Lessons to Be Learned: The FDA Experience

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Benchmarks in Pediatric Drug Development

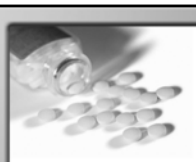
- 1994 – Pediatric Labeling rule; extrapolation introduced
- 1997 – FDAMA/Exclusivity provision
- 1998 – Final Rule: Pediatric Studies Required
- 2001 – Subpart D-Interim Rule: *Additional Safeguards for Children in Clinical Investigations of FDA-regulated products*
- 2002 – Best Pharmaceuticals for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

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

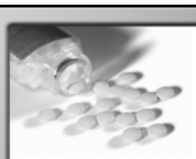
BPCA

- 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



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



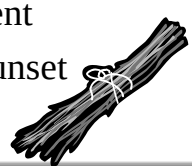
BPCA vs. PREA

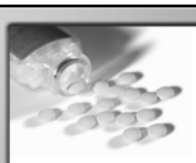
BPCA

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

PREA

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





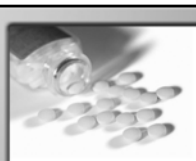
Pediatric Exclusivity Stats

(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



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.

Summary

PREA

BPCA

On-patent process

Off-patent process

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New Pediatric Information in Labels

FDA Pediatric Experience

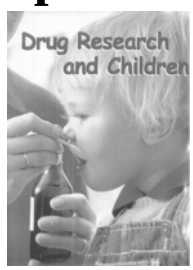
- 326 Written Requests
  - Involving 732 studies
  - Involving at least 43,000 children
- What lessons have we learned?

Lesson Learned

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

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**

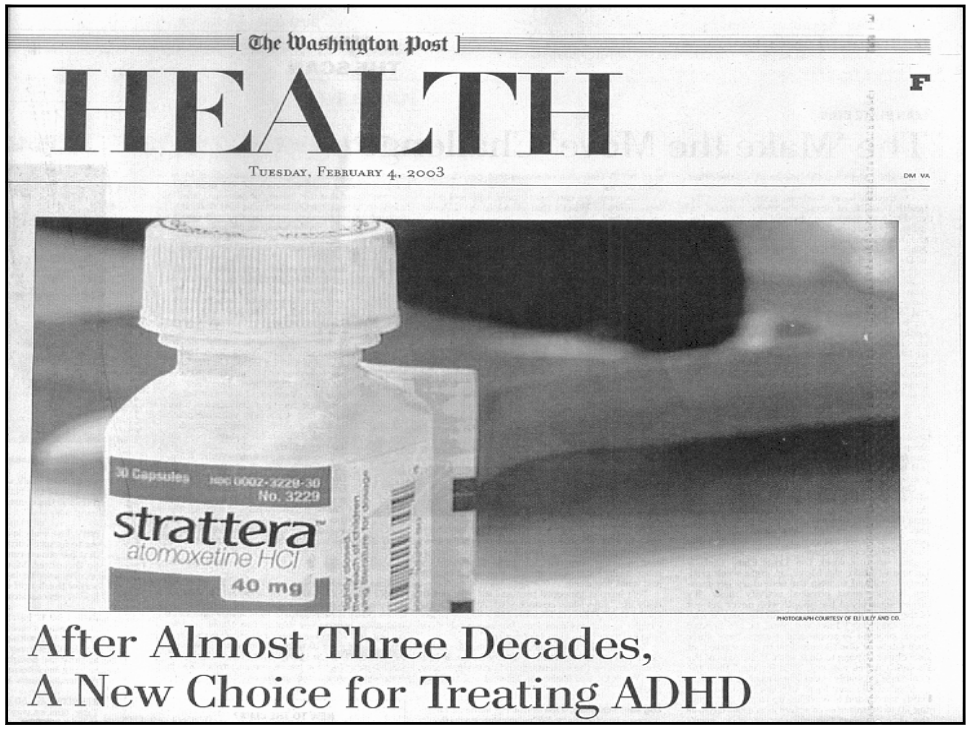
Subpart D

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"*

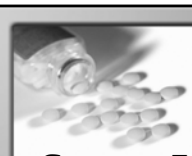
Lessons Learned

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



Strattera (atomoxetine HCl)

