Pediatric Studies Conducted under BPCA and PREA

FDA Presentation and Discussion
Institute of Medicine
December 17, 2010
Agenda - Overview

• Overview and impact of pediatric legislation (since 1997)
  – Dianne Murphy, M.D., Office of Pediatric Therapeutics (15 minutes)
• Elements of FDAAA 2007 and implementation within CDER
  – Lisa Mathis, M.D., Center for Drug Evaluation and Research (5 minutes)
• Elements of FDAAA 2007 and their implementation within CBER and comments on IOM tasks 5, 6 and 7
  – Jennifer Ross, Ph.D., Center for Biologics Evaluation and Research (10 minutes)
Agenda – IOM Task Order

• Overview of the IOM task order, including data available
  – Robert “Skip” Nelson, M.D., Ph.D., Office of Pediatric Therapeutics (5 minutes)

• Comments on specific topics for IOM assessment
  – Drug labeling (IOM tasks 1 and 2) (5 minutes)
    • Dianne Murphy, M.D., Office of Pediatric Therapeutics
  – Extrapolation (IOM task 3)
    • Julia Dunne, M.D., Office of Pediatric Therapeutics (5 minutes)
  – Ethics, neonates, alternate endpoints (IOM Task 3)
    • Robert “Skip” Nelson, M.D., Ph.D., Office of Pediatric Therapeutics (10 minutes)
  – Adverse events (IOM task 4)
    • Judith Cope, M.D., M.P.H. Office of Pediatric Therapeutics (5 minutes)

• Questions from the committee
Disclosure

• The individual views and opinions offered during this presentation and discussion do not necessarily reflect those of the Department of Health and Human Services or the Food and Drug Administration.
Overview and impact of the pediatric legislation (since 1997)

Dianne Murphy, M.D.
Director, Office of Pediatric Therapeutics
Office of the Commissioner
Goals

• Provide condensed historical background to better understand how we arrived at the present place in pediatric drug development

• Provide some thoughts on where we are now
The Problem: \( N = 1 \)

- Ignorance is poor public policy and yet it best describes what has been the status of our understanding of how best to use therapeutics in the pediatric population.
- Each child becomes an experiment of 1. There is no methodical data accrual to guide safe and efficacious drug administration and few if any controlled trials to test the current prescribing hypothesis.
FDA and Pediatric Health

• Therapeutic crises historically involved children, but resulting laws actually benefited adults

• Information on use of therapeutics in children remained inadequate

• Finally, in the late part of the 20th century, laws were passed to specifically address drug use in children
Benchmarks (20th Century)

Pediatric Drug Development

- 1977 - AAP statement concerning the need to conduct trials in children
- 1979 - FDA “requires” trials in children parallel to adult process
- 1994 - FDA requires sponsors to update label; introduces “extrapolations”
- 1997 - Congress passes FDAMA/Exclusivity Provision – “Incentives” (voluntary)
- 1998 - FDA publishes Pediatric Rule (mandatory)
Benchmarks (21st Century)

Pediatric Product Development

- 2002- Court Enjoins Pediatric Rule of 1998
- 2002- FDAMA Exclusivity Sunsets
- 2002- Congress passes Best Pharmaceuticals for Children Act (BPCA)
- 2003- Congress passes Pediatric Research Equity Act (PREA)
- 2007- Sunset for BPCA & PREA
- 2007- FDA Amendments Act (FDAAA)
Benchmarks (21st Century)  
Pediatric Product Development  
(continued)

• 2002 – Congress passes BPCA
  – renewed Exclusivity
  – provides process for “off-patent” drug development (NIH)
  – public posting of studies (summaries)
  – reporting of all AE’s 1 year after Exclusivity granted

• 2003 – Congress passes PREA
  – Requires the study of drugs and biologics for pediatric population except in defined situations
  – Creates Pediatric Advisory Committee (from Subcommittee)
Important Components of FDAAA

- Mandated labeling for almost all submitted pediatric studies (Drugs and Biologics)
- Transparency enhanced by increasing the data being posted from the studies and requiring posting of the Written Request
- Expansion of the focused pediatric safety reviews
- Extending reach to Devices
- Requiring Pediatric input into all components
Legislation encouraging pediatric studies and availability of quality pediatric data IS resulting in new product labeling. Our job is to ensure those products are safe and labeled to reflect emerging safety signals that occur once the product is used in larger numbers of the pediatric population.
ONGOING LESSONS LEARNED

1. Pharmacokinetics are more variable than anticipated.
2. Pediatric specific adverse reactions are being defined and are common.
3. Trial designs are being modified as we learn from submitted studies.
4. Pediatric-specific ethical issues continue to be a challenge and more education is needed at many levels.
5. Pediatric expertise only recently being applied more consistently to process.
6. Legislation is “in parts” and still contributes to a fragmented approach.
The Knowledge Gap in Pediatric Therapeutics Continues

• How did we get to this state of ignorance?
• Why was it acceptable that a population that is growing, developing and inherently highly variable would not be studied while the more stable, not growing and less variable adult population was?
• We have just begun to understand how much we do not know or were wrong in our assumptions
You don’t know what you don’t know.

Pediatric Drug Development: It is like turning over rocks and discovering how much you did not know about what was under the rock. The next problem is how to communicate what is under the rock and how to answer questions that arise from looking.
Acronyms

• FDAMA: Food and Drug Administration Modernization Act
• BPCA: Best Pharmaceuticals for Children Act
• PREA: Pediatric Research Equity Act
• WR: Written Request (FDA issues)
• PPSR: Proposed Pediatric Study Request (sponsor submits)
• FDAAA – FDA Amendments Acts
Elements of FDAAA 2007 and implementation within CDER

Lisa Mathis, M.D.
Pediatric and Maternal Health Staff, Office of New Drugs, Center for Drug Evaluation and Research
Objectives

• Review major changes to BPCA and PREA under FDAAA
• Describe Pediatric Review Committee
• Discuss implementation of FDAAA in CDER
BPCA and PREA

• Provided requirements and incentives to obtain data in the pediatric population
• Reauthorization improved quality and consistency
• Provided for greater transparency
Changes under FDAAA: Improved Quality and Consistency

• Established Internal Pediatric Review Committee (PeRC) to provide consistency in pediatric drug development requirements and requests across divisions in CDER and CBER

• PeRC meets weekly to review and provide recommendations for both drugs and biologic
Changes under FDAAA: Improved Quality and Consistency (cont)

• PREA review includes
  – Pediatric Assessments before approval
  – Waivers and deferrals of required studies
  – Pediatric Plans before approval
    • Not protocols

