

**Adverse Event Review and Reporting
as Mandated by Best Pharmaceuticals
for Children Act:
Summary of Committee Feedback and
Options for Improvement**

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Best Pharmaceuticals for Children Act (BPCA)

(1/4/02)

- **Section 17: Adverse Event (AE) Reporting**
 - review AEs reported during the one-year period after pediatric market exclusivity is granted
 - report to the Pediatric Advisory Sub-Committee for review (renamed Pediatric Advisory Committee)

BPCA-Mandated AE Review Program

- Developed an internal process and template for pediatric post-marketing adverse event review
- Office of Pediatric Therapeutics (OPT) provides oversight and coordination
- Office of Drug Safety (ODS) performs primary reviews of drug use and adverse event reports
- Division of Pediatric Drug Development (DPDD):
 - prepares the background materials
 - evaluates and synthesizes the overall safety review including the clinical studies
 - presents review to the PAC for public discussion

BPCA-Mandated AE Review Program (cont.)

- Improvements in quality and content of material presented to PAC
 - Enhancements to background package:
 - ODS written primary reviews of drug use and adverse events
 - Written summary of the clinical and pharm tox review of pediatric exclusivity studies
 - Slide presentations by DPDD
 - Timeline
 - Improved timeline for mailing background materials

Program Status and Outcomes

- 6 Pediatric Advisory Committee Meetings (2003-2005)
- 34 drugs: AE reviews presented for public discussion
- Safety issues (action)
 - Neonatal withdrawal syndrome/toxicity from maternal exposure to SSRIs (new labeling added)
 - Suicidal behavior from anti-depressant use in pediatric patients (new labeling including boxed warning, med-guide, PHA, talk papers)
 - Pediatric deaths from inappropriate use of fentanyl transdermal patch (new labeling added, risk minimization plan initiated)

Summary of Committee Feedback

- **Feedback requested on BPCA-mandated post-marketing adverse event reporting**

Committee Feedback Themes

- **Denominator Data (exposure) Problems**
- **Numerator Data (adverse events) Problems**
- **Active Surveillance**
- **Sponsor issues**

Summary of Committee Feedback

- **Denominator Data (exposure) Problems:**
 - Event rates, background rates
 - Measures of risk (excess risk, rate ratios, pediatric to adult ratios, p-values, confidence intervals)
 - Assessment of public health importance
- **Response:**
 - Acquired larger pediatric inpatient drug use database (Premier)
 - Funded feasibility study of pediatric inpatient drug use projection project (CHCA inpatient data)
 - Continued access to multiple drug use data resources (IMS Health, Caremark, etc)
 - Collaborated with NIH to estimate frequency of outpatient medication use (Medicaid, HMO, PBO)

Summary of Committee Feedback

- **Numerator (adverse event report) problems**
 - Standardize AE coding across drug programs to enable pooling of safety data for analysis
 - Grading system for serious adverse events for follow-up investigation
- **Response:**
 - MedRA coding is standard for post-marketing reports (since 1997).
 - Trained Medical Officers (DPDD) to search AERS; quarterly Pediatric review in place
 - DPDD secondary hands-on review of case reports and follow-up

Summary of Committee Feedback

- **Active surveillance**
 - Develop an active population based surveillance system
 - Build upon existing active systems
 - Collaborate/consult with other stakeholders
- **Response:**
 - Under consideration

Summary of Committee Feedback

- **Sponsor issues:**
 - Share safety reviews with sponsors early
 - Consider pre-AC meeting with sponsor
- **Response:**
 - Sponsors notified of meeting 1-2 months prior to the PAC meeting date
 - Sponsors receive copy of slide presentations 3 days before PAC meeting
 - Some sponsors have provided additional case information

Improving Postmarketing Pediatric Adverse Event Reporting and Review: Options for Discussion

- **With current resources**
- **With additional resources**

With Current Resources: Content and Format of Safety Presentation

No Safety Signal Detected

Definition

- no AEs reported or reported AEs raise no potential safety concern
- all labeled events, no increase in frequency or severity

Action

- Provide abbreviated written summary report

With Current Resources: Content and Format of Safety Presentation

Possible Safety Signal Detected

Definition

- increase in frequency or severity of expected adverse events
- unexpected serious adverse events
- events that are unique to pediatric patients

Action

- In depth background and safety review
- PAC presentation and public discussion

Content and format of presentation (cont.)

- **Full public presentation will include a review of:**
 - Drug use and reported adverse events
 - Pediatric exclusivity studies and relevant safety labeling
 - Review of the literature
- AND**
- When possible, an analysis of
 - event incidence rate (reporting rates), background rates
 - biologic plausibility

Options with Current Resources: Dissemination

- **Post summary of the safety findings and outcome on the OPT web-page;**
- **Develop linkages to relevant reviews and labels**
- **Publish an annual summary of the BPCA-mandated safety review results**

Potential Programs with Additional Resources

- **Active post-marketing drug AE surveillance**
- **Administrative/claims database**
- **Linkages between AERS and registries (exposure or disease/outcome registries, COG)**
- **Require long-term safety studies**
- **Active surveillance programs containing drug use information**
- **Outreach to increase number, quality and completeness of AE reports**

Active Postmarketing Surveillance

- Can be health facility/network or physician-office based sentinel system
- Need to have capacity to monitor specific populations such as children, pregnant women, specific outcomes or drug exposures
- Strength
 - Higher quality, prospectively collected data
 - Better handle on denominator (exposed) and numerators (events)
- Limitation
 - Can be expensive
 - Representativeness?

