U.S. FOOD & DRUG ADMINISTRATION

Clinical Trials and Research in Children

FDA's Perspectives for the development of antiviral products for the treatment of HIV infection in children: Regulatory considerations

Pediatric HIV Cure Meeting

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Disclaimer

The views expressed in this presentation are my own and do not necessarily reflect those of the Food and Drug Administration.

Objectives

Outline:

- Considerations for clinical trials in children
  - Ethics
  - Regulatory requirements
- Approaches to pediatric drug development
- Considerations for HIV cure clinical trials in children
- Rare diseases and orphan drug designation

General Principles

- Pediatric patients should have access to drug products that have undergone appropriate evaluation for safety and efficacy.

- Drug development programs should include pediatric studies when pediatric use is anticipated.

Pediatric Research

- Best Pharmaceuticals for Children Act, *BPCA* (voluntary pediatric studies)
  - Passed by Congress in 2002
  - Section 505A of the Federal Food, Drug , and Cosmetic Act
  - Provides a financial incentive to companies to **voluntarily** conduct pediatric studies
  - Provides mechanisms for studying off-patent drugs in children (via NIH program)

- Pediatric Research Equity Act , *PREA* (Mandatory pediatric studies)
  - Passed by Congress in 2003
  - Section 505B of the Federal Food, Drug, and Cosmetic Act
  - **Requires** companies to assess safety and effectiveness of certain products in pediatric patients

Pediatrics Ethics: 21 CFR 50 Subpart D Risk and Benefit Considerations

Research involving children either

- Must be restricted to “minimal” risk or a “minor increase over minimal” risk, if there is no potential for direct benefit to the enrolled child
  - 21 CFR 50.51/53;45 CFR 46.404/406

or

- If more than minimal risk, the risk must be justified by anticipated direct benefits to the child…the balance of which is at least as favorable as any available alternatives
  - 21 CFR 50.52;45 CFR 46.405

Prior to Initiating a Pediatric Clinical Trial…

…in which the investigational product poses more than 'minimal risk', required to establish

- prospect of direct benefit to justify increased risk
  - Evidence maybe from acceptable animal models or adult human clinical trials
- The benefit/risk ratio for the investigational product is, at minimum, as favorable as alternative treatments for the enrolled subject

21 CFR 50.52 / 45 CFR 46.405

Prospect of Direct Benefit (PDB)

- "Direct benefit"
  - The intervention/investigational product from the research may improve the health or well-being of the study participant

- What evidence of benefit is available for the intervention/product?
  - Source of data: adult, animal model

- Consider the overall risks and benefits from participating in trial, even when PDB has been established:
  - Is the disease/condition life-threatening?
  - Are there effective alternative treatments?
  - How toxic is the investigational product?