• BPCA review includes
  – Pediatric Written Requests

• Duties also included retrospective review and tracking and posting of statistics
Pediatric Review Committee

• Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and the Office of the Commissioner (OPT), including:
  – Pediatrics - Clinical pharmacology
  – Statistics - Chemistry
  – Legal issues - Ethics
  – Toxicology - Safety
Pediatric Review Committee

• PeRC is an additional duty for all members.
• Pediatric expertise introduced at the end of the application process.
• Review not at protocol level.
Pilot Program

• To address need for pediatric expertise in development process, pilot program established
• Involves PMHS and pediatric experts from the Office of Clinical Pharmacology
• 3 Divisions
• Intervention at NDA filing,
  – By integrating a pediatric medical reviewer and regulatory expert with the review team at the time of NDA submission, deficiencies identified and planning improved
• Goal would be to expand across all 18 review divisions, intervene in IND phase
Changes under FDAAA: Increased Transparency

• When studies are submitted in response to PREA post marketing commitments and/or a Written Request, information must be included in labeling

• Written Requests posted after exclusivity determination

• Posting of medical, statistical, and clinical pharmacology review for products labeled
Changes under FDAAA: Increased Transparency

- Safety review to be performed at 1 year post labeling for all PREA assessments/WR responses with presentation to Pediatric Advisory Committee
- Study information (types of studies, Countries where studies were conducted, number of pediatric patients, etc) posted
Elements of FDAAA 2007 and their implementation within CBER and comments on IOM tasks 5-7

Jennifer Ross, Ph.D.
Center for Biologics Evaluation and Research
Overview

• Introduction to CBER
• Pediatrics and CBER
• Comments on Tasks 5-7
Examples: CBER-regulated products

- Vaccines
  - preventive and therapeutic
- Blood products
  - clotting factors, immunoglobulins, and related recombinant products
- Gene Therapy
- Cellular Products
- Allergenics
Pediatrics & CBER

• CBER Pediatric working group
  - Cross-cutting working group meets monthly
  - Activities include:
    - Forum for intracenter information exchange, brainstorming
    - Discussion of novel issues
    - CBER pediatric webpage
    - PREA stats

• PeRC membership
• PAC process
• 30% of medical officers are pediatricians
Tasks 5-7

• **Task 5:** Review and assess the number and importance of biological products for children that are being tested as a result of the Biologics Price Competition and Innovation Act of 2009 and the importance …of labeling changes made as a result of such testing

• **Task 6:** Review and assess the number, importance, and prioritization of any biological products that are not being tested for pediatric use

• **Task 7:** Offer recommendations for ensuring pediatric testing of biological products, including consideration of any incentives, such as those provided under section 505A of the FD&C Act or section 351(m) of the PHS Act
Overview of the IOM task order, including data available

Robert “Skip” Nelson, M.D., Ph.D.
Office of Pediatric Therapeutics
Office of the Commissioner
Creating the Task Order

• The Task Order follows closely the language found in FDAAA 2007.
• There was internal discussion of the challenges that the IOM committee will face in addressing one or more of these tasks.
• FDA did not believe it had the authority to modify or omit any of the tasks.
What Data are Available?

• FDA understands that data provided to IOM are posted to a public docket. This policy presents a challenge for FDA to be able to provide non-public data to IOM.

• Given this situation, FDA decided (after discussion with IOM) to limit task order to review of publicly available data.

• Publicly available data on BPCA and PREA activities may be sufficient (with supplementation as needed) for the Committee to accomplish the tasks.

• FDA is committed (while recognizing of legal and resource constraints) to working with the Committee to provide adequate data in support of a meaningful assessment of BPCA and PREA.
Avenues for Data Supplementation

- Put selected documents through the internal FDA clearance process
  - Limited option given current staffing of office that provides clearance.
  - Similar to FOIA review process for the posting of data in Drugs@FDA.
- Perform FDA internal analysis of documents; providing aggregate and/or de-identified data to the committee
- Provide selected documents/data to individual committee members (e.g., SGE) who can report to committee
- Identifying for IOM where public data can be found based on FDA internal analysis
- Other ways compatible with IOM and FDA procedures
Three Public Data “Eras”

1. FDAMA (1997-2002)
   - Lists of Written Requests and Exclusivity Determinations (i.e., no documents other than Drugs@FDA)

2. BPCA (2002-2007)
   - Summaries of Medical and Clinical Pharmacology Reviews for Drugs granted Exclusivity (BPCA only)

3. FDAAA (2007-present)
   - Medical, Statistical, and Clinical Pharmacology Reviews (BPCA and PREA)
   - Pediatric Study Characteristics
   - List of Exclusivity Determinations Including Written Request

- Pediatric Labeling Changes (1997-present)
Context for IOM Assessment

• BPCA/PREA should be evaluated in light of their stated purpose to improve pediatric labeling.
• There have also been significant changes in the pediatric program at FDA in response to legislation.
• Two examples:
  – Prior to FDAAA 2007, legal interpretation restricted WRs to either “on” or “off” indication studies. This “forced” choice may have left some indications “off the table.”
  – Prior to FDAAA 2007, there was no requirement for pediatric input (e.g., PeRC) into either BPCA or PREA divisional activities.
• Thus, an assessment of more recent FDA activities may be more useful to inform future implementation.
Comments on Specific Tasks: Drug labeling (IOM tasks 1 and 2)

Dianne Murphy, M.D.
Office of Pediatric Therapeutics
Office of the Commissioner
Tasks 1 and 2

1. Review and assess a representative sample of written requests issued by the Secretary and studies conducted under BPCA since 1997, and labeling changes made as a result of such studies;

2. Review and assess a representative sample of studies conducted since 1997 under PREA or precursor regulations, and labeling changes made as a result of such studies;
Task 1: WR’s & Labeling

- The process to implement the exclusivity component (incentive) involves FDA issuing a Written Request (WR).
- From 1997-2007 we were told by our lawyers we could not put both “on” and “off” label indications in same WR.
- We ask a series of questions to determine if we should issue a WR.
- If we decide to issue a WR, we ask for studies for as many indications and populations we think are justified by the present state of knowledge.
Task 1: (cont’d)

• Sponsor could decline WR or later ask for amendments
• Sponsor submits requested studies in the time specified
• FDA’s internally constructed Exclusivity Board reviews the division’s determination if the sponsor has “fairly met” the terms of the WR. If the answer is yes, and the board agrees, the sponsor is granted the additional 6 months of marketing exclusivity
• Even if the sponsor “failed” to obtain the indication, they can receive the marketing exclusivity.
• Irrespective of success or failure, FDA began to put the information in the label.
Task 1: Labeling

• Putting information in a label for a “failed” study requires careful wording to provide information without providing the sponsor a “de facto” marketing indication

• Labeling = information. We consider this the “metric” that is the deliverable

• Information will hopefully provide more informed utilization of pediatric products
Task 2: Studies and Labeling

• For Adults, FDA does NOT usually put anything in the label about failed studies and often cannot (because of confidentially laws) even say if the study was done.

