Pediatric Safety Surveillance Workshop

Pediatric Safety: Better Surveillance for Children

Dianne Murphy, MD, FAAP
Office of Pediatric Therapeutics
Office of the Commissioner, FDA
September 13-14th, 2010
Children deserve the same level of evidence that is required for adults to determine that therapies used by children are safe, effective and properly dosed.

Children are a heterogeneous group who undergo rapid metabolic, hormonal, physiologic and developmental change.

Over the last two decades, FDA has actively supported many efforts to encourage development of information on appropriate use of therapies in the pediatric population.
Present Solutions

- Provide an incentive and requirement: pediatric exclusivity (the Written Request Process in the US) and data protection (in Europe)
- Require pediatric plans be implemented with development of products used in pediatrics
- Extrapolation of Efficacy if appropriate
- Ensure ethical oversight
- Make the process and the data generated from the process transparent
- Additional emphasis on safety assessments
How product development is different for children

- **Adult product development:**
  - Industry driven
  - FDA does have authority to require post-marketing studies

- **Pediatric product development:**
  - Government driven
  - The Written Request: Issued by FDA. Incentive If sponsor does what FDA requests
  - A Requirement Component-Related to submissions for adult indication which has a pediatric counter-part

- Pediatric information is more public
- Pediatric program has additional safety component
Why Is a Pediatric Focused Safety Review Important?

- Pediatric Studies are small in size
- Even more of the Pediatric population will be exposed post-marketing as there is a much higher “off-label” use in pediatrics
- There are many subpopulations and studies seldom include them all
- Even with small numbers, controlled trials have shown up to 20% of the time a new pediatric specific or higher incidence of adverse event
New Drug Development

Discovery / Screening

Synthesis and Purification

Animal Testing

Pre-IND  IND  NDA

Clinical Studies

Phase 1

Phase 2

Phase 3

Short-term

Long-term

Avg: 5 - 7 yrs

Avg: 6 - 7 yrs

Avg: 1 yr - Standard

Avg: 6 mo - Priority

This is when Pediatrics is often discussed
Pediatric Focused Safety Review-1 year after labeling

- Congressional mandate
- The process involves public discussion
- The Pediatric Advisory Committee
- The web posting of safety reviews

Summary of results thus far:

- 135 products have been reviewed
- Additional pediatric safety information requested to be added to label = 20%
Pediatric Safety statistics since FDAAA 2007

PAC Safety Reporting 9/27/07-12/09
5 meetings; n=46 drug products

PAC discussion and action recommendations

- 25 Return to routine monitoring
- 6 Led to changes of labeling, Medication Guide or Patient Package Insert (PPI)
- 6 Continued monitoring or further analysis
- 9 Recommended labeling change, no changes yet*
  (Abilify, Aldara, Artiss, Asmanex, Derma-Smoother, Diovan, Provigil, Serevent, Ventolin)

*3/9/10
Projected Future Reviews to PAC

2006 (n=8)
2007 (n=9)
2008 (n=15)
2009 (n=27) planned
2010 (n=44) anticipated
BPCA and PREA: Lessons Learned

Out of 385 products studied through June 2010:

- Efficacy not established/ data insufficient to recommend pediatric use: 69

- Safety profile may differ between pediatric and adult patients: 72 (19%)
Limitations of Present Process

- Adverse Event Reporting system (AERS)
- Passive System
- Content of report usually limited
- Massive Under-reporting
- Limited ability to gather additional information
- No Query capabilities re proactive surveillance
Frustration

The pediatric Advisory Committee members have repeatedly requested

1) better data
2) some form of a denominator
3) additional information not available from present system
How Can YOU Help?

The Pediatric Safety program needs resources that can do the following:

- Provide data that has age down to months and weeks for neonates
- Provide information on indications that are pediatric specific
- Provide information on pediatric specific parameters such as growth and development
How Can YOU Help?
continued

❖ Provide data on in-patient and out-patient events with specific needs for information from neonatal ICUs, pediatric ICUs, pediatric subspecialty clinics and pediatric emergency room visits

❖ Ideal system would also be able to address specific “prospective” initiatives = based on a “high level” protocol, data would be collected prospectively on adverse events and specific therapies. Confirmation would be possible from medical records
Goals

- Provide a clear picture of what FDA’s PEDIATRIC needs in this area are
- Obtain a better idea of what systems exist that might be able to address some of these pediatric needs
- Develop a dialogue for ongoing future pediatric queries or projects
- Encourage you to participate in the pediatric advisory committee’s safety assessments
So Where are we now?
FDA Homepage

Drug Information Association www.diahome.org

Science & Research
- Combination Products
- Critical Path Initiative
- Clinical Trials
- Pediatrics
- Rare Diseases
- Toxicological Research

More Science & Research

Regulatory Information
- How to Comment on Proposed Regulations
- Code of Federal Regulations
- Dockets Management
- FDA Federal Registers (FR)
- Laws FDA Enforces

Benadryl Gel: Use on Skin Only

Get Updates
- E-mail Updates
- RSS RSS Feeds
- RSS Help

FDA Basics
Ask Questions, Get Answers, Meet FDA Staff

Spotlight
- HHS Resources for Haiti
- HHS 2011 Budget Announced
- FDA Budget
- HHS Budget
- Transparency Task Force
- Expanded Access to Investigational Drugs
- Strategic Plan for Risk Communication

News & Events
- May 12, 2010 - FDA: Serious Side Effects from Swallowing Topical Benadryl Product
- May 11, 2010 - ‘Bad Ad Program’ to Help Health Care Providers Detect, Report Misleading Drug Ads
- May 10, 2010 - Federal and State Officials Confirm Link Between Bagged Romaine Lettuce and E. coli O145 Illness
- May 10, 2010 - Federal and State Officials Confirm Link Between Bagged Romaine Lettuce and E. coli O145 Illness
Science & Research
Home > Science & Research > Science and Research Special Topics > Pediatrics

Pediatrics

Resources for You
- Pediatric Drug Development
- MedWatch: The FDA Safety Information and Adverse Event Reporting Program
- Pediatric Medical Devices
- MedSun: Medical Product Safety Network
- Vaccines, Blood & Biologics
- Vaccine Adverse Events
- Foods
- FDA 101: Infant Formula

New Pediatric Labeling (PDF - 1221 KB)
Safety Reporting Updates
Pediatric Studies Characteristics (PDF - 1620 KB)

Ethics
Provides information on ethical issues raised in the development and use of FDA-regulated products in infants, children and adolescents.

