Pediatric Drug Development: FDA Perspective

Liver Forum - Pediatric Cholestatic Disease Working Group
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Disclosure Statement

• I have no financial relationships to disclose relating to this presentation

• The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA
Outline

• Statutory Requirements for Drug* Approval
• Regulatory Flexibility
• Rare, Serious or Life-Threatening Pediatric-Specific Diseases
• Opportunities to Interact with FDA

* Refers to both small molecules and biological products regulated by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research
Benchmark

Pediatric Drug Legislation and Regulation

1997  Food and Drug Modernization Act (FDAMA)
2001  Subpart D Final Rule: Additional Safeguards for Children in Clinical Investigations of FDA-regulated products
2002  Best Pharmaceuticals for Children Act (BPCA)
2003  Pediatric Research Equity Act (PREA)
2007  Food and Drug Administration Amendments Act (FDAAA)
2010  Patient Protection and Affordable Care Act (ACA)
2012  FDA Safety and Innovation Act (FDASIA)
2017  FDA Reauthorization Act (FDARA)
FDA Evidentiary Standard

- Pediatric drug development held to **same standard** as adults for approval
  - Demonstrate substantial evidence of effectiveness for treatment of proposed indication
  - Adequate safety information must be included in the application to allow for appropriate risk benefit analysis
- Manufacturing ensures product identity, strength, quality (purity)
- Evidence-based labeling that adequately guides patients and prescribers how to use drug safely and effectively

Food Drug and Cosmetic [FDC] Act 505(d)
Measures of Clinical Benefit

• Clinical Outcome ("clinically meaningful endpoint")
  – Direct measure of an outcome that describes or reflects how an individual
    • Feels (e.g. pain, dyspnea, depression);
    • Functions (e.g. ability to perform activities in their daily lives); or
    • Survives (e.g. mortality, stroke, pulmonary exacerbation)

• Comparative advantage in treatment of disease
• Comparative reduction in treatment-related toxicity

FDC Act Section 507(e)(9)
Measures of Clinical Benefit

Biomarker
- Measure of normal biological or pathogenic processes or responses to an exposure or intervention, including therapeutic interventions
- Diagnostic, monitoring, prognostic, predictive, safety, pharmacodynamic/response
- **Not a measure** of how an individual feels, functions, or survives

Surrogate Endpoint
- **Used as substitute for direct measure** of how a patient feels, functions, or survives
- **Expected to predict clinical benefit or harm** based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence
- Validated, reasonably likely, candidate surrogate endpoints

FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource
US Approval Pathways

Traditional Approval
• Based on clinically meaningful or validated surrogate endpoint

Accelerated Approval
• Based on surrogate endpoint reasonably likely to predict clinical benefit or intermediate clinical endpoint
• Product must be for serious or life-threatening disease or condition AND provide a meaningful advantage over available therapies
• Post-marketing confirmatory trial generally required to verify and describe the anticipated effect on irreversible morbidity or mortality or mortality or other clinical benefit
• Expedited withdrawal of drug approval if confirmatory trial fails to verify clinical benefit or does not demonstrate sufficient clinical benefit to justify drug-related risks

21 CFR 314: Subpart H--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses
# Measures of Clinical Benefit

<table>
<thead>
<tr>
<th>Surrogate Endpoint</th>
<th>Predicted Clinical Outcome</th>
<th>Approval Pathway</th>
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<tbody>
<tr>
<td>LDL Cholesterol Reduction</td>
<td>Reduction of adverse cardiovascular events</td>
<td>Traditional</td>
</tr>
<tr>
<td>Hemoglobin A1C Reduction</td>
<td>Reduce microvascular complications in diabetes mellitus</td>
<td>Traditional</td>
</tr>
<tr>
<td>SBP Reduction</td>
<td>Reduce rates of stroke, myocardial infarction, and mortality due to hypertension</td>
<td>Traditional</td>
</tr>
<tr>
<td>HIV RNA Reduction</td>
<td>Control of clinical HIV disease</td>
<td>Traditional</td>
</tr>
<tr>
<td>Reduction in Iron Stores</td>
<td>Decrease in transfusion-related adverse events due to iron overload in thalassemia</td>
<td>Accelerated</td>
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Substantial Evidence of Effectiveness

• Requires studies designed well enough “to distinguish the effect of a drug from other influences, such as spontaneous change... placebo effect, or biased observation” (21 CFR 314.126)
• FDA generally interprets efficacy standard to consist of 2 adequate and well-controlled trials to independently substantiate clinical benefit in affected population
• 1997 FDAMA included revised definition to include 1 adequate and well-controlled trial and “confirmatory evidence” in some instances

1998 Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
Regulatory Flexibility

• “While the statutory standards apply to all drugs, the many kinds of drugs...and wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.” (21 CFR 314.105)

Does not mean marketing approval will be granted before demonstration of substantial evidence of effectiveness
Pediatric Extrapolation

• An approach to improve efficiency and success of pediatric drug development

• Relies on series of evidence-based assumptions that reference (adult or other pediatric) and target pediatric populations would be expected to have sufficiently similar
  – Disease course
  – Expected response to therapy

• Relatively lower prevalence and/or incidence of a condition in pediatric vs adult population alone does not justify use of extrapolation
Pediatric Extrapolation: Factors to Consider

**Goal:** To predict how a drug will behave in pediatric patients based on data generated in adults

- What evidence supports disease and response similarity?
- If disease/response are similar, what data are needed to support approval?