• Putting information about the Studies is important for pediatrics because it is unlikely that any additional studies will be conducted.
Task 2: (cont’d)

• Extrapolation is a unique pediatric process that allows us to maximize “prior” information and not require efficacy trials.

• In this situation the usual trials requested are Pk, Pk/Pd (some form of exposure/response) and safety studies.

• FDA’s standard request for trials in adults and pediatrics is NOT powered for safety questions.
Where To Find Information

• “Labeling” Table on [www.FDA.gov](http://www.FDA.gov)
  - Click on Pediatrics
    - [Table of Medicines with New Pediatric Information](http://www.FDA.gov)
  - Is robust but not comprehensive: It was started for Exclusivity and only in 2002 did we add the PREA labels we could find
  - There are about 400 products with new pediatric information
  - About 3 dozen of the PREA studies did not actually involve NEW pediatric studies
  - At first even products studied for Exclusivity did not have negative information added to the label = did not have a label change.
  - (These might be found by looking at the Exclusivity determinations list and the labeling table and see what is missing)
Where To Find Information

• The Pediatrics Web site has lots of information
• Pre-FDAAA information on the studies is not public but we do have the information and have provided it to GAO.
• We have all of the WR’s but the pre 2007 WR’s are not public.
Information

• The Pediatricians would love to share all this information with you, but we do not want to go to jail.

• There are approaches that can be used and these will be discussed today.
Comments on Specific Tasks: Extrapolation (IOM task 3)

Julia Dunne, M.D.
Office of Pediatric Therapeutics
Office of the Commissioner
Task 3

• Using a representative sample of written requests issued by the Secretary and studies conducted under BPCA since 1997 and studies conducted since 1997 under PREA or precursor regulations, review and assess (a) the use of extrapolation for pediatric subpopulations; (b) the use of alternative endpoints for pediatric populations; (c) neonatal assessment tools; and (d) ethical issues in pediatric clinical trials;
Final Pediatric Rule

Where:
q the course of the disease and
q the effects of the drug...
are sufficiently similar in adults and pediatric patients -

FDA may conclude:
  • can extrapolate pediatric effectiveness from adequate and well controlled studies in adults
  • usually supplemented with other information obtained in pediatric patients, eg, pharmacokinetic studies
  • may not need studies in each pediatric age group, if data from one age group can be extrapolated to another
FDA extrapolation working group

• Representatives from
  – Office of Pediatric Therapeutics (OC)
  – Pediatrics and Maternal Health Staff (CDER)
  – Office of Translational Sciences (CDER)
  – Office of Pharmaceutical Sciences (CDER)
  – 6 review divisions*

* cardiorenal; pulmonary and allergy; psychiatry and neurology; gastroenterology; antiviral; anesthesia, analgesia and rheumatology (74%[102/142] WRs)
Tasks

• Examined WRs with responding pediatric data and exclusivity determination prior to 2/28/2009

• Reviewed WRs, studies submitted, exclusivity determination and final labeling

• Classified use of extrapolation using FDA pediatric study decision tree (1994)
Summary of approaches

- FDA standard to establish efficacy — “adequate and well-controlled trials” (≥2)
- No extrapolation
  - 2 adequate and well-controlled trials
- Complete extrapolation
  - PK data (NB topically administrated)
  - Safety data
- Partial extrapolation
  - Range of data requirements
Lessons learned

• No simple formula to determine whether can extrapolate

• Portfolio of evidence
  – Knowledge of disease and natural history in adults and pediatric populations
  – Interactions between developmental changes and disease and response to therapy
  – Experience with other drugs in same class and for same indication
  – Validity of pediatric efficacy end-points
Lessons learned (continued)

• The greater the certainty regarding the scientific basis for extrapolation and therefore the ability to extrapolate, the greater the likelihood of successful new pediatric labelling
Lessons learned (continued)

Failed/uninterpretable studies can be minimized by

- establishing correct dose beforehand
- using age-appropriate end-points
- adequately powering studies
- adequate study design (eg including placebo arm in dose response study)
Lessons learned (continued)

- Evolving process
- Approaches are changing with increased knowledge and experience
Conclusions and Next Steps

• Extrapolation is useful tool to increase the efficiency of pediatric drug development and avoid unnecessary pediatric trials

• Paper submitted to peer-reviewed journal with summary tables of all published data available on-line

• Exercise to be completed for remaining review divisions
Is it reasonable to assume that children, when compared to adults, have a similar: (a) disease progression? (b) response to intervention?  

- **No**  
  - Is it reasonable to assume a similar exposure-response (ER) in children when compared to adults?  
    - **No**  
    - Conduct PK studies to establish dose, then pediatric safety and efficacy trials  
    - **Yes**  
    - Conduct PK/PD studies to establish an ER in children for the PD measurement, conduct PK studies to achieve target concentrations based on ER, then safety trials at the correct dose  

- **Yes to both**  
  - Is there a PD measurement that can predict efficacy in children?  
    - **No**  
    - Conduct PK/PD studies to establish an ER in children for the PD measurement, conduct PK studies to achieve target concentrations based on ER, then safety trials at the correct dose  
    - **Yes**  
    - Conduct PK studies to achieve drug levels similar to adults, then safety trials at the correct dose
Comments on Specific Tasks: Alternate Endpoints, Neonates, Ethics (IOM Task 3)

Robert “Skip” Nelson, M.D., Ph.D.
Office of Pediatric Therapeutics
Office of the Commissioner
Task 3

• Using a representative sample of written requests issued by the Secretary and studies conducted under BPCA since 1997 and studies conducted since 1997 under PREA or precursor regulations, review and assess (a) the use of extrapolation for pediatric subpopulations; (b) the use of alternative endpoints for pediatric populations; (c) neonatal assessment tools; and (d) ethical issues in pediatric clinical trials;
Alternate Endpoints

• “Alternate” to what?
  – To endpoints used in adult product development.