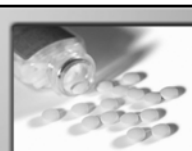
- New molecular entity
- New class of ADHD drug – non-stimulant
- Adult and pediatric populations studied in parallel
- Efficacy and safety studies performed:
  - Children/adolescents – 4
  - Adults – 2
- 6000 patients exposed in clinical trials
- Approved: 11/26/2002



New Warning 12/17/04

Severe Liver Injury

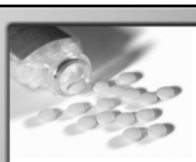
- Postmarketing reports indicate Strattera can cause severe liver injury in rare cases
- No liver injury in clinical trials - 6000 pts
- 2 million pts during first 2 yrs postmarketing
  - Two reported cases of markedly elevated hepatic enzymes and bilirubin
  - One pt, liver injury, manifested by elevated 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



New Warning 12/17/04 (cont.)

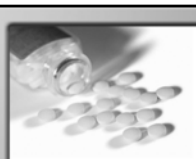
Severe Liver Injury

- 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**)**



Lessons Learned

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



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)?

More Questions – What Do We Know About the Drug?

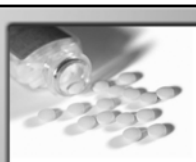
- Are there any safety signals?
  - Animals?
  - Adult trials?
  - Spontaneous reports?
- Is there enough safety information to start clinical trials in children?
- Is there an appropriate risk/benefit?

What Do Children Do?

Grow

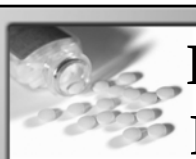
and

Develop



Lesson Learned

For drugs used chronically – remember to always measure growth

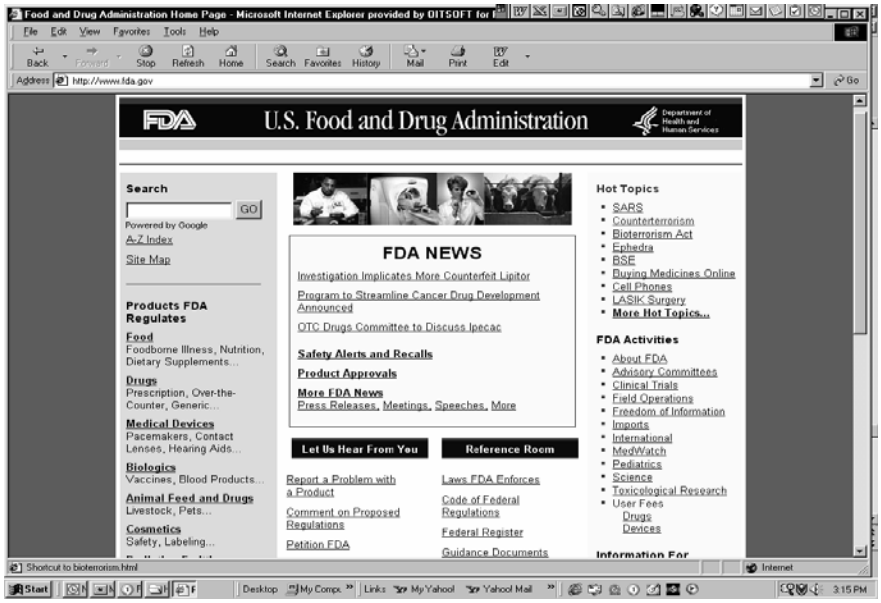


How Can Information from Pediatric Trials be Shared?

- 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

FDA Web Page



CDER Pediatric Web Page