



Lessons to Be Learned: The FDA Experience

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Benchmarks in Pediatric Drug Development

- 1994 – Pediatric Labeling rule; extrapolation introduced
- 1997 – FDAMA/Exclusivity provision
- 1998 – Final Rule: Pediatric Studies Required
- 2001 – Subpart D-Interim Rule: *Additional Safeguards for Children in Clinical Investigations of FDA-regulated products*
- 2002 – Best Pharmaceuticals for Children Act
- 2002 – 1998 Final Rule enjoined (October 2002)
- 2003 – Pediatric Research Equity Act



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Acronyms

- **FDAMA:** Food & Drug Administration Modernization Act
- **BPCA:** Best Pharmaceuticals for Children Act
- **PREA:** Pediatric Research Equity Act
- **WR:** Written Request
- **PPSR:** Proposed Pediatric Study Request
- **IRB:** Institutional Review Board



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BPCA

- Signed into law January 4, 2002
- Renewed pediatric exclusivity incentive
- Provides process for “off-patent” drug development
- Public posting of pediatric study results
- Reporting of all AE’s for 1 year after pediatric exclusivity granted



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PREA

- Signed into law December 3, 2003
- Drugs and Biologics affected
- Pediatric Assessment required for certain applications unless waived or deferred (*similar to Pediatric Rule*)
- Established the Pediatric Advisory Committee



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BPCA vs. PREA

BPCA

- Studies are voluntary
- Includes orphan drugs and orphan drug indications
- Studies on whole moiety
- 10-1-07 Sunset



PREA

- Studies are required
- Orphan drugs designated exempt
- Studies limited to drug/indication under development
- 10-1-07 Sunset



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Pediatric Exclusivity Stats (Through August 2006)

- Proposed Pediatric Study Requests 478
- Written Requests issued 326
- Exclusivity granted 119
- Label changes 114

Medical/Clinical Pharmacology Review Summaries:

- # posted on public website 64



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Pediatric Exclusivity Stats (Through June 2006*)

- Total Studies Requested 732
 - Efficacy/Safety 254 (35%)
 - PK/Safety 208 (29%)
 - PK/PD 62 (9%)
 - Safety 111 (15%)
 - Other 98 (12%)
- # of studies with patients specified 454
- # of patients requested 43,427

*These statistics are posted quarterly. Other pediatric statistics are posted monthly.



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Summary



PREA

BPCA

On-patent process

Off-patent process



New Pediatric Information in Labels



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FDA Pediatric Experience

- 326 Written Requests
 - Involving 732 studies
 - Involving at least 43,000 children
- What lessons have we learned?



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Lesson Learned

Ethical considerations are always important in pediatric trials and are becoming more defined in the US



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General Principles*

- Pediatric patients should be given medicines that have been properly evaluated for their use in the intended population
- Product development programs should include pediatric studies when pediatric use is anticipated
- Pediatric development should not delay adult studies nor adult availability



- Shared responsibility among companies, regulatory authorities, health professionals, and society as a whole

*from ICH E-11



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Subpart D

Title 21 Code of Federal Regulations Part 50

- Regulations outline criteria for IRB review of clinical trials involving children
- IRB may refer a research protocol to a federally-mandated ethics panel
- If FDA-regulated drug involved, issue presented to FDA ethics panel
- First panel held September 10, 2004 - *Effects of a Single Dose of Dextroamphetamine in ADHD: A Functional MRI Study*”



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Lessons Learned

No matter how carefully the clinical trials are designed, rare/uncommon adverse events are not likely to be discovered



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HEALTH

TUESDAY, FEBRUARY 4, 2003



After Almost Three Decades, A New Choice for Treating ADHD



Strattera (atomoxetine HCl)

- New molecular entity
- New class of ADHD drug – non-stimulant
- Adult and pediatric populations studied in parallel
- Efficacy and safety studies performed:
 - Children/adolescents – 4
 - Adults – 2
- 6000 patients exposed in clinical trials
- Approved: 11/26/2002





New Warning 12/17/04

Severe Liver Injury

- Postmarketing reports indicate Strattera can cause severe liver injury in rare cases
- No liver injury in clinical trials - 6000 pts
- 2 million pts during first 2 yrs postmarketing
 - Two reported cases of markedly elevated hepatic enzymes and bilirubin
 - One pt, liver injury, manifested by elevated hepatic enzymes (40x ULN) and jaundice (bilirubin 12x ULN); recurred upon rechallenge and was followed by recovery upon drug discontinuation
 - Providing evidence that Strattera caused the liver injury



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New Warning 12/17/04 (cont.)

Severe Liver Injury

- Strattera should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted
- Laboratory testing to determine liver enzyme levels should be done upon first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained “flu-like” symptoms)



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Lessons Learned

There are important questions to ask before requesting or requiring pediatric studies



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Public Health Benefit?

- Is this a serious, life-threatening condition?
- How frequently does disease/condition occur? How serious?
- Are there therapeutic options approved for this indication, and are they labeled for use in pediatrics?
- How often is this drug or others like it used in children (off-label use)?



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More Questions – What Do We Know About the Drug?

- Are there any safety signals?
 - Animals?
 - Adult trials?
 - Spontaneous reports?
- Is there enough safety information to start clinical trials in children?
- Is there an appropriate risk/benefit?



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What Do Children Do?

Grow



and

Develop



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Lesson Learned

*For drugs used chronically – remember
to always measure growth*



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How Can Information from Pediatric Trials be Shared?

- Disclosure Requirements:
 - BPCA (section 9) requires posting of summaries of the medical and clinical pharmacology reviews of pediatric studies conducted –
 - Posted regardless of approval/non-approval
 - Summaries posted for 64 drugs
- www.fda.gov/cder/pediatric/summaryreview.htm**



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FDA Web Page

The screenshot shows the FDA Home Page in Microsoft Internet Explorer. The browser title is "Food and Drug Administration Home Page - Microsoft Internet Explorer provided by DITSOFT for". The address bar shows "http://www.fda.gov". The page features the FDA logo and the text "U.S. Food and Drug Administration" and "Department of Health and Human Services". A search bar is located on the left. The main content area is titled "FDA NEWS" and includes a photograph of several people. Below the news section are two buttons: "Let Us Hear From You" and "Reference Room". The right sidebar contains "Hot Topics" and "FDA Activities" lists. The bottom of the browser window shows the taskbar with the Start button, desktop icons, and system tray.

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CDER Pediatric Web Page

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U.S. Food and Drug Administration
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