Institute of Medicine

Forum on Drug Discovery, Development, and Translation

Addressing the Barriers to Development in Pediatrics

Incentives and Disincentives for Pediatric Drug Development

Tom Hassall, R.Ph, MS
Sr. Dir., Global Scientific, Medical, & Regulatory Affairs
Abbott

Abbott
A Promise for Life

Barriers, Incentives, and Disincentives to Drug Development in Pediatrics

- Pediatrics in context of drug development environment
- Pediatrics in the mid-1990's
- Disincentives and incentives
- Pediatric exclusivity -- FDA Modernization Act (FDAMA) – 1997
- Changes since FDAMA
- Where we are today

Drug Development is High Risk Research

		Clinical Trials				
	Discovery / Preclinical Testing	Phase I	Phase II	Phase III	FDA	Phase IV
Years	6.5	1.5	2	3.5	1.5	Additional post-marketing testing required by FDA
Test Population	Laboratory and animal studies	20 to 100 healthy volunteers	100 to 500 patient volunteers	1,000 to 5,000 patient volunteers	Review process / approval	
Purpose	Assess safety, biological activity and formulations	Determine safety and dosage	Evaluate effectiveness look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use		
Success Rate	5,000 compounds evaluated	5 enter trials			1 approved	

Intrinsic incentive

Market forces provide intrinsic incentives and disincentives for drug development

- Need
- Size of patient population
- Size of potential market
- Potential for future indications
- Available treatments
- Intellectual property protection
- Return on investment

Competition for finite resources

Candidate products compete internally for resources with

- other investigational programs
- programs to extend uses of approved products
- other post-marketing research (PMCs)
- pediatric programs

Candidates undergo regular review – “go/no-go” decisions

Pediatrics in the mid-1990's

Perception* was:

- Physicians are treating children with adult products
- Lack of dosing information risks avoidable adverse reactions
- Lack of safety information risks age specific adverse consequences
- Absence of testing exposes children to ineffective treatment
- Absence of information on new products denies children access to best available therapy
- Extemporaneous formulations may be poorly or inconsistently bioavailable.

*63 FR 66632, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients," December 2, 1998

Disincentives for Pediatric Drug Development

In considering FDAMA (Sec. 111), Congress identified **disincentives*** for sponsors to study drugs in children…

- Use in Children expected to generate little revenue
- Pediatric studies pose ethical/moral issues
- Substantial product liability/medical malpractice issues
- Difficult to attract pediatric patients into studies
- Pediatric use represents more difficult administration & patient compliance issues (for some drugs)

These still exist today

*Report from the Committee on Labor & Human Resources on FDAMA – page 51 (July 1, 1997)

Extrinsic incentives/disincentives

Intended to motivate stakeholders to choose options other than those dictated by intrinsic incentives.

- In an environment of competing options, goal is to promote selection of otherwise less attractive course of action (for public good) by making it more attractive
  - Offer of remuneration or other benefit
  - Imposition of penalty for failure to comply

Size of incentive

The more unattractive the behavior you want to promote, the greater the extrinsic incentive needed.

- Make the “promoted” behavior as attractive as possible
- Avoid making the “promoted” behavior more onerous

Focus on achieving the primary goal

Size of incentive

The more attractive the competing options the greater the extrinsic incentive necessary to promote choice of the “desired behavior.”

- An incentive designed to make the natural choice even more attractive in exchange for the “desired behavior” should be highly effective.

Pediatric exclusivity

•Advantage –

- Incentive linked to return on investment for development of the active moiety
  - Enhances the value of the natural choice (based on market forces)
  - Makes the promoted behavior more attractive

•Disadvantage –

- Size of the incentive linked to market for adult product
- Complexity and cost of needed pediatric studies unrelated to size of incentive

The Pediatric incentive…

…in the beginning

Abbott
A Promise for Life

Statutory solution

The Food and Drug Administration Modernization Act (FDAMA) Section 111:

- **Limited scope of "promoted" behavior, thus avoiding making it more onerous**
  - **Conduct studies to generate pediatric data**
    - **Results do not have to be positive**
  - **Revise labeling (data submitted in application)**
- **Voluntary participation**
- **Made intrinsic choices more valuable through additional market exclusivity for entire product line**

Focused on the goal of generating pediatric data and improving pediatric information in labeling

Prescription Drug User Fee Act (PDUFA 2) – pediatric applications exempt from fees

Was Sec. 111 successful?

"As a result of the pediatric exclusivity provision…, critical drugs used to treat a variety of conditions… have or soon will have pediatric use information in their labeling."

"In less than 3 years, over 58 pediatric studies have already been conducted, study reports submitted, and exclusivity granted to 25 drugs."

"***The pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date."***

The Pediatric Exclusivity Provision: January 2001 Status Report to Congress, Dept. of Health & Human Services, U.S. Food and Drug Administration

Today's environment…

How have things changed?

Abbott
A Promise for Life

Pediatric Rule, Best Pharmaceuticals for Children Act (BPCA), Pediatric Research Equity Act (PREA)

"Pediatric Rule" (eff.date Dec. 2000) – now PREA

- Requires pediatric studies in all new applications (same uses) and certain supplements (unless waived)
- Requires safety and efficacy assessments in all relevant pediatric subpopulations
- Introduced requirement for "appropriate pediatric formulations" for each age group

BPCA included provision for referral of declined studies to the NIH Foundation

- Foundation funded only by gifts, grants, and donations

Today

Same intrinsic disincentives for pediatric development exist as in the ’90’s

Pediatric Rule/PREA –

- Requires studies & formulation development without incentive
- Creates potential disincentives for intrinsically attractive programs
  - e.g., new adult indication, dose, regimen or route triggers full pediatric product development

BPCA WR template now includes requirement to commercialize a pediatric formulation (makes “promoted choice” less attractive)

Costs of all drug development (including pediatric studies) have risen considerably

Focus shifted to full development program to create and market “new pediatric product”

Today

Impression that Written Requests are calling for more extensive programs

Exclusivity may be reserved for unique pediatric indications (because PREA requires pediatric studies for claimed uses)

Some Written Requests declined by sponsors and referred to NIH (suggests “the game isn’t worth the candle”)

Pediatric applications subject to user fees

- For FY 2006, application $767,400; Supplement $383,700; Annual Product fee $42,130

US Exclusivity incentive the same as in 1997

Proposed EU Pediatric legislation – similar incentive

“Lower Priced Drugs Act” proposal (S.2300) – would reduce incentive

Expectations for pediatric drug development have evolved since 1997.

How do we strike the right balance between expectations and incentives for the next decade?

Thank you

Abbott
A Promise for Life