Safety
Resource for pediatric safety information related to drugs, biologics, and devices.

Related Links
- Children's Oncology Group
- American Academy of Pediatrics
- Glaser Pediatric Research Network
- European Medicines Agency (EMA)
- HHS for Kids
- Bill and Melinda Gates Foundation
- Get Email Updates

Spotlight
- Safety Concerns About Testosterone Gel
- AAP News FDA Update
- NIH Children and Clinical Studies

Contact Us
OC-Office of Pediatric Therapeutics
- 301-827-1996
- 301-827-1917
Resources for You

- Pediatric Drug Development
- MedWatch: The FDA Safety Information and Adverse Event Reporting Program
- Pediatric Medical Devices
- MedSun: Medical Product Safety Network
- Vaccines, Blood & Biologics
- Vaccine Adverse Events
- Foods
- FDA 101: Infant Formula

Related Links

- NIH Children and Clinical Studies
- Table of Medicines with New Pediatric Information - Searchable (PDF - 1221 KB)
- Safety Reporting Updates
- Pediatric Studies Characteristics (PDF - 1620 KB)

Ethics
Provides information on ethical issues raised in the development and use of FDA-regulated products in infants, children, and adolescents.

Safety
Resource for pediatric safety information related to drugs, biologics and devices

Scientific Activities and Statistics
Resource for information related to pediatric studies, written request for pediatric studies and literature articles

International Collaborations
Exchange of scientific and regulatory information related to pediatric therapeutics.

Contact Us
OC - Office of Pediatric Therapeutics
☎ 301-796-8659
✉ OPT@fda.hhs.gov
## Safety Reporting

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. Click on the Drug Name to go to the meeting materials.

N=123

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date Exclusivity Granted</th>
<th>Date Reported to Advisory Committee</th>
<th>*Pediatric Advisory Committee Recommendations and Subsequent Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoloft (sertraline)</td>
<td>2-1-02</td>
<td>6-12-03</td>
<td>February 2, 2004 Pediatric Subcommittee (PS) in conjunction with the Psychopharmacologic Drugs Advisory Committee (PDAC) requested re-analysis of Selective Serotonin Reuptake Inhibitor (SSRI) data once the cases are reclassified and for FDA to issue a warning in the interim on the potential side effects of the SSRIs. <strong>February 3, 2004</strong> PS agreed to future update on SSRIs, neonatal withdrawal, and eye malformation; On <strong>March 22, 2004</strong> FDA issued a Public Health Advisory; <strong>Antidepressant Public Health Advisory</strong> June 9, 2004 PS endorsed class labeling for neonatal toxicity/withdrawal syndrome; <strong>September 13, 2004</strong> PAC in conjunction with the PDAC Neuropsychiatry Committee after reviewing...</td>
</tr>
<tr>
<td>Product</td>
<td>Approval Date</td>
<td>Committee Meeting Date</td>
<td>Committee Recommendations</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------</td>
<td>------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Evinil [fibrin sealant (human)]</td>
<td>NA</td>
<td>12-08-09</td>
<td>December 8, 2009 Committee recommended return to standard, ongoing monitoring for adverse events.</td>
</tr>
<tr>
<td>Artiss [fibrin sealant (human)]</td>
<td>NA</td>
<td>12-08-09</td>
<td>December 8, 2009 Committee recommended that FDA consider revising the label to include information on specific ages of those studied in the pre-market clinical trials. Committee discussed the use of this product in very young children with burns. And recommended that its use be studied in children less than 1 year. Committee recommended return to standard, ongoing monitoring for adverse events.</td>
</tr>
<tr>
<td>Cancidas (caspofungin)</td>
<td>4-15-08</td>
<td>12-08-09</td>
<td>December 8, 2009 Committee agreed that FDA: 1) update the labeling to clarify the hepatobiliary events that have been reported in pediatric and adult patients; 2) conduct a study in infants who were less than 3 months of age who had fungal infections and needed this therapy; 3) return to standard, ongoing monitoring for adverse events. January 28, 2010, revised label.</td>
</tr>
<tr>
<td>Ventolin HFA (albuterol)</td>
<td>8-27-08</td>
<td>12-08-09</td>
<td>December 8, 2009 Committee discussed route of drug administration (HFA and nebulizer) for children 0-4 years of age and discussed the safety risk from lack of efficacy for this product for children less than 4. Committee recommended that FDA return to ongoing safety monitoring, and recommended that the label be amended to include additional information including warnings for children 0-4 years of age.</td>
</tr>
<tr>
<td>Ocrenia (abatacept)</td>
<td>NA</td>
<td>12-08-09</td>
<td>December 8, 2009 Committee recommended return to standard, ongoing monitoring for adverse events.</td>
</tr>
<tr>
<td>Humira (adalimumab)</td>
<td>NA</td>
<td>12-08-09</td>
<td>December 8, 2009 Committee recommended return to standard, ongoing monitoring for adverse events.</td>
</tr>
</tbody>
</table>