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

Gerri R. Baer, M.D., FAAP
Lead Medical Officer, Office of Pediatric Therapeutics
Office of the Commissioner
U.S. FDA

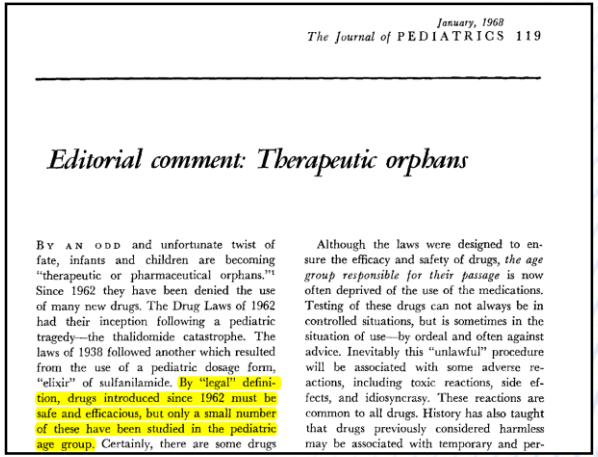
Disclaimer

- 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

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

Shirkey, H. Pediatrics. 1968.



January, 1968
The Journal of PEDIATRICS 119

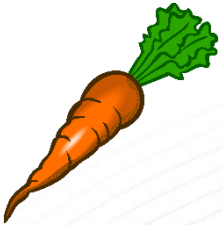
Editorial comment: Therapeutic orphans

BY AN ODD and unfortunate twist of fate, infants and children are becoming "therapeutic or pharmaceutical orphans."[1] Since 1962 they have been denied the use of many new drugs. The Drug Laws of 1962 had their inception following a pediatric tragedy—the thalidomide catastrophe. The laws of 1938 followed another which resulted from the use of a pediatric dosage form, "elixir" of sulfanilamide. By "legal" definition, drugs introduced since 1962 must be safe and efficacious, but only a small number of these have been studied in the pediatric age group. Certainly, there are some drugs

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 medications. Testing of these drugs can not always be in controlled situations, but is sometimes in the situation of use—by ordeal and often against advice. Inevitably this "unlawful" procedure will be associated with some adverse reactions, including toxic reactions, side effects, and idiosyncrasy. 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

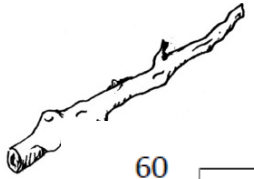
BPCA (2002)

- 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

PREA and BPCA



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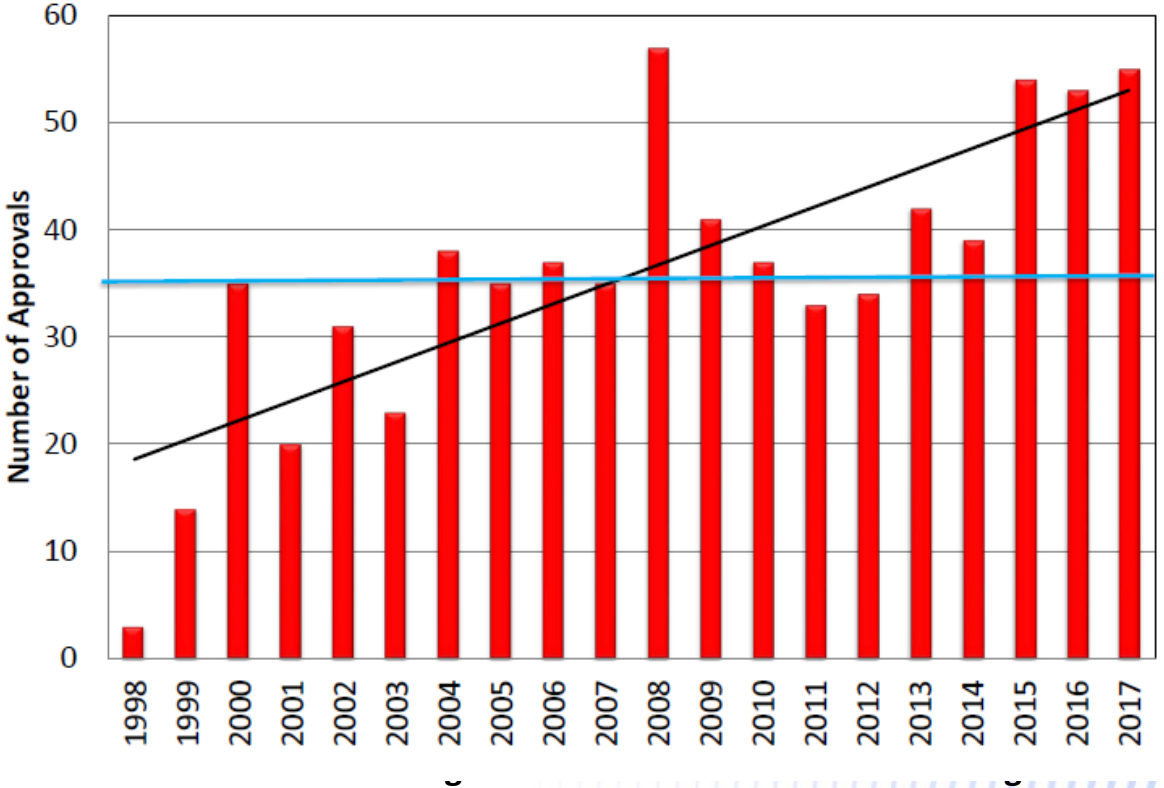

