Pediatric Exclusivity and other Emerging Issues in Clinical Trials Management

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Agenda

- Pediatric Exclusivity
  - Why, What and How of Exclusivity
  - FDA Guidelines
  - EMEA Guidelines
- Emerging Issues in Pediatric Trial Management
  - Implications for Industry
    - SSRI Suicidality/Vioxx labeling
    - Placebo
    - Informed Consent
    - Exportation of clinical trials ex-US

Pediatric Exclusivity

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Why Exclusivity?

- Many or most medications used in children have never been studied in this population or for the used indication
- Originally, no legal obligation to do studies in children
- Little incentive for Pharmaceutical Companies to pursue for small niche market and high cost of research

Conroy S et al. Br Med J. 2000;320:79-82
Chalumeau M et al. Arch Dis Child. 2000;83: 502-5

What is Exclusivity?

- An incentive developed by congress
- Enforced by FDA
- Provides marketing protection
  - Prevents marketing of identical generic
    - By preventing submission/application
  - For specified period of time
- Applies ONLY to existing patents or exclusivities

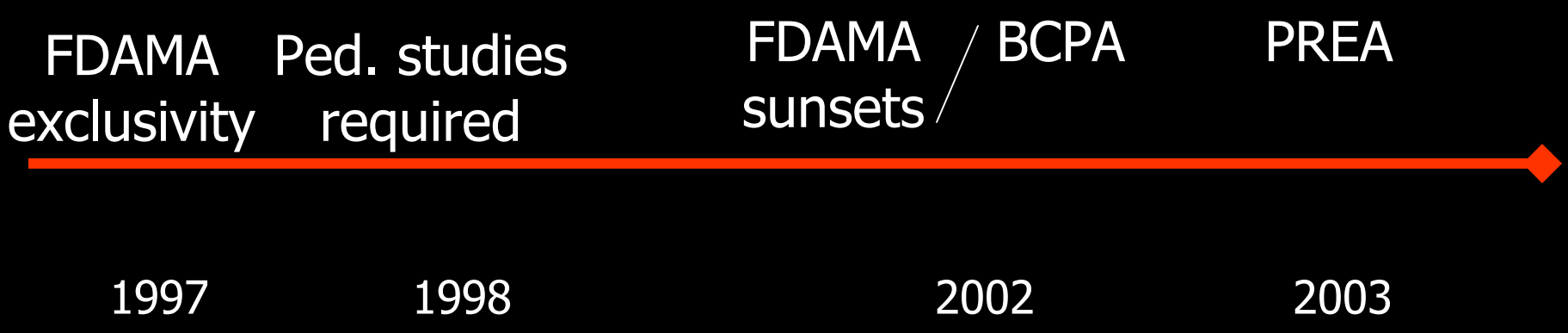
Why Obtain Pediatric Exclusivity?

- Extends patent life or other exclusivity protection by 6 mos
- Possible delay of generic approvals
- 2nd period of exclusivity
  - Glyburide/Metformin¨(Bristol-Myers Squibb)
  - Ibuprofen¨/pseudoephedrine (Whitehall-Robbins Healthcare)
  - For supplemental application only
    - New use, not in approved label

How: To What Does it Apply?

- Applications
  - Containing active moiety
  - Held by same sponsor
- Unapproved applications upon approval
- Later filed NDAs/sNDAs

Pediatric Research Benchmarks



Sunset Rule

- Pediatric Exclusivity rule expired in 2002
- FDA can still issue written request if:
  - Application submitted ≤ 1/1/2002

  AND
  - Drug was in commercial distribution 11/21/1997

  AND
  - Drug is on List 1/1/2002

  AND
  - FDA finds:
    - Continuing need for information
    - Drug may provide health benefit
- FDA cannot issue a written request for a drug with 1st application > 1/1/2002

Best Pharmaceuticals for Children Act (BCPA)

- Reauthorized exclusivity incentive program for pediatric studies through FDAMA
- Mandates FDA/NIH study drugs not pursued by industry
  - Provides mechanism for studies of off-patent drugs
- Public dissemination of studies conducted for Exclusivity
- Public review of safety of drugs granted Exclusivity

Pediatric Research Equity Act

- Retroactive for all applications to 4/99
- Mimics 1998 Pediatric Rule
  - Requires studies of drugs with new:
    - Indication
    - Dosage form
    - Dosing regimen
    - Route
    - Active ingredient
  - Establishes Pediatric Advisory Committee

