General Considerations for the Development of Antibacterial Drugs for Children – U.S. FDA Perspective

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21 June 2018

General Principles

- Pediatric patients should have access to antibacterial drugs that have been appropriately evaluated.
- Antibacterial drug development programs should include pediatric studies when pediatric use is anticipated.

Pediatric Drug Development Laws in the U.S.

- Pediatric Research Equity Act (PREA)
  - **Requires** companies to assess safety and effectiveness of certain products in pediatric patients
- Best Pharmaceuticals for Children Act (BPCA)
  - Provides a financial incentive for companies to **voluntarily** conduct pediatric studies
  - FDA and the National Institutes of Health partner to obtain information to support labeling of products used in pediatric patients

Evidentiary Standard for Approval

- For approval, pediatric drug development is held to same evidentiary standard as adult drug development.
- A drug approved for children must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit**
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
    - Improvement or delay in progression of clinically meaningful aspects of the disease

Substantial Evidence of Effectiveness

- Evidence consisting of adequate and well – controlled investigations on the basis of which it could fairly and reasonably be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling.

Extrapolation of Efficacy/Effectiveness for Children

- Efficacy may be extrapolated from adequate and well-controlled studies in adults to pediatric patients if:
  - The course of the disease is sufficiently similar
  - The response to therapy is sufficiently similar
- Dosing cannot be fully extrapolated.
- Safety cannot be fully extrapolated.

Special Considerations for Pediatric Drug Development

- Ethical considerations
  - Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults)
  - Absent a prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clinical trial must be "not greater than minimal"
  - Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care
- Feasibility considerations
  - The prevalence and/or incidence of a condition is generally much lower compared to adult populations

PREA vs. BPCA

PREA

- 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 labeled.

BPCA

- 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 labeled.

PREA

- Signed into law in 2003 (but retroactive to April 1, 1999) after more than a decade of legislative and regulatory attempts to address the lack of pediatric use information in drug product labeling
- PREA requires all applications (or supplements to an application) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral.
- PREA does not apply to Orphan Drugs or to most Generic Drugs.

Required Pediatric Assessment Under PREA

- Data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to:
  - Assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations
  - Support dosing and administration for each pediatric subpopulation for which the drug or the biological product has been assessed to be safe and effective

- Examples of PREA waivers/partial waivers
  - The number of patients in an age group are so small studies would be highly impracticable.
  - Evidence strongly suggests the drug would be ineffective or unsafe in an age group.
  - The drug does not represent a meaningful therapeutic benefit over existing therapies for an age group.
  - Reasonable attempts to produce a pediatric formulation for that age group have failed.
- Example of PREA deferral
  - The drug is ready for approval in adults before pediatric studies are complete.

PREA Example – Cefaroline Fosamil Injection

- Approved 2010 for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia with required pediatric studies.
- In 2016, the sponsor submitted supplementary applications to expand the two approved indications to include children 2 months to < 18 years of age.
  - Two pediatric PK studies
  - Three randomized active controlled trials in children 2 months to < 18 years (one skin infection, two pneumonia (not powered for inference testing as efficacy was extrapolated)
  - Studies in children < 2 months of age: deferral extension

Prescribing Information:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/200327s016s017lbl.pdf

Initial Pediatric Study Plans

- Since 2012, a sponsor planning to submit a marketing application for a drug that is subject to PREA is required to submit an Initial Pediatric Study Plan (iPSP).
- Generally, sponsors are required to submit the iPSP no later than 60 days after the end-of-phase 2 meeting or as early as practicable before the initiation of any phase 3 studies.
- iPSP contents include any waiver/deferral requests, plans for extrapolation of efficacy, summary of planned nonclinical and clinical studies, and plans for age-appropriate formulation development.
- Through FDA review and discussion with the sponsor, the goal is an agreed iPSP.

BPCA Incentives

- BPCA provides an incentive of additional marketing exclusivity to sponsors who voluntarily complete pediatric clinical studies outlined in a Written Request issued by FDA.
  - BPCA Incentive Example: An antibacterial drug approved for the treatment of complicated skin and skin structure infection could be studied in a clinical trial enrolling children with osteomyelitis (trial would need to be powered for inference testing as efficacy could not be extrapolated).

BPCA Off-Patent Studies

- BPCA provides a mechanism for the National Institutes of Health (NIH) to identify drugs no longer under patent that need to be studied in children due to a lack of dosing, safety or efficacy data. FDA works with the NIH to ensure that data from the clinical studies is considered for labeling modification.
  - BPCA Off-Patent Example: Meropenem was originally approved in 1996. In 2015, a PK and safety study in infants <91 days of age with complicated intra-abdominal infections was submitted for review, having been conducted through the BPCA Off-Patent program. The study was not statistically powered to establish efficacy as extrapolation of efficacy to pediatric populations from adult populations was acceptable. Labeling was updated, including dosing recommendations for the use of meropenem in neonates and infants < than 91 days of age with abdominal infection.

https://www.federalregister.gov/articles/2015/05/28/2015-12848/pediatric-studies-of-meropenem-conducted-in-accordance-with-the-public-health-service-act

Addressing the Challenges in Pediatric Clinical Trials for Antibacterial Drugs

CLINICAL TRIALS TRANSFORMATION INITIATIVE

https://www.ctti-clinicaltrials.org/projects/peds-trials

- Collaboration with CTTI, FDA, industry, other stakeholders
- CTTI conducted research and meetings to identify the challenges of conducting pediatric antibacterial trials.
- With input from diverse stakeholders, CTTI developed recommendations to address these challenges and published these in 2017.

Conclusions

- Children are protected THROUGH research, not from it.
  - The PREA and BPCA laws in the U.S. have led to incorporation of pediatric-specific labeling for more than 600 drug products.
- Economic, scientific, and feasibility challenges impact the development of antibacterial drugs for children.
- FDA is committed to work with international regulatory colleagues and stakeholders to increase the availability of safe and effective treatments for children.


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