• “Endpoints”?
  – May include clinical, surrogate, physiological or biomarker endpoints.
  – Attention should be paid to endpoint validation so that an alternate endpoint can be used in support of product labeling.
Use of Alternative Endpoints in Pediatric Clinical Trials

- OPT will conduct a study to identify and evaluate alternate endpoints which have and/or can be used in pediatric clinical trials. The Institute of Medicine (IOM) also will be conducting such an analysis using publicly available data as mandated by FDAAA 2007. OPT will evaluate this same question using all data available to FDA, focusing on products in one therapeutic area of importance to pediatrics (e.g., neurology, cardiovascular, or metabolic/endocrine). The results of this study will greatly enhance FDA's ability to identify critical improvements in the path for pediatric product development.

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<thead>
<tr>
<th>Milestone Description</th>
<th>Milestone Date</th>
<th>Milestone Status</th>
<th>Milestone Completion Date</th>
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<tbody>
<tr>
<td>B. Identify Area of Therapeutic Focus</td>
<td>4/1/2011</td>
<td>On Track</td>
<td></td>
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<tr>
<td>C. Establish Working Group; Identify Tasks</td>
<td>6/1/2011</td>
<td>Not Yet Started</td>
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<tr>
<td>D. Preliminary Analysis</td>
<td>10/1/2011</td>
<td>Not Yet Started</td>
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<tr>
<td>E. First Draft of Assessment</td>
<td>12/31/2011</td>
<td>Not Yet Started</td>
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Neonatal Assessment Tools

• Appropriate labeling for products used in neonates remains a challenge.

• Approximately 15% of products studied under BPCA included neonates.

• However, this percentage...
  - Does not reflect neonatal studies to support desired indication (e.g., MTCT HIV, HMD) and thus not done under BPCA/PREA
  - Should be adjusted for drugs that lack a neonatal indication (i.e., denominator may be lower)
  - Neonatal indications may be overrepresented in the “off label” indications not included in WRs prior to 2007
Neonatal Assessment Tools

- Should task be viewed as an assessment of alternate endpoints in a specific population?
- Should “assessment tools” be viewed as a broader category than “endpoints”?
- FDA would welcome recommendations on improving our efforts to utilize BPCA and PREA to improve product labeling for use in neonates.
Selected Ethical Issues

• Enrollment of children without a disorder or condition (i.e., healthy) into more than minimal risk trails (e.g., PK trials under 21 CFR 50.53)

• Excessive risk exposure in control group (e.g., placement of central line for placebo administration to maintain blinding).

• Failure to establish a sufficient prospect of direct benefit to justify risk exposure in “first-in-human” pediatric trials (under 21 CFR 50.52)

• Inadequate dosing regimen (and thus prospect of direct benefit) in phase 1 pediatric trials to justify risks (under 21 CFR 50.52).

• Many of these issues arose in studies not being conducted under either BPCA or PREA.
Assessment of Ethical Issues

• One approach would be to assess studies that are at “high risk” for ethical issues
  – E.g., phase 1 trials, placebo-controlled trials

• Context:
  – FDA did not adopt additional safeguards for children (Subpart D) until April 2001.
  – Pediatric ethicist hired under BPCA in 2003.
  – Since FDAAA, central role on PeRC; growing consultation service (now averaging ≥ 1 consult/week).
  – Growing integration into CDER/CBER training programs
Comments on Specific Tasks: Adverse events (IOM task 4)

Judith Cope, M.D., M.P.H.
Office of Pediatric Therapeutics
Office of the Commissioner
Mandated Post Marketing Pediatric Focused Safety Review

- Mandated 1 year Postmarketing Pediatric Safety Review
- Beginning with BPCA (2002) and enhanced to include PREA (2007)
- Requires results of pediatric studies under BPCA or PREA be included in label, regardless of outcome (positive, negative or inconclusive).
- Requires post-marketing safety reporting for all products studied under BPCA or PREA.
- FDAAA strengthened safety reporting to include not only drugs, but biologics and pediatric HDE devices as well
- Required public discussion – Safety reviews go before the Pediatric Advisory Committee for review and recommendations
OPT, Pediatric Safety Review Process, & PAC

- **OPT**: Manages PAC; coordinates review process of AERs reports for drugs granted pediatric exclusivity; with presentation to PAC.
- **Process**: Identify any concerns, includes formal OSE safety review; after FDAAA, developed into broader assessment, not just 1-year of AEs; public presentation of safety reporting to the PAC
- **PAC**: Assesses safety reviews, presentations and responds to FDA questions; advises and makes recommendations to FDA for action.
- **FDA** takes these recommendations into consideration and may:
  - Return product to routine monitoring
  - Change product labeling
  - Request or conduct additional safety studies
  - Conduct additional AE reviews or monitoring
  - Expand outreach and risk minimization activities (e.g., revise Medication Guides, issue Public Healthcare Notification or Public Health Advisory)
Accomplishments

Pediatric Safety Reviews to PAC

18 meetings Jun 2003-Jun 2010; n=134 products

- PAC discussion and action recommendations*
- 94 Return to routine monitoring
- 33 Labeling Recommendations
  - 25 Led to changes of labeling, Medication Guide or Package Insert (PPI)
  - 5 recommended labeling changes were NOT made because Division concluded labeling was adequate.
  - 3 recommended labeling changes have NOT yet made
- 16 Continued monitoring or further analysis

*note there may be more than 1 recommendation per product
Percentage of Drug Products by Therapeutic Specialty
June 2003 through December 2010

- HemeOnc: 14%
- Endocrine: 13%
- Infectious: 19%
- Psychiatry: 8%
- Cardiac: 7%
- Allergy: 10%
- Eye: 7%
- Neurology: 8%
- GU: 19%
- Derm: 14%
- GI: 74%
Examples of Post-marketing Safety Signals

• AndroGel (testosterone gel) –
  – Studied in pediatric population for delayed puberty in males.
  – The failed study information put in label.

• Ditropan (oxybutynin) –
  – new information on central nervous system effects including hallucinations
Safety Reporting Updates
Safety Reporting Updates – web page

- Listed below are the products that have had a report on adverse events presented to the Pediatric Advisory Committee. Click on the drug name to go to the meeting materials. To search this page, select "Edit" on the Explorer Menu Bar, select "Find on this Page", enter the search term in the "Find" box and click "Next".