Key Summary #1

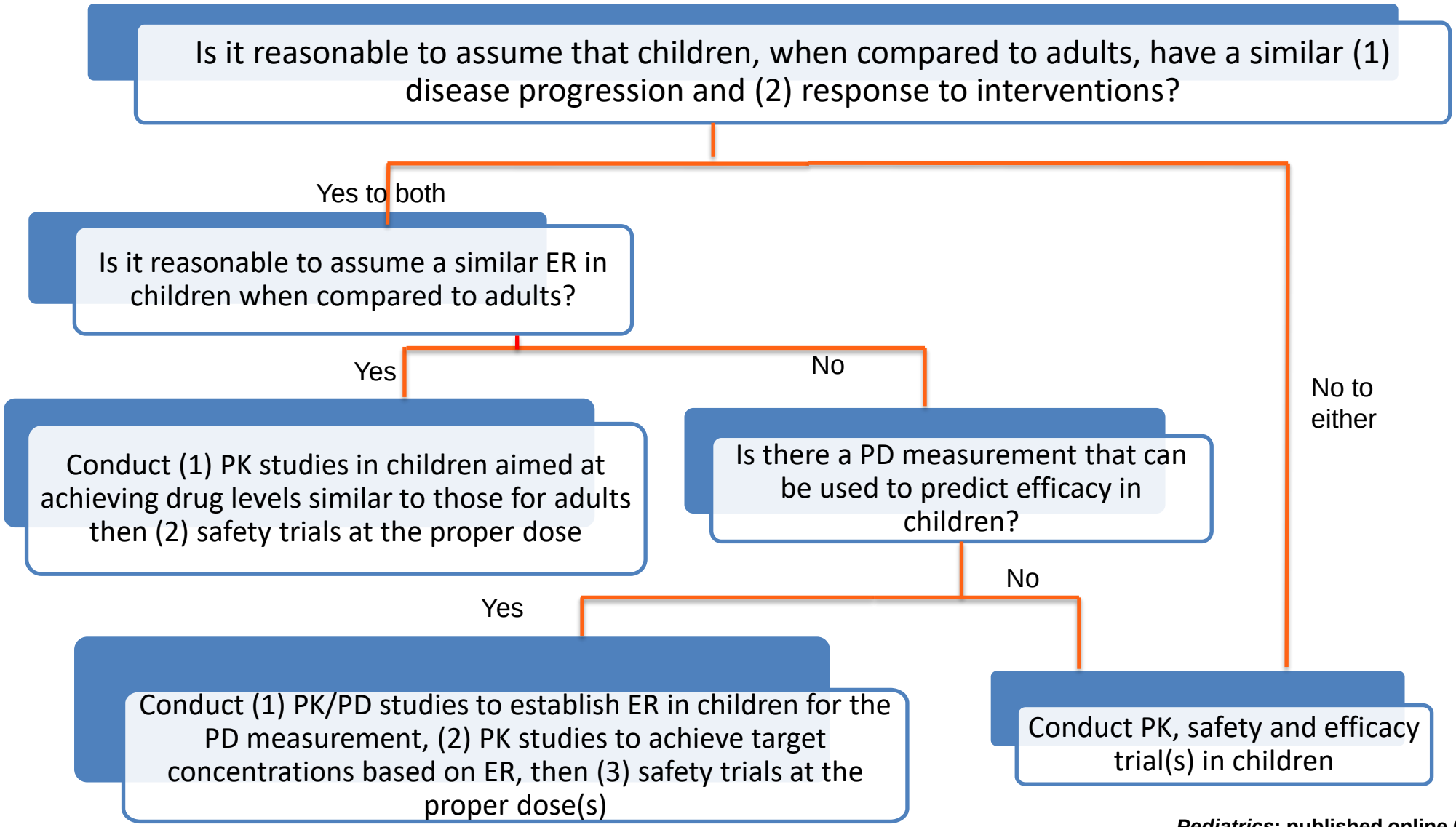
- **If a drug is being developed to treat a disease that exists in adults and children, the law requires that the drug also be developed for children.**

- **Ideally, pediatric approval for a product should be at the same time as the adult approval, provided sufficient early safety/efficacy data and appropriate pediatric formulations are available to support pediatric trial initiations.**

Principles of Pediatric Drug Development

- Pediatric Research Equity Act (PREA) (2003): for new drugs, assessments of safety and effectiveness are required for all relevant pediatric subpopulations
  - Adequate and well-controlled studies
  - Extrapolation under limited circumstances
- 1. **Dosing** (PK) cannot be extrapolated (particularly in neonates)
- 2. **Safety** cannot be extrapolated
- 3. Extrapolating **effectiveness** depends on a number of criteria including disease similarity and treatment response