Administrative Claims Databases

- Large automated, longitudinal databases that link prescription dispensing information (dose, duration, date) to claims data for outcomes of interest (e.g. diagnosis, procedures, interventions, etc)
 - **Strength**
 - Population based, longitudinal drug utilization data
 - Cohorts of unexposed patients for comparison
 - Hypothesis testing, signal detection, and quantification
 - **Limitations**
 - No in-hospital drug exposure data
 - Difficulty obtaining medical records
 - Difficult to ascertain death

FDA's Cooperative Agreement Databases

<u>Site</u>	<u>Healthcare Setting</u>	<u>Location</u>	<u>Size (Millions)</u>	<u>Years of Data</u>
Vanderbilt	Medicaid	TN; Cal	1.5; 3.0	20; 2
Harvard	3 HMOs	MA; MN	~2.0	5
UnitedHealth	IPA	10 states	~3.0	7

Examples of Recent Analysis Using Claims Data from FDA's Cooperative Agreement Program

- **2000 cisaperide use in contraindicated settings**
- **2000 alosteron use and ischemic colitis**
- **2001 Claritin D-24 Hour use and esophageal obstruction**
- **2002 leflunomide use patterns**
- **2003 statin use and risk of rhabdomyolysis**

Linkages with Existing Registries

- **Exposure (drug) registry**
 - Pregnancy registry, e.g. anti-epileptic drugs
- **Event (outcome) registries**
 - acute liver failure, aplastic anemia
 - Cancer registries: state-based, Children's Oncology Group
 - State-based birth defects registries

Long-Term Pediatric Safety Studies

- Incorporate assessment of growth as a routine part of the safety studies in pediatric written request
- Where appropriate, request a longer term safety studies after submission of results for exclusivity
- Types of studies may include:
 - Controlled studies
 - Open label extensions
 - Cohort studies
 - Registry studies

Analysis of Other Existing Active Surveillance Systems

- National Electronic Injury Surveillance System (NEISS)
- Drug Abuse Warning Network (DAWN)
- Toxic Exposure Surveillance System (TESS)

NEISS

- Data are gathered from a probability sample of 64 Emergency Departments (ED) of U.S. hospitals
- All injuries treated in EDs including drug related
- Strengths:
 - Nationally representative, active surveillance system
 - ED medical records (demographics, cause of injury, outcome)
 - Relatively inexpensive
- Limitations:
 - Acute events with onset in outpatient settings (overdoses, anaphylaxis, rashes, etc.)
 - Presented to EDs and clinically confirmed cases

Drug Abuse Warning Network (DAWN)

- Data gathered from emergency department visits
 - stratified probability sample of short-term, general, non-Federal hospitals (n=900 EDs)
- Medical examiner/coroners: 300 jurisdictions in 48 metropolitan target areas
 - New DAWN 2003: Implementation of redesigned system

New Drug Abuse Warning Network (New DAWN)

- Strengths
 - Extensive drug information:
 - illicit, prescription, OTC, dietary supplements
 - non-pharmaceutical inhalants
 - High and low frequency events
 - New and old drugs
 - Statistically valid ED estimates, trends
- Limitations
 - incidental reporting of drugs taken for legitimate therapeutic purposes
 - Non-specific drug reporting: brand, chemical name, etc.

Toxic Exposure Surveillance System (TESS)

- Began in 1983
- Data gathered from calls to 64 participating poison control centers across 48 states and D.C. (as of 2001)
- Data:
 - Demographics
 - substance (name of Px, OTC, pesticide, plant, etc.)
 - reason for exposure: intentional, unintentional, adverse drug reaction
 - route of exposure
 - duration of exposure, duration of clinical effects

Toxic Exposure Surveillance System (TESS)

- Strength
 - Large number of reports, 2 million plus in 2001, >34 million poison exposure data since its inception
 - Able to describe patterns of poisoning by substance, demographics and outcome
- Limitation
 - No national projections possible
 - Cannot examine overall trend (due to year-to-year changes in participating centers)

More Options With Additional Resources: Outreach Program

- Increase the number and quality of AE reporting to MedWatch
 - Public outreach (PSA, brochures, website, etc.)
 - Professional outreach (CME courses, mailings, e-mail reminders)
 - Hospital and clinic outreach (brochures, mailings)
 - Video broadcast

Final Thoughts Before the Discussion

- Current post-marketing data systems are problematic for assessing drug safety signals in the pediatric population.
- We need your advice on how best to utilize information to optimize pediatric drug safety monitoring.