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date Exclusivity Granted</th>
<th>Date Reported to the PAC</th>
<th>PAC recommendations Subsequent Outcomes</th>
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<tbody>
<tr>
<td>Example: Androgel testosterone</td>
<td>8-22-07</td>
<td>6-23-09</td>
<td>June 23, 2009 Committee recommended FDA examine the effects of low level secondary exposure and encourage studies of the transfer of drug product from inanimate objects to people. The Committee also provided specific labeling recommendations including (1) revising text using descriptive, easy to understand language, (2) defining the term &quot;virilization&quot; for the consumer, (3) adding information on the pediatric studies performed and the risks, other than just bone effects, of secondary exposure to Section 8.4 Pediatric Use, and (4) revising the illustration in Section 17.3 FDA-Approved patient Labeling to be consistent with application instructions. The Committee recommended measures be taken immediately to reduce risk of exposure, including changing skin application sites and limiting use in families with children.</td>
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Task 4

4. Using a representative sample of studies conducted since 1997 under PREA or precursor regulations, review and assess the number and type of pediatric adverse events.

• If this was interpreted to require a similar review for PREA products prior to 2007 that currently is being conducted by FDA for both BPCA (since 2002) and PREA (since 2007), the workload would be considerable and much of the data (apart from the publicly available AERS database) may not be accessible.
Summary Points

• The appropriate (i.e., representative) sample will depend on the task, and how it is interpreted.
• Some tasks will be more difficult than others.
• Enriching the sampling for more recent activity (i.e., post-FDAAA) would be more useful to assess current FDA policies and procedures.
• FDA is committed (while recognizing of legal and resource constraints) to working with the Committee to provide adequate data in support of a meaningful assessment of BPCA and PREA.
Thank you.
Pediatric Studies Conducted under BPCA and PREA

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• Information on use of therapeutics in children remained inadequate
• Finally, in the late part of the 20th century, laws were passed to specifically address drug use in children
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- 1979- FDA “requires” trials in children parallel to adult process
- 1994- FDA requires sponsors to update label; introduces “extrapolations”
- 1997- Congress passes FDAMA/Exclusivity Provision – “Incentives” (voluntary)
- 1998- FDA publishes Pediatric Rule (mandatory)
Benchmarks (21st Century)
Pediatric Product Development

- 2002- Court Enjoins Pediatric Rule of 1998
- 2002- FDAMA Exclusivity Sunsets
- 2002- Congress passes Best Pharmaceuticals for Children Act (BPCA)
- 2003- Congress passes Pediatric Research Equity Act (PREA)
- 2007- Sunset for BPCA & PREA
- 2007- FDA Amendments Act (FDAAA)
Benchmarks (21\[^{st}\] Century)
Pediatric Product Development
(continued)

• 2002 – Congress passes BPCA
  – renewed Exclusivity
  – provides process for “off-patent” drug development (NIH)
  – public posting of studies (summaries)
  – reporting of all AE’s 1 year after Exclusivity granted

• 2003 – Congress passes PREA
  – Requires the study of drugs and biologics for pediatric population except in defined situations
  – Creates Pediatric Advisory Committee (from Subcommittee)
Important Components of FDAAA

- Mandated labeling for almost all submitted pediatric studies (Drugs and Biologics)
- Transparency enhanced by increasing the data being posted from the studies and requiring posting of the Written Request
- Expansion of the focused pediatric safety reviews
- Extending reach to Devices
- Requiring Pediatric input into all components
Legislation encouraging pediatric studies and availability of quality pediatric data IS resulting in new product labeling. Our job is to ensure those products are safe and labeled to reflect emerging safety signals that occur once the product is used in larger numbers of the pediatric population.
ONGOING LESSONS LEARNED

1. Pharmacokinetics are more variable than anticipated.
2. Pediatric specific adverse reactions are being defined and are common.
3. Trial designs are being modified as we learn from submitted studies.
4. Pediatric-specific ethical issues continue to be a challenge and more education is needed at many levels.
5. Pediatric expertise only recently being applied more consistently to process.
6. Legislation is “in parts” and still contributes to a fragmented approach.
The Knowledge Gap in Pediatric Therapeutics Continues

- How did we get to this state of ignorance?
- Why was it acceptable that a population that is growing, developing and inherently highly variable would not be studied while the more stable, not growing and less variable adult population was?
- We have just begun to understand how much we do not know or were wrong in our assumptions
You don’t know what you don’t know.

Pediatric Drug Development: It is like turning over rocks and discovering how much you did not know about what was under the rock. The next problem is how to communicate what is under the rock and how to answer questions that arise from looking.
Acronyms

- FDAMA: Food and Drug Administration Modernization Act
- BPCA: Best Pharmaceuticals for Children Act
- PREA: Pediatric Research Equity Act
- WR: Written Request (FDA issues)
- PPSR: Proposed Pediatric Study Request (sponsor submits)
- FDAAA – FDA Amendments Acts
Elements of FDAAA 2007 and implementation within CDER

Lisa Mathis, M.D.
Pediatric and Maternal Health Staff, Office of New Drugs, Center for Drug Evaluation and Research
Objectives

• Review major changes to BPCA and PREA under FDAAA
• Describe Pediatric Review Committee
• Discuss implementation of FDAAA in CDER
BPCA and PREA

• Provided requirements and incentives to obtain data in the pediatric population
• Reauthorization improved quality and consistency
• Provided for greater transparency
Changes under FDAAA: Improved Quality and Consistency

• Established Internal Pediatric Review Committee (PeRC) to provide consistency in pediatric drug development requirements and requests across divisions in CDER and CBER

• PeRC meets weekly to review and provide recommendations for both drugs and biologic
Changes under FDAAA: Improved Quality and Consistency (cont)

• PREA review includes
  – Pediatric Assessments before approval
  – Waivers and deferrals of required studies
  – Pediatric Plans before approval
    • Not protocols

• BPCA review includes
  – Pediatric Written Requests

• Duties also included retrospective review and tracking and posting of statistics
Pediatric Review Committee

- Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and the Office of the Commissioner (OPT), including:
  - Pediatrics - Clinical pharmacology
  - Statistics - Chemistry
  - Legal issues - Ethics
  - Toxicology - Safety
Pediatric Review Committee

- PeRC is an additional duty for all members.
- Pediatric expertise introduced at the end of the application process.
- Review not at protocol level.
Pilot Program

• To address need for pediatric expertise in development process, pilot program established
• Involves PMHS and pediatric experts from the Office of Clinical Pharmacology
• 3 Divisions
• Intervention at NDA filing,
  – By integrating a pediatric medical reviewer and regulatory expert with the review team at the time of NDA submission, deficiencies identified and planning improved
• Goal would be to expand across all 18 review divisions, intervene in IND phase
Changes under FDAAA: Increased Transparency

• When studies are submitted in response to PREA post marketing commitments and/or a Written Request, information must be included in labeling
• Written Requests posted after exclusivity determination
• Posting of medical, statistical, and clinical pharmacology review for products labeled
Changes under FDAAA: Increased Transparency

- Safety review to be performed at 1 year post labeling for all PREA assessments/WR responses with presentation to Pediatric Advisory Committee
- Study information (types of studies, Countries where studies were conducted, number of pediatric patients, etc) posted
Elements of FDAAA 2007 and their implementation within CBER and comments on IOM tasks 5-7

Jennifer Ross, Ph.D.
Center for Biologics Evaluation and Research
Overview

• Introduction to CBER
• Pediatrics and CBER
• Comments on Tasks 5-7
CBER Organization

Office of the Director
Director, Karen Midthun, M.D.