Pediatric Research Equity Act

- Studies can be waived if:
  - Impossible or highly impractical
  - Evidence suggesting unsafe or ineffective
  - Not a meaningful therapeutic improvement AND not likely to be used
- Studies can be deferred if:
  - Adult approval given
  - Additional safety/efficacy data needed
  - Another appropriate reason with due diligence shown

Pediatric Exclusivity: FDA Guidelines On-Patent

- FDA issues written request*
  - Indication
  - Population
  - Type of studies
  - Safety parameters
  - Duration
  - When to conduct

* can be initiated by Sponsor or FDA

Pediatric Exclusivity: FDA Guidelines Off-Patent

- FDA chooses which drugs require study
- FDA issues written request
- Sponsor has 30 days to respond
  - Yes – same procedure as on-patent
  - No – FDA/NIH study

Success of Exclusivity

FDA has Granted Pediatric Exclusivity for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act:

- Total Exclusivity Determinations = 120
- Total Approved Moieties Granted Exclusivity = 104
- Total Approved Drugs Granted Exclusivity = 110

Last Updated: March 4, 2005
(http://www.fda.gov/cder/pediatric/exgrant.htm)

Pediatric Trials: EMEA Guidelines

- Currently, no legal obligation
- 1998 – EC supported ICH guideline development
- 2001 – Directive on GCP included
  - Specific issues in conducting pediatric trials
  - Criteria for protecting children in these trials
- 2002 – ICH E11 became enforced European guideline
- Pediatric Board
  - A new Scientific Committee at the EU Agency
- EMEA will coordinate a pediatric network for performing studies
- Draft guidance under development for *Pediatric Exclusivity* as of March 2005

Emerging Issues in Executing Pediatric Studies

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Unique Aspects of Pediatric Drug Development

- When
  - Timing (versus adult studies)
- What
  - Indications
- Who
  - Multiple age groups (changing PK, safety, clinical endpoints)
- How
  - Recruitment (global trials)
- Why
  - Safety
  - Ethical considerations

Key Issues in Pediatric Trials: When

- Timing of studies
  - Phase 2/3 data in adults should generally be available

  or

  - Disease/indication life-threatening?
  - Only impacts pediatric population?
  - Major therapeutic advance?
  - Data should be submitted with application or justified

Key Issues in Pediatric Trials: What

- Type of studies
  - Same indication, similar disease process:
    - comparable expected result – data extrapolation + PK + safety
  - Similar disease process BUT blood levels ≠ correspond to efficacy:
    - comparable expected result – PK/PD + safety
  - Novel indication, different disease course, or different therapy outcome – clinical efficacy study

Key Issues in Pediatric Trials: What

- Key Issues in Design
  - Diagnosis (e.g. DSM-IV vs ICD-10)
  - Endpoints
    - Scales (e.g. CNS – PANSS vs kiddie-PANSS)
  - Dosing
  - Safety

Key Issues in Pediatric Trials: What

- Safety endpoints
  - PK is variable
  - Pediatric-specific adverse reactions
  - Pediatric-specific drug interactions
  - Impact on growth and development
    - Physical and cognitive
    - Short-term and long-term
  - Limited database at approval
    - Post-marketing surveillance important

Key Issues in Pediatric Trials: Who

- **Preterm newborn infants**
  - Heterogeneous - stratify
  - Immature hepatic/renal clearance
  - Unique neonatal disease states
- **Newborn infants (0-27 days)**
  - BBB not fully mature
  - Unreliable oral absorption
- **Infants and toddlers (28 days-3 months)**
  - Clearance may exceed adults
- **Children (2-11 years)**
  - Variable onset of puberty
  - Growth/development – skeletal, weight, performance
- **Adolescents (12-16/18 years)**
  - Non-compliance
  - Pregnancy testing
  - Drug screens

Key Issues in Pediatric Trials: Why

Ethical considerations in non-consenting, vulnerable populations:

- IRB/IEC
- Informed Consent/Assent
- Placebo
- Recruitment
- Patients vs. subjects
- Vulnerable populations
- Risk/distress (suicidality)

Key Issues in Pediatric Trials: How

Key Issue: Fewer patients, fewer investigators

- Industry shifting conduction of clinical trials outside of United States
  - Advantages:
    - Patients are readily available
    - Strong patient-provider relationships
    - Lower cost
  - Disadvantages:
    - Uniformity of regulations, GCP, etc.
    - Logistics (Training at a distance, CROs, supplies)
    - Comparability of study populations

Questions & Answers