Efficacy and Extrapolation- Trial Design



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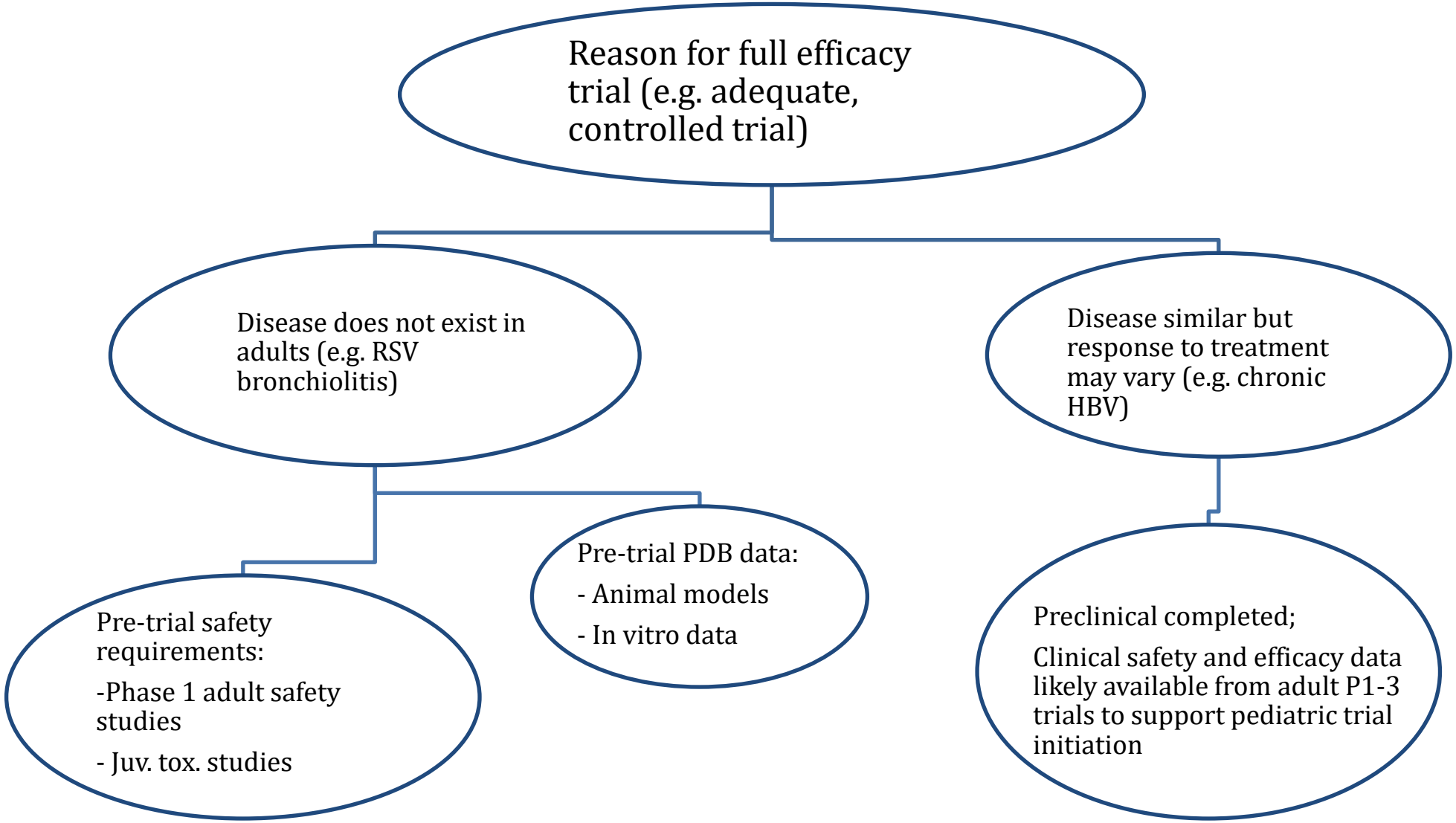
Scenario A- Extrapolation Example: Treatment of HIV

- Phase 1, 2 trials completed in adults
- Toxicology studies complete
- Adolescent trial can be initiated along the Phase 3 adult clinical trial
  - Rely on Phase 1,2 data to establish safety and activity
  - Single arm design acceptable, as PK is pivotal data
- Non-adolescent pediatric trial (e.g. 1 month to 12 years old) can be initiated as soon as appropriate dosage(s)/formulation(s) are available
  - Rely on Phase 1, 2 data to establish safety and activity
  - Single arm trial acceptable

Scenario B: Full Pediatric Study
Example: RSV, Chronic HBV



Key Summary #2

- **Approach to pediatric trial design is dependent on whether the disease is similar in adults and children, and response to interventions is similar between the two population**
  - **IF similar, extrapolation of efficacy is adequate**
  - **If dissimilar, adequate and well controlled trial design required in children**

HIV Cure Pediatric Research: General Considerations

- Does the disease/condition exist in children?
  - Yes
- If a product is under development for cure in adults, would PREA be triggered?
  - Yes
  - PREA waiver/deferral may be considered, if appropriate, for some or all pediatric populations [e.g. considerations of product's safety profile; alternative (safer) product under development; lack of sufficient number of pediatric patients]
- Is it reasonable to assume that children, when compared to adults, have a similar (1) disease and (2) **response to interventions**?
  - Considerations: product's mechanism of action and host target
  - Yes to adolescents/children?
  - No to neonates?
- Overall risks/benefits considerations for pediatric population
  - Pre-clinical data
  - Toxicity profile of the product
  - Efficacy data

Scenario A: Extrapolation of Efficacy for an HIV Cure Product

Disease and response to intervention is similar between adults and children

Considerations of the risks/benefits of the product favors development of product in children

- Adolescent trial can be initiated along with adult once safety, efficacy are established from Phase 1, Phase 2 data,
- **Product maybe evaluated in the non-adolescent population as soon as formulation is available**
- **If parenteral formulation, trial could be initiated in younger children (including neonates) along Phase 3 adult trials**

Scenario B: No Extrapolation of Efficacy for an HIV Cure Product

Full efficacy trial required in pediatrics

What should we think about early in the development?

- What is the safety profile of the product?
  - Pre-clinical (including juvenile tox study), clinical (adult, phase 1)
- Ethics, risks/benefits considerations:
  - SOC