Encouraging Development of Effective and Safe Pediatric Therapies: A Regulatory Perspective

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Disclaimer

• The views presented here are personal and do not necessarily reflect the views of the Agency

• All specific drug development questions should be discussed with the relevant review division

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From “Protected From Research” to “Protected Through Research”

- **1962**: Kefauver-Harris Amendment required that both efficacy and safety had to be demonstrated for FDA approval
  
- Children were excluded from trials and drug labeling


**Editorial comment: Therapeutic orphans**

Although the laws were designed to ensure the efficacy and safety of drugs, the age group responsible for their passage is now often deprived of the use of the new drugs. Testing of these drugs can not always be in controlled situations, but it sometimes in the situation of use—by need or often against advice. Irresolutely this "unlawful" procedure will be associated with some adverse reactions, including toxic reactions, side effects, and idiosyn.cracy. These reactions are common to all drugs. History has also taught that drugs previously considered harmless may be associated with temporary and per-

- **1970s**: AAP Committee on Drugs issued guidelines for evaluating drugs for pediatric use
  
- **1977**: AAP issued ethics guidelines for pediatric drug studies
  
- Advocacy eventually yielded pediatric legislation (1997 – present)
PREA and BPCA

**PREA (2003)**

- Drugs and biologics
- **Required** studies
- Studies may only be required for approved indication(s)
- Products with orphan designation are exempt from requirements*
- Pediatric studies must be included in labeling

**BPCA (2002)**

- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire moiety and may expand indications
- Studies may be requested for products with orphan designation
- Pediatric studies must be included in labeling

* RACE for Children Act (2017) – Elimination of orphan exemption from pediatric studies for cancer drugs directed at relevant molecular targets

Slide Courtesy of Susan McCune, MD
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Learning From Prior Efforts is Critical

• Up to 42% of pediatric drug trials failed to establish efficacy and/or safety

• Reasons included:
  – Suboptimal dosing
  – Lack of feasibility for small populations
  – Placebo effect
  – Differences between adult and pediatric disease process
  – Other trial design issues, such as choice of superiority or non-inferiority margins

What About Conditions That Occur Only or Primarily in Children?

• FDA and EMA Orphan Product Programs
  – Developers of products for life-threatening and rare diseases may apply for orphan designation
  – Incentives such as fee reduction and extended exclusivity are available

• Partnerships and collaboration are critical to doing high-quality studies (pre-clinical, early phase, pivotal)
  – Basic scientists, clinical researchers, industry, families/patients, regulators

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Innovative Trial Designs

• Dependent on context, examples are:
  – Single arm
  – Crossover
  – Randomized withdrawal
  – Factorial
  – Adaptive
  – Enrichment
  – And others

• Approvals include:
  – Carglumic acid for NAGS deficiency (rare urea cycle disorder)
    • Single arm retrospective study with historical controls
  – Cysteamine bitartrate for nephropathic cystinosis
    • Two OL studies, comparing PK and PD marker with historical controls
  – Alglucosidase alfa for infantile Pompe
    • Single arm trials with clinical endpoints compared to historical controls

Adapted from Susan McCune, MD
What Did These Have in Common?

• Highly plausible mechanistic hypothesis
• Natural history data on untreated patients
• Highly plausible biomarkers; most could be measured in a standard manner
• Serious unmet medical need
• Relatively large treatment effect
Patient-focused drug development (PFDD) is a systematic approach to help ensure that patients’ experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. As experts in what it is like to live with their condition, patients are uniquely positioned to inform the understanding of the therapeutic context for drug development and evaluation.
Benefits of Trial Networks

• Improved efficiency and feasibility
  • Needed for rare conditions
• Trial-ready sites
• Investigator and staff training
• Operational efficiencies (IRB, CRFs, data standards)
• Systematic input from parent/patient advocacy groups
• Broader geographical representation of participants
We Have Traveled Far, but We Have Not Yet Arrived

If you can’t fly then run.
If you can’t run then walk.
If you can’t walk then crawl.
But whatever you do, you have
TO KEEP MOVING
Forward.

MARTIN LUTHER KING JR.
Thank You.

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