Office of Management

Office of Blood Research and Review
Office of Biostatistics and Epidemiology

Office of Vaccines Research and Review
Office of Compliance and Biologics Quality

Office of Cellular, Tissue and Gene Therapies
Office of Communication, Outreach and Development
Examples: CBER-regulated products

• Vaccines
  – preventive and therapeutic
• Blood products
  – clotting factors, immunoglobulins, and related recombinant products
• Gene Therapy
• Cellular Products
• Allergenics
Pediatrics & CBER

• CBER Pediatric working group
  • Cross-cutting working group meets monthly
  • Activities include:
    o Forum for intracenter information exchange, brainstorming
    o Discussion of novel issues
    o CBER pediatric webpage
    o PREA stats

• PeRC membership
• PAC process
• 30% of medical officers are pediatricians
Tasks 5-7

• **Task 5:** Review and assess the number and importance of biological products for children that are being tested as a result of the Biologics Price Competition and Innovation Act of 2009 and the importance … of labeling changes made as a result of such testing

• **Task 6:** Review and assess the number, importance, and prioritization of any biological products that are not being tested for pediatric use

• **Task 7:** Offer recommendations for ensuring pediatric testing of biological products, including consideration of any incentives, such as those provided under section 505A of the FD&C Act or section 351(m) of the PHS Act
Overview of the IOM task order, including data available

Robert “Skip” Nelson, M.D., Ph.D.
Office of Pediatric Therapeutics
Office of the Commissioner
Creating the Task Order

• The Task Order follows closely the language found in FDAAA 2007.
• There was internal discussion of the challenges that the IOM committee will face in addressing one or more of these tasks.
• FDA did not believe it had the authority to modify or omit any of the tasks.
What Data are Available?

• FDA understands that data provided to IOM are posted to a public docket. This policy presents a challenge for FDA to be able to provide non-public data to IOM.

• Given this situation, FDA decided (after discussion with IOM) to limit task order to review of publicly available data.

• Publicly available data on BPCA and PREA activities may be sufficient (with supplementation as needed) for the Committee to accomplish the tasks.

• FDA is committed (while recognizing of legal and resource constraints) to working with the Committee to provide adequate data in support of a meaningful assessment of BPCA and PREA.
Avenues for Data Supplementation

- Put selected documents through the internal FDA clearance process
  - Limited option given current staffing of office that provides clearance.
  - Similar to FOIA review process for the posting of data in Drugs@FDA).
- Perform FDA internal analysis of documents; providing aggregate and/or de-identified data to the committee
- Provide selected documents/data to individual committee members (e.g., SGE) who can report to committee
- Identifying for IOM where public data can be found based on FDA internal analysis
- Other ways compatible with IOM and FDA procedures
Three Public Data “Eras”

1. FDAMA (1997-2002)
   - Lists of Written Requests and Exclusivity Determinations (i.e., no documents other than Drugs@FDA)

2. BPCA (2002-2007)
   - Summaries of Medical and Clinical Pharmacology Reviews for Drugs granted Exclusivity (BPCA only)

3. FDAAA (2007-present)
   - Medical, Statistical, and Clinical Pharmacology Reviews (BPCA and PREA)
   - Pediatric Study Characteristics
   - List of Exclusivity Determinations Including Written Request
• Pediatric Labeling Changes (1997-present)
Context for IOM Assessment

- BPCA/PREA should be evaluated in light of their stated purpose to improve pediatric labeling.
- There have also been significant changes in the pediatric program at FDA in response to legislation.
- Two examples:
  - Prior to FDAAA 2007, legal interpretation restricted WRs to either “on” or “off” indication studies. This “forced” choice may have left some indications “off the table.”
  - Prior to FDAAA 2007, there was no requirement for pediatric input (e.g., PeRC) into either BPCA or PREA divisional activities.
- Thus, an assessment of more recent FDA activities may be more useful to inform future implementation.
Comments on Specific Tasks:
Drug labeling (IOM tasks 1 and 2)

Dianne Murphy, M.D.
Office of Pediatric Therapeutics
Office of the Commissioner
Tasks 1 and 2

1. Review and assess a representative sample of written requests issued by the Secretary and studies conducted under BPCA since 1997, and labeling changes made as a result of such studies;

2. Review and assess a representative sample of studies conducted since 1997 under PREA or precursor regulations, and labeling changes made as a result of such studies;
Task 1: WR’s & Labeling

• The process to implement the exclusivity component (incentive) involves FDA issuing a Written Request (WR).
• From 1997-2007 we were told by our lawyers we could not put both “on” and “off” label indications in same WR.
• We ask a series of questions to determine if we should issue a WR.
• If we decide to issue a WR, we ask for studies for as many indications and populations we think are justified by the present state of knowledge.
Task 1: (cont’d)

• Sponsor could decline WR or later ask for amendments
• Sponsor submits requested studies in the time specified
• FDA’s internally constructed Exclusivity Board reviews the division’s determination if the sponsor has “fairly met” the terms of the WR. If the answer is yes, and the board agrees, the sponsor is granted the additional 6 months of marketing exclusivity
• Even if the sponsor “failed” to obtain the indication, they can receive the marketing exclusivity.
• Irrespective of success or failure, FDA began to put the information in the label.
Task 1: Labeling

• Putting information in a label for a “failed” study requires careful wording to provide information without providing the sponsor a “de facto” marketing indication

• Labeling = information. We consider this the “metric” that is the deliverable

• Information will hopefully provide more informed utilization of pediatric products
Task 2: Studies and Labeling

• For Adults, FDA does NOT usually put anything in the label about failed studies and often cannot (because of confidentially laws) even say if the study was done.