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Slide Courtesy of Susan McCune, MD

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

Momper J et al. Clin. Pharmacol. Ther. 98:245-251(2015).

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

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

Innovative Trial Designs


Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document

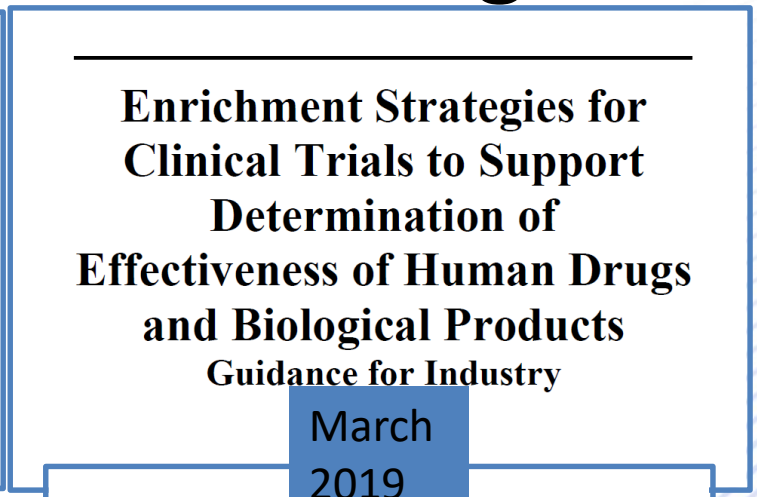
t purposes only.

Comments and suggestions regarc

submitted within 60 days of publication in the *Federal Registe*

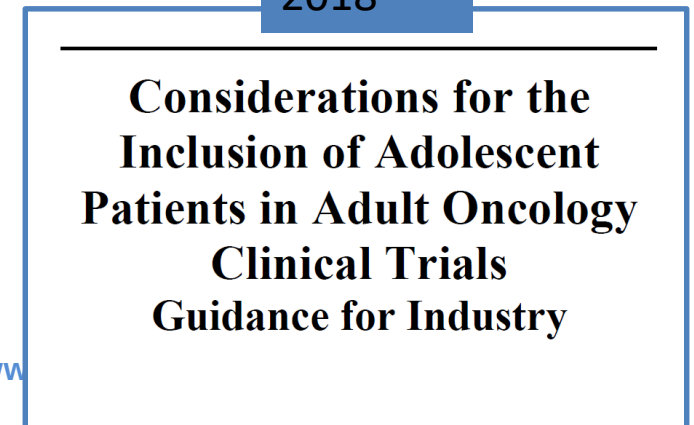
ilability of the draft

October 2018

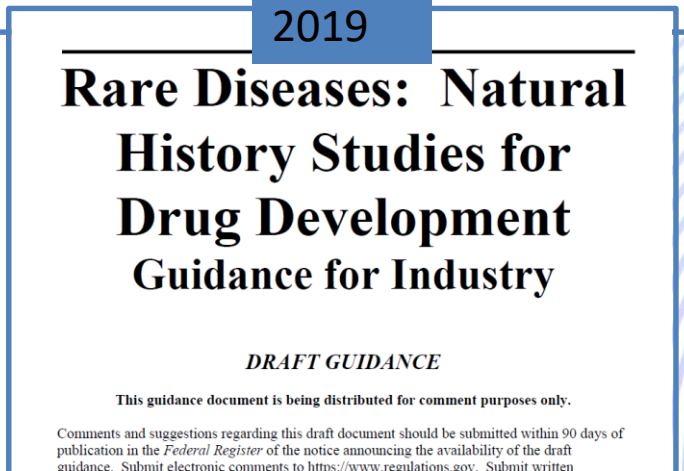

Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products

Guidance for Industry

March 2019


Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials

Guidance for Industry


Rare Diseases: Natural History Studies for Drug Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written

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T1D TYPE 1 DIABETES CONSORTIUM

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Patient-focused drug development (PFDD) is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfu incorporated into drug development and evaluation. As experts in what it is like to liv with their condition, patients are uniquely positioned to inform the understanding of therapeutic context for drug development and evaluation.

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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

Thank You.

gerri.baer@fda.hhs.gov