**Techniques to make optimal use of available data:**
modelling and simulation, adaptive designs, Bayesian statistics, meta-analytic approaches, etc.
Pediatric Extrapolation: Questions to Consider

• What is the strength of evidence of efficacy in reference population?
• What evidence supports
  – Common pathophysiology, natural history, and similarity of disease course?
  – Biomarker or surrogate endpoint in reference populations relevant to pediatric population?
  – Similar exposure-response?
• What uncertainties and/or limitations in existing data (e.g., clinical or historical data and published literature) and about pediatric population?
• What additional information should be generated (e.g., information from modelling and simulation, animal, adult, pediatric subgroup studies) to inform acceptability of extrapolation?
Extrapolation Approaches in Pediatric Programs

Increasing level of evidence required from pediatric studies

Increasing level of confidence in similarity of disease/response

~60% Pediatric Programs require at least 1 adequate, well-controlled efficacy trial (clinical or surrogate endpoint)

1 or more adequate-well controlled studies powered on a clinically meaningful endpoint
- Bipolar disorder, systemic juvenile idiopathic arthritis, major depression, migraine, polyarticular JIA (pJIA), bronchopulmonary dysplasia, ADHD, nausea/vomiting, partial seizures (<4 y/o), respiratory syncytial virus, prophylaxis of venous thromboembolism, atopic dermatitis, etc.

1 or more adequate-well controlled studies powered on a surrogate endpoint
- Diabetes, anemia, idiopathic thrombocytopenia, treatment of venous thromboembolism, hypertension, hypercholesterolemia, asthma, etc.

Controlled study without formal statistical power
- Community acquired pneumonia, nosocomial infections, skin and skin structure infections, etc.

Descriptive efficacy study without concurrent control
- Plaque psoriasis, Neurogenic detrusor over-activity, pJIA (NSAIDs), etc.

Small dose-ranging studies (randomization to multiple dose levels)
- Sedation, ulcerative colitis, Crohn’s, etc.

Small PK/PD studies (single dose level matching adult exposures)
- HIV, erosive esophagitis (infants), anesthetics, pulmonary arterial hypertension,

PK/safety only (single dose level matching adult exposures)
- Gastroesophageal reflux disease, bacterial sinusitis, herpes simplex, analgesics/anesthetics (well known MOAs; over 2 y/o), imaging products, melanoma (adolescents)

List partially adapted from Dunne et al. Pediatrics 2011
Pediatric Dose Selection

- Pediatric dosing cannot be fully extrapolated
- PK studies may be needed to identify dosing regimen that results in exposure range or distribution comparable to those observed in reference population (most often adults)
- Modelling and simulation can explore variety of pediatric dosing strategies to achieve a target range of exposures that may need to be confirmed in a pediatric study
Pediatric Safety

• Cannot be fully extrapolated from adults
• Developing systems may respond differently to drug exposure than matured adult organs
  – New safety signals
  – Increased susceptibility to observed safety signal in adults
Rare Diseases

• ~ 7,000 rare diseases affecting 30 million people in US
• Challenges with drug development
  – Natural history often poorly understood or characterized
  – Small populations often restrict study design and replication
  – Phenotypic and genotypic diversity within a disorder adds to complexity
  – Well defined and validated endpoints and biomarkers often lacking
  – Lack of precedent for drug development
  – Ethical considerations with initiating first in pediatric clinical trials

FDA Voices: https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm632217.htm
Orphan Drug Act of 1983

• “any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States…”

• Financial Incentives
  – 7 years of marketing exclusivity
  – Tax credits up to half of qualified clinical trial costs
  – Waiver of Prescription Drug User Fee Act filing fee at time of marketing application submission

21 CFR 316
FDA Evidentiary Standard

• Rare disease drug development held to **same standard** as common diseases for approval
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Food Drug and Cosmetic [FDC] Act 505(d)
Ethical Considerations

• Can scientific and/or public health objective(s) be met by enrolling subjects who can provide informed consent personally (i.e., adults)?
  – Subjects capable of informed consent (i.e., adults) should be enrolled prior to children (21 CFR 56.111(a)(1) and (b))
  – Do not enroll children unless essential (i.e., no other option, whether animal or adult human)

• Does trial participation offer prospect of direct benefit?
  – If no, then risks to which a child would be exposed in a clinical trial must be “low” (21 CFR 50.51 and 50.53)