• Putting information about the Studies is important for pediatrics because it is unlikely that any additional studies will be conducted.
Task 2: (cont’d)

- Extrapolation is a unique pediatric process that allows us to maximize “prior” information and not require efficacy trials.
- In this situation the usual trials requested are Pk, Pk/Pd (some form of exposure/response) and safety studies.
- FDA’s standard request for trials in adults and pediatrics is NOT powered for safety questions.
Where To Find Information

• “Labeling” Table on www.FDA.gov
  - Click on Pediatrics
    - Table of Medicines with New Pediatric Information
  - Is robust but not comprehensive: It was started for Exclusivity and only in 2002 did we add the PREA labels we could find
  - There are about 400 products with new pediatric information
  - About 3 dozen of the PREA studies did not actually involve NEW pediatric studies
  - At first even products studied for Exclusivity did not have negative information added to the label = did not have a label change.
  - (These might be found by looking at the Exclusivity determinations list and the labeling table and see what is missing)
Where To Find Information

• The Pediatrics Web site has lots of information
• Pre-FDAAA information on the studies is not public but we do have the information and have provided it to GAO.
• We have all of the WR’s but the pre 2007 WR’s are not public.
Information

• The Pediatricians would love to share all this information with you, but we do not want to go to jail.

• There are approaches that can be used and these will be discussed today.
Comments on Specific Tasks: Extrapolation (IOM task 3)

Julia Dunne, M.D.
Office of Pediatric Therapeutics
Office of the Commissioner
Task 3

- Using a representative sample of written requests issued by the Secretary and studies conducted under BPCA since 1997 and studies conducted since 1997 under PREA or precursor regulations, review and assess (a) the use of extrapolation for pediatric subpopulations; (b) the use of alternative endpoints for pediatric populations; (c) neonatal assessment tools; and (d) ethical issues in pediatric clinical trials;
Final Pediatric Rule

Where:
q the course of the disease and
q the effects of the drug…
are sufficiently similar in adults and pediatric patients -

FDA may conclude:
  - can extrapolate pediatric effectiveness from adequate
    and well controlled studies in adults
  - usually supplemented with other information obtained in
    pediatric patients, eg, pharmacokinetic studies
  - may not need studies in each pediatric age group, if data
    from one age group can be extrapolated to another
FDA extrapolation working group

• Representatives from
  – Office of Pediatric Therapeutics (OC)
  – Pediatrics and Maternal Health Staff (CDER)
  – Office of Translational Sciences (CDER)
  – Office of Pharmaceutical Sciences (CDER)
  – 6 review divisions*

* cardiorenal; pulmonary and allergy; psychiatry and neurology; gastroenterology; antiviral; anesthesia, analgesia and rheumatology (74%[102/142] WRs)
Tasks

• Examined WRs with responding pediatric data and exclusivity determination prior to 2/28/2009

• Reviewed WRs, studies submitted, exclusivity determination and final labeling

• Classified use of extrapolation using FDA pediatric study decision tree (1994)
Summary of approaches

- FDA standard to establish efficacy – “adequate and well-controlled trials” (≥2)
- No extrapolation
  - 2 adequate and well-controlled trials
- Complete extrapolation
  - PK data (NB topically administered)
  - Safety data
- Partial extrapolation
  - Range of data requirements
Lessons learned

• No simple formula to determine whether can extrapolate

• Portfolio of evidence
  – Knowledge of disease and natural history in adults and pediatric populations
  – Interactions between developmental changes and disease and response to therapy
  – Experience with other drugs in same class and for same indication
  – Validity of pediatric efficacy end-points
Lessons learned (continued)

• The greater the certainty regarding the scientific basis for extrapolation and therefore the ability to extrapolate, the greater the likelihood of successful new pediatric labelling
Lessons learned (continued)

Failed/uninterpretable studies can be minimized by

- establishing correct dose beforehand
- using age-appropriate end-points
- adequately powering studies
- adequate study design (eg including placebo arm in dose response study)
Lessons learned (continued)

- Evolving process
- Approaches are changing with increased knowledge and experience
Conclusions and Next Steps

- Extrapolation is a useful tool to increase the efficiency of pediatric drug development and avoid unnecessary pediatric trials.
- Paper submitted to peer-reviewed journal with summary tables of all published data available online.
- Exercise to be completed for remaining review divisions.
Is it reasonable to assume that children, when compared to adults, have a similar: (a) disease progression? (b) response to intervention?

- No

Is it reasonable to assume a similar exposure-response (ER) in children when compared to adults?

- No
  - Is there a PD measurement that can predict efficacy in children?
    - No
      - Conduct PK studies to establish dose, then pediatric safety and efficacy trials
    - Yes
      - Conduct PK/PD studies to establish an ER in children for the PD measurement, conduct PK studies to achieve target concentrations based on ER, then safety trials at the correct dose
  - Yes
    - Conduct PK studies to achieve drug levels similar to adults, then safety trials at the correct dose

Yes to both
Comments on Specific Tasks: Alternate Endpoints, Neonates, Ethics (IOM Task 3)

Robert “Skip” Nelson, M.D., Ph.D.
Office of Pediatric Therapeutics
Office of the Commissioner
Task 3

• Using a representative sample of written requests issued by the Secretary and studies conducted under BPCA since 1997 and studies conducted since 1997 under PREA or precursor regulations, review and assess (a) the use of extrapolation for pediatric subpopulations; (b) the use of alternative endpoints for pediatric populations; (c) neonatal assessment tools; and (d) ethical issues in pediatric clinical trials;
Alternate Endpoints

• “Alternate” to what?
  – To endpoints used in adult product development.

• “Endpoints”?
  – May include clinical, surrogate, physiological or biomarker endpoints.
  – Attention should be paid to endpoint validation so that an alternate endpoint can be used in support of product labeling.
Use of Alternative Endpoints in Pediatric Clinical Trials

- OPT will conduct a study to identify and evaluate alternate endpoints which have and/or can be used in pediatric clinical trials. The Institute of Medicine (IOM) also will be conducting such an analysis using publicly available data as mandated by FDAAA 2007. OPT will evaluate this same question using all data available to FDA, focusing on products in one therapeutic area of importance to pediatrics (e.g., neurology, cardiovascular, or metabolic/endocrine). The results of this study will greatly enhance FDA's ability to identify critical improvements in the path for pediatric product development.

