Accelerating Drug Development for pJIA Workshop

Exposure-matching vs confirmation of efficacy: Pros, cons, and remaining uncertainties

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Disclosure Statement

- I have no financial interests or conflicts of interest with any pharmaceutical company to disclose relating to this presentation

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Challenges with pJIA Drug Development

- Rare disease population
- Heterogeneous disease
- Pediatric-specific manifestations, i.e. uveitis, MAS, ILD, etc.
- Availability of effective therapies
- Concerns with use of placebo
- Limited appropriate endpoints for JIA subsets
- Feasibility of conducting pJIA clinical studies

Extrapolation of Efficacy

- To initiate pediatric studies, evidence is needed to support a prospect of direct benefit to justify the risks of exposing children
  - Usually during adult development; ideally along with phase 3 in adults
  - Assumes some degree of extrapolation
- Efficacy and benefit-risk of a new product are generally established first in adults
  - This generates prior knowledge to support the consideration of extrapolation to pediatric patients

Extrapolation of Efficacy

The foundation of pediatric extrapolation is the degree of **response similarity** between adults and pediatric patients which is determined by:

Disease Similarity

- Natural history
- Pathophysiology
- Diagnostic criteria
- Clinical management
- Response to other therapies
- Placebo response
- Similar endpoints

Pharmacology

- ADME
- Mode of action
- Ontogeny of targets
- Genetics/genomics

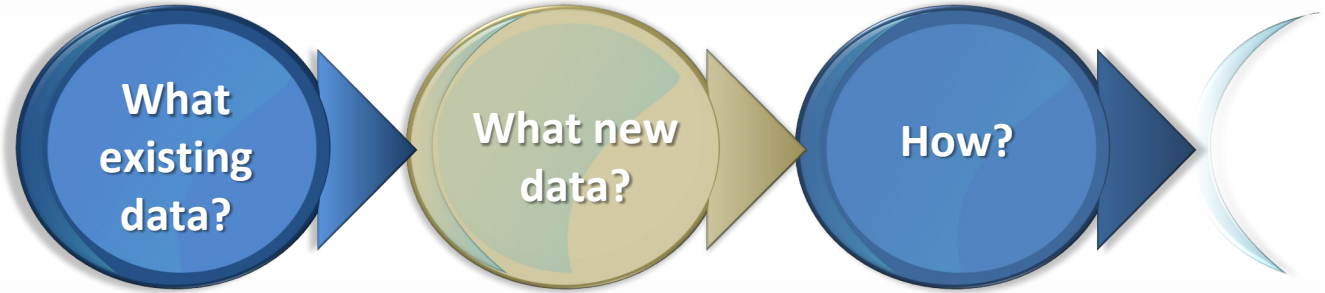
Extrapolation of Efficacy

Existing data?

What adult data, if any, could be leveraged and to which pediatric age group does it apply?

How?

What is the optimal trial design to obtain the necessary data



What new data?

What additional data are needed in the pediatric population?

Extrapolation of Efficacy:

Disease/response "similarity" is a continuum

Different	Dissimilar	Similar	Same
No overlap between adult and pediatric condition	Some degree of overlap with significant differences between adult and pediatric condition	Large degree of overlap with some differences between adult and pediatric condition	Significant overlap; no known significant differences between adult and pediatric condition

Increasing relevance of adult information to pediatric population with increasing confidence in similarity between adult and pediatric condition

AWC pediatric trial(s)

Bridging biomarker, Bayesian borrowing, etc.

Exposure matching

Current Understanding Supporting Extrapolation of Efficacy in pJIA

- Disease similarity between RA and pJIA
- Prior knowledge of similarity in response between RA and pJIA with comparable exposures
  - Several classes/MOA of drugs

Acknowledging the Uncertainties with Extrapolation in pJIA

- Adequacy of dose exploration/selection in pediatric patients
- Examples of programs that did not meet their objectives
- Limited prior information on new classes/MOA
- Cannot extrapolate dosing
- Cannot extrapolate safety
  - Impact on growth, bone, sexual maturation
  - Impact of immunomodulatory drugs on developing immune system
  - Immunogenicity for biologics

Addressing the Uncertainties with Extrapolation in pJIA

- Increased scientific knowledge on disease process
- Increased understanding of overall pediatric drug development
- Increased experience in the use of pediatric extrapolation in drug development
- Borrow prior information from adult and pediatric trials

Evidentiary Standard for Approval

- A product approved for children must demonstrate substantial evidence of clinical benefit/effectiveness
  - Clinical benefit
  - Evidence of effectiveness
- Adequate safety information must be included in the application to allow for appropriate benefit risk analysis

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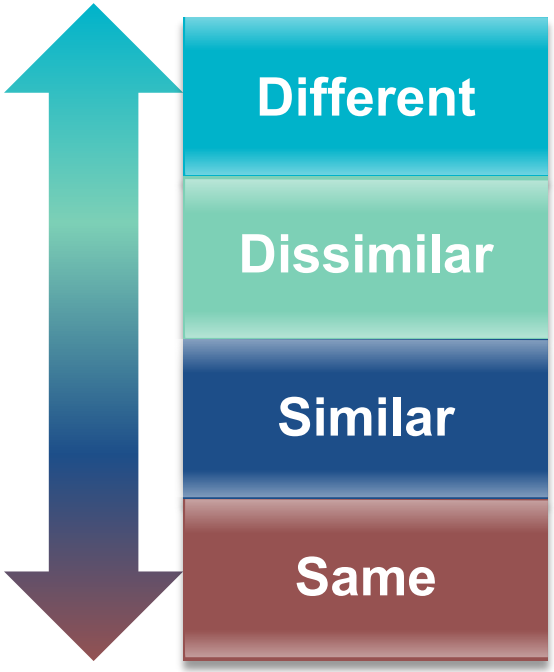
Moving Forward



A. **Need confirmation of efficacy from adequate and well-controlled trial(s) on a clinically meaningful endpoint**

B. **Some degree of confidence that the diseases and responses are similar such that evaluation of dose/exposure effect on a biomarker or clinical endpoint would be sufficient**

C. **PK/safety only, i.e. single dose level matching adult exposures**

Moving Forward: Questions to the Panel

1. What are the Pros for each potential path?
2. What are the Cons for each potential path?
3. What uncertainties remain, if any, for acceptance of a specific path?
4. What data should be generated in future clinical programs to address these uncertainties?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