• 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
Ethical Considerations

• Institutional Review Board (IRB) approval of research generally justified
  – Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result (21 CFR 56.111(a)(2))

• Knowledge to be able to treat others not considered a direct benefit
  – Informed adult can make this decision
  – Pursuit of knowledge more restricted regarding allowable risk in children

• Expanded access ("compassionate use")
  – Appropriate when patient ineligible for trial inclusion
  – Potential benefit must still justify potential risks of treatment
Pediatric-Specific Diseases: Nonclinical Studies

• Mandated part of drug development
• Provide evidence that drug is reasonably safe to conduct proposed clinical investigations
• Enable estimation of safe starting human dosage, dose-escalation plan, route of administration
• Inform safety measures to be monitored in clinical trial based on observed toxicologic profile
Pediatric-Specific Diseases:
Natural History of Disease

- Knowledge of natural history of rare disease **critical** to successful drug development
  - Define disease population and identify key disease subtypes
  - Inform clinical trial design (e.g. entry criteria, study duration)
  - Inform selection of primary outcome measure(s)
  - Potentially provide external control group

- Design elements
  - Broad inclusion criteria to characterize wide spectrum of phenotypes and severity
  - Sufficient duration to capture clinically meaningful outcomes and variability
  - Identify when specific manifestations develop and are likely to persist
  - Standardized methods to collect relevant clinical data

- Make these data publicly available to promote drug development

March 2019 draft Guidance for Industry: Rare Diseases: Natural History Studies for Drug Development
Pediatric-Specific Diseases: Premarketing Safety

• Design elements
  – Characterize safety profile at intended exposures and anticipated duration of use
  – Adequately represent intended treatment population
  – Size of safety database governed by estimated disease prevalence
  – Consider utility of comparative long-term safety (e.g. placebo, no treatment, standard of care, active drug, multiple doses)

• Additional sources of supportive safety data
  – Relevant data from trials evaluating drug for other indications or for drugs in same class
Pediatric Post-Marketing Safety

• Pediatric-specific rare and delayed-onset adverse reactions may not be detected pre-marketing

• Post-marketing surveillance, long-term follow-up studies, or both may be needed to assess impact of chronic use on growth and development

• FDA Congressionally mandated to review all adverse event reports for 18 months after approval of any pediatric labeling change
Opportunities to Interact with FDA

• FDA formal advice through milestone meetings (e.g. pre-IND, end-of-phase 1, end-of-phase 2) with relevant review division
  – Type C meeting for discussion of novel surrogate endpoints
• Common Commentary issued after monthly pediatric cluster tcons with regulatory counterparts outside US
• Critical Path Innovation Meetings (CPIM) for early scientific discussions among CDER staff, industry, academia, patient advocates about enhancing drug development efficiency

April 2015 Guidance for Industry: Critical Path Innovation Meetings
February 2019 Guidance for Industry: Rare Diseases: Common Issues in Drug Development
Patient Empowerment

"It turns out that what is really bothering the patient and what is really bothering the doctor can be radically different things....patients are true experts in their disease”.

“It's clear you have to start with an understanding of the impact of the disease on the people who have it, and what they value most in terms of alleviation before you set up a measurement and go forward with truly patient-focused drug development.“

- Janet Woodcock, Director
  CDER, FDA

PDUFA V Clinical Outcome Assessments Public Workshop, April 1, 2015
Patient-Focused Drug Development (PFDD)

- Initiative launched in 2013 to host 20 disease-specific meetings
- Program extended in 2015 to encourage externally led meetings organized by patient organizations in other disease areas
- Attendees: patients, caregivers, patient advocates, researchers, drug developers, healthcare providers, FDA

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<thead>
<tr>
<th>Meeting</th>
<th>Date</th>
<th>Host Organization</th>
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<tr>
<td>Ig A Nephropathy</td>
<td>8/19/19</td>
<td>National Kidney Foundation (NKF)</td>
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<tr>
<td>Alport Syndrome</td>
<td>8/3/18</td>
<td>Alport Syndrome Foundation, NKF</td>
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<tr>
<td>C3G</td>
<td>8/4/17</td>
<td>NKF</td>
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<tr>
<td>Patients Who Have Received an Organ Transplant</td>
<td>9/27/16</td>
<td>FDA</td>
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Final Thoughts

• Children are protected through research not from it
  – We’ve made tremendous progress over past 20 years but more work to be done
• Pediatric and rare disease drug development held to same statutory requirements for approval as adult and more common diseases
• Regulatory flexibility needed in achieving this standard for pediatric patients
  – Utilizing existing knowledge (e.g. efficacy extrapolation)
  – Rare, serious pediatric-specific diseases require unique considerations
• FDA’s role
  – Ensure protection of human subjects during all phases of drug development
  – Review data to determine if statutory requirement for drug approval has been met
  – Promote collaboration to facilitate pediatric drug development
Thank You!