<table>
<thead>
<tr>
<th>Milestone Description</th>
<th>Milestone Date</th>
<th>Milestone Status</th>
<th>Milestone Completion Date</th>
</tr>
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<tbody>
<tr>
<td>B. Identify Area of Therapeutic Focus</td>
<td>4/1/2011</td>
<td>On Track</td>
<td></td>
</tr>
<tr>
<td>C. Establish Working Group; Identify Tasks</td>
<td>6/1/2011</td>
<td>Not Yet Started</td>
<td></td>
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<tr>
<td>D. Preliminary Analysis</td>
<td>10/1/2011</td>
<td>Not Yet Started</td>
<td></td>
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<tr>
<td>E. First Draft of Assessment</td>
<td>12/31/2011</td>
<td>Not Yet Started</td>
<td></td>
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Neonatal Assessment Tools

- Appropriate labeling for products used in neonates remains a challenge.
- Approximately 15% of products studied under BPCA included neonates.
- However, this percentage...
  - Does not reflect neonatal studies to support desired indication (e.g., MTCT HIV, HMD) and thus not done under BPCA/PREA
  - Should be adjusted for drugs that lack a neonatal indication (i.e., denominator may be lower)
  - Neonatal indications may be overrepresented in the “off label” indications not included in WRs prior to 2007
Neonatal Assessment Tools

• Should task be viewed as an assessment of alternate endpoints in a specific population?
• Should “assessment tools” be viewed as a broader category than “endpoints”?
• FDA would welcome recommendations on improving our efforts to utilize BPCA and PREA to improve product labeling for use in neonates.
Selected Ethical Issues

- Enrollment of children without a disorder or condition (i.e., healthy) into more than minimal risk trails (e.g., PK trials under 21 CFR 50.53)
- Excessive risk exposure in control group (e.g., placement of central line for placebo administration to maintain blinding).
- Failure to establish a sufficient prospect of direct benefit to justify risk exposure in “first-in-human” pediatric trials (under 21 CFR 50.52)
- Inadequate dosing regimen (and thus prospect of direct benefit) in phase 1 pediatric trials to justify risks (under 21 CFR 50.52).
- Many of these issues arose in studies not being conducted under either BPCA or PREA.
Assessment of Ethical Issues

• One approach would be to assess studies that are at “high risk” for ethical issues
  – E.g., phase 1 trials, placebo-controlled trials

• Context:
  – FDA did not adopt additional safeguards for children (Subpart D) until April 2001.
  – Pediatric ethicist hired under BPCA in 2003.
  – Since FDAAA, central role on PeRC; growing consultation service (now averaging ≥ 1 consult/week).
  – Growing integration into CDER/CBER training programs
Comments on Specific Tasks: Adverse events (IOM task 4)

Judith Cope, M.D., M.P.H.
Office of Pediatric Therapeutics
Office of the Commissioner
Mandated Post Marketing Pediatric Focused Safety Review

- Mandated 1 year Postmarketing Pediatric Safety Review
- Beginning with BPCA (2002) and enhanced to include PREA (2007)
- Requires results of pediatric studies under BPCA or PREA be included in label, regardless of outcome (positive, negative or inconclusive).
- Requires post-marketing safety reporting for all products studied under BPCA or PREA.
- FDAAA strengthened safety reporting to include not only drugs, but biologics and pediatric HDE devices as well
- Required public discussion – Safety reviews go before the Pediatric Advisory Committee for review and recommendations
OPT, Pediatric Safety Review Process, & PAC

- OPT: Manages PAC; coordinates review process of AERs reports for drugs granted pediatric exclusivity; with presentation to PAC.
- Process: Identify any concerns, includes formal OSE safety review; after FDAAA, developed into broader assessment, not just 1-year of AEs; public presentation of safety reporting to the PAC
- PAC: Assesses safety reviews, presentations and responds to FDA questions; advises and makes recommendations to FDA for action.
- FDA takes these recommendations into consideration and may:
  - Return product to routine monitoring
  - Change product labeling
  - Request or conduct additional safety studies
  - Conduct additional AE reviews or monitoring
  - Expand outreach and risk minimization activities (e.g., revise Medication Guides, issue Public Healthcare Notification or Public Health Advisory)
Accomplishments
Pediatric Safety Reviews to PAC
18 meetings Jun 2003-Jun 2010; n=134 products

- PAC discussion and action recommendations*
- 94 Return to routine monitoring
- 33 Labeling Recommendations
  - 25 Led to changes of labeling, Medication Guide or Package Insert (PPI)
  - 5 recommended labeling changes were NOT made because Division concluded labeling was adequate.
  - 3 recommended labeling changes have NOT yet made
- 16 Continued monitoring or further analysis

*note there may be more than 1 recommendation per product
Percentage of Drug Products by Therapeutic Specialty
June 2003 through December 2010

- HemeOnc: 14%
- Endocrine: 13%
- Infectious: 19%
- Psychiatry: 8%
- Cardiac: 7%
- Allergy: 10%
- Eye: 10%
- Neurology: 7%
- GU: 8%
- Derm: 8%
- GI: 74
Examples of Post-marketing Safety Signals

• AndroGel (testosterone gel) –
  – Studied in pediatric population for delayed puberty in males.
  – The failed study information put in label.

• Ditropan (oxybutynin) –
  – new information on central nervous system effects including hallucinations
Safety Reporting Updates – web page

- Listed below are the products that have had a report on adverse events presented to the Pediatric Advisory Committee. Click on the drug name to go to the meeting materials. To search this page, select "Edit" on the Explorer Menu Bar, select "Find on this Page", enter the search term in the "Find" box and click "Next".

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date Exclusivity Granted</th>
<th>Date Reported to the PAC</th>
<th>PAC recommendations Subsequent Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Example: Androgel</td>
<td>8-22-07</td>
<td>6-23-09</td>
<td>June 23, 2009 Committee recommended FDA examine the effects of low level secondary exposure and encourage studies of the transfer of drug product from inanimate objects to people. The Committee also provided specific labeling recommendations including (1) revising text using descriptive, easy to understand language, (2) defining the term &quot;virilization&quot; for the consumer, (3) adding information on the pediatric studies performed and the risks, other than just bone effects, of secondary exposure to Section 8.4 Pediatric Use, and (4) revising the illustration in Section 17.3 FDA-Approved patient Labeling to be consistent with application instructions. The Committee recommended measures be taken immediately to reduce risk of exposure, including changing skin application sites and limiting use in families with children.</td>
</tr>
</tbody>
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Task 4

4. Using a representative sample of studies conducted since 1997 under PREA or precursor regulations, review and assess the number and type of pediatric adverse events.

• If this was interpreted to require a similar review for PREA products prior to 2007 that currently is being conducted by FDA for both BPCA (since 2002) and PREA (since 2007), the workload would be considerable and much of the data (apart from the publicly available AERS database) may not be accessible.
Summary Points

• The appropriate (i.e., representative) sample will depend on the task, and how it is interpreted.
• Some tasks will be more difficult than others.
• Enriching the sampling for more recent activity (i.e., post-FDAAA) would be more useful to assess current FDA policies and procedures.
• FDA is committed (while recognizing of legal and resource constraints) to working with the Committee to provide adequate data in support of a meaningful assessment of BPCA and PREA.
Thank you.