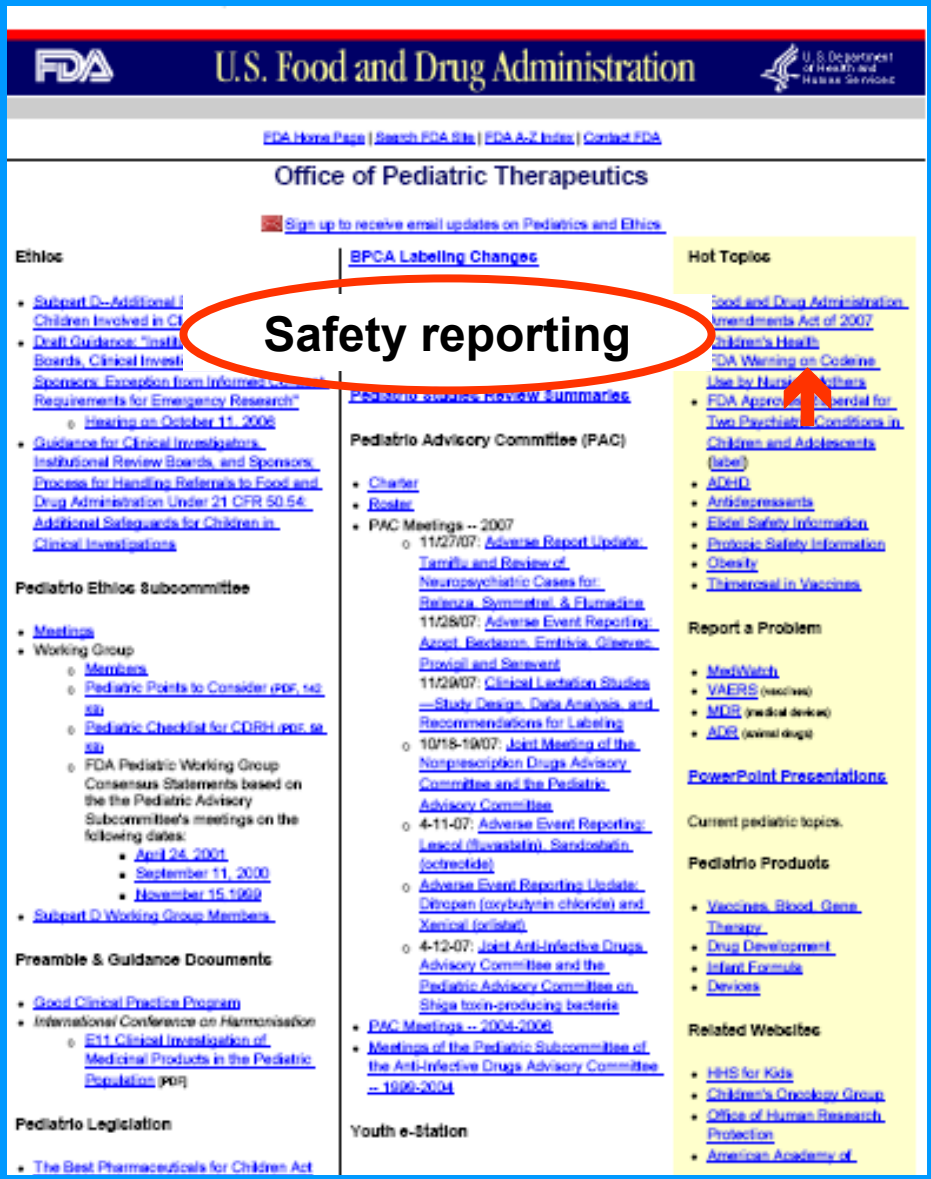
Different AE databases: (VAERS, AERS, etc)

Summary

- Brief overview of pediatric safety legislation
- Pediatric focused safety review reporting process
- PAC meetings
- What we have learned and actions taken
- How will the new legislation change things?

New FDA homepage www.fda.gov





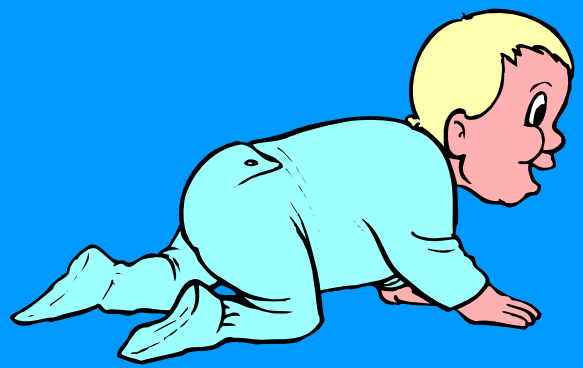
http://www.fda.gov/oc/opt/default.htm

U.S. Food and Drug Administration

Safety Reporting

Drugs Granted Pediatric Exclusivity

Listed below are the drugs granted pediatric exclusivity which have had a report on adverse events presented to the Pediatric Advisory Committee as mandated under Section 17 of the BPCA.

Drug	Date Exclusivity Granted	Date Reported to Advisory Committee	Pediatric Advisory Committee Outcomes
Zoloft (sertraline)	2-1-02	6-12-03	**February 2, 2004,** PAC requested (1) re-analysis of SSRI data once the cases are reclassified; (2) update on neonatal withdrawa syndrome and (3) maternal SSRI'S exposure and congenital eye malformation in infants; June 9, 2004 endorsed class labeling for neonatal toxicity/withdrawal syndrome; **September 13, 2004** In conjunction with the Neuropsychiatry Committee after reviewing t re-analysis of pediatric cases suicidality, the committee voted for MedGuide and warning to be applied to all antidepressants. **October 15, 2004** FDA directs manufacturers of all antidepressar medications to add a "black box" warning and develop a patient medication guide (MedGuide). See templates for proposed chang labeling (http://www.fda.gov/cder/drug/antidepressants/PI_template.pdf) a MedGuide (http://www.fda.gov/cder/drug/antidepressants/MG_template.pdf)
Ditropan (oxybutynin)	2-8-02	6-12-03	**June 12, 2003** PAC requested future review after additional marketing experience. **November 16, 2006** Preliminary reassessment. **April 11, 2007** The PAC requested labeling to include additional information concerning postmarketing reports o hallucinations and agitated behavior in the pediatric population. They noted prescribers might wish to first try decreasing the dose before discontinuing, depending on the circumstances of the adverse event.
Lipitor (atorvastatin)	2-22-02	6-12-03	**June 12, 2003** PAC requested future review after additional marketing experience. **November 16, 2006** Committee recommended return to routine monitoring for adverse events (AE in all populations.
Zocor (simvastatin)	2-22-02	6-12-03	**June 12, 2003** PAC requested future review after additional marketing experience. **November 16, 2006** Committee recommended return to routine monitoring for adverse events (AE in all populations.
Busulfex (busulfan)	3-12-02	10-29-03	**October 29, 2003** Committee recommended return to routine monitoring for adverse events (AEs) in all populations.
Zyrtec (cetirizine)	3-13-02	10-29-03	**October 29, 2003** Committee recommended return to routine monitoring for adverse events (AEs) in all populations.
Cozaar (losartan)	3-20-02	10-29-03	**October 29, 2003** Committee recommended return to routine monitoring for adverse events (AEs) in all populations.

Acknowledgements