Pediatric Drug Development: A Regulatory Perspective

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A (very brief) History of FDA Initiatives to Promote Pediatric Drug Development

- 1979—Pediatric Use subsection in labeling
- 1995—Re-examine pediatric use in labels
- 1997—FDAMA, written requests
- 1998—Pediatric Rule, authority to require studies
- 2001—BPCA
- 2003—PREA
- 2007—FDAAA
- 2012—BPCA and PREA up for renewal

Goal: Improved Pediatric Labeling

Progress in Labeling

- Indications extrapolated from adult research

vs.

- Several medications now list clinical study data demonstrating efficacy
- Trials that did not show efficacy or that had additional safety findings are also in labeling

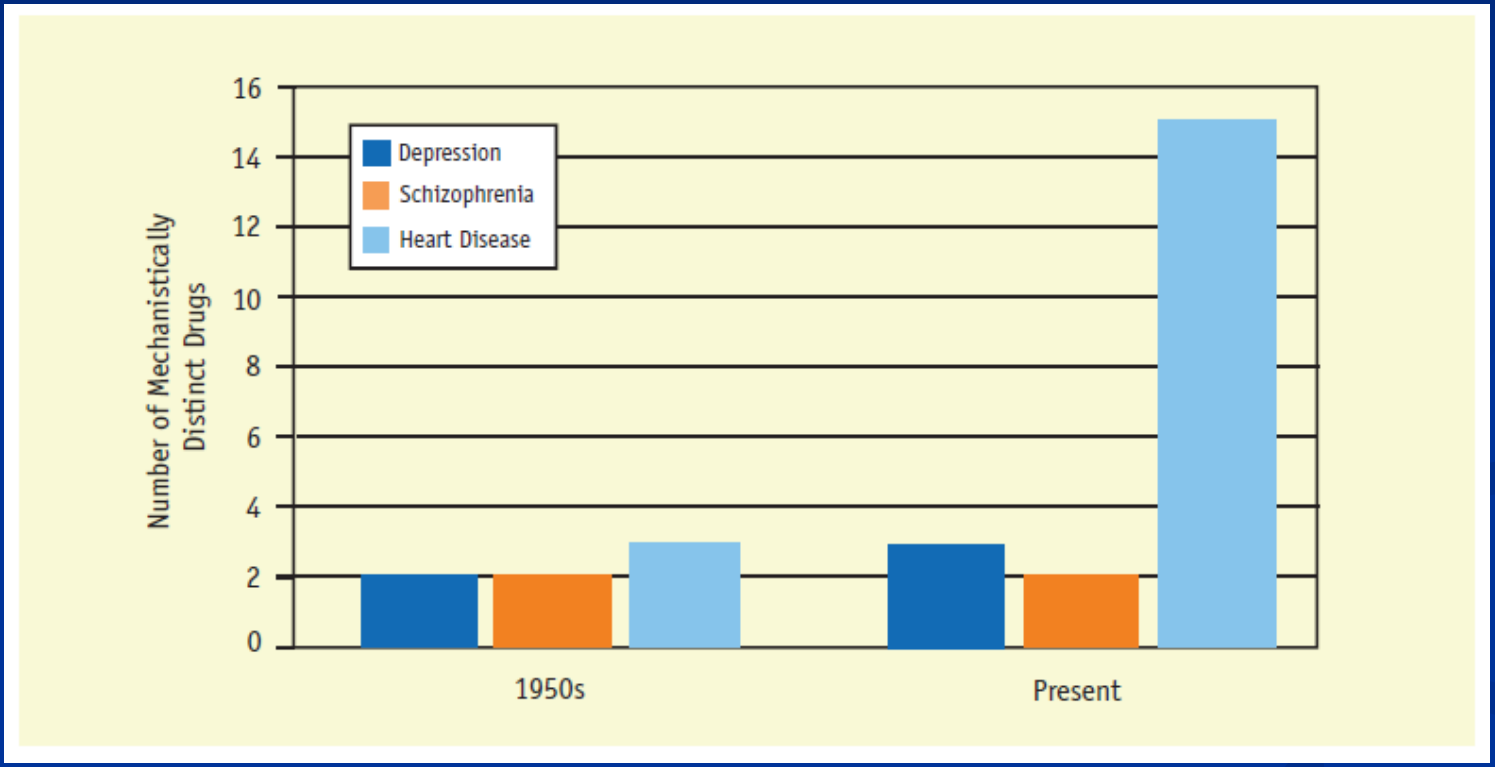
But there's a catch

- BPCA and PREA effectively encourage pediatric trials of drugs already in development for adults
- What if drugs that are effective in adults don't have the same efficacy in children?
- How do we find the treatments that are effective mainly in the pediatric but not adult population?

Other Regulatory Challenges

- Conduct Disorder
- Impulsive Aggression
- Long-term Safety
- Suicidality in Antidepressant Use
- Stimulant Use and Sudden Cardiac Death

When you understand pathophysiology…



From Discovery to Cure: Accelerating the Development of New and Personalized Interventions for Mental Illnesses
Report of the National Advisory Mental Health Council's Workgroup
August, 2010

What About "Biomarkers"?

- **Biomarker** is defined as measurable characteristics that reflect physiological, pharmacological, or disease processes in animals or humans.
- Categories:
  - **Diagnostic**: show or suggest that the disease is present
  - **Prognostic**: predict likelihood of worsening
  - **Predictive**: signal likelihood of response to treatment
- Endpoints:
  - **Clinical**: A characteristic or variable that describes how a patient feels or functions, or whether he/she survives
  - **Surrogate**: A biomarker that is intended to substitute for clinical endpoint

Ref: 1) Laughren TP, J Clin Psych 71,9: 1196-1204, 2010; 2) Draft Guidance, Qualification Process for Drug Development Tools, Oct 2010.

Biomarker Development in Psychiatry

- Focus here is on interest in finding biomarkers that can predict efficacy or safety risk associated with drug treatment
- An approach to sub-grouping the larger population into:
  - Responsive/non-responsive (Efficacy determination)
  - At risk/not at risk (for AE of interest)
- Problem in psychiatry:
  - Limited understanding of biology/pathophysiology
  - Search for biomarkers is largely speculative
- Examples of possible biomarkers include:
  - Imaging Measures
  - Serum Assays
  - Genomic, Proteomic and Metabolomic Markers
  - Physiologic Measures
  - Composite Marker?

Ref: Laughren, TP J Clin Psych 71,9: 1196-1204, 2010

Possible Outcomes for Prospective Hypothesis Testing of Biomarker (M+/M-) (Testing M+ Subgroup First)

Population	Efficacy	Possible Labeling Claims
1st Scenario M+ M-	Yes (Drug>Pbo) No (Drug=Pbo)	-Claim limited to M+ -Question: What needed to rule out benefit in M-?
2nd Scenario M+ M-	Yes (Drug>Pbo) Yes (Drug>Pbo)	-Claim limited to broad population
3rd Scenario Same as #2, but also show M+>M-	Drug M+>Drug M-	-Claim for broad population -Claim for M+ as well

Possible Outcomes for Prospective Hypothesis Testing of Biomarker (M+/M-) (Testing Overall Population First)

Population	Efficacy	Possible Labeling Claims
1st Scenario*		
Total population	Yes (Drug>Pbo)	-Claim for broad population?
M+	Yes (Drug>Pbo)	(Maybe not if no effect in M-)
M-	No (Drug=Pbo)	-Claim for M+
2nd Scenario*		
Total population	Yes (Drug>Pbo)	-Claim limited to broad population
M+	Yes (Drug>Pbo)	
M-	Yes (Drug>Pbo)	

* If can't show efficacy in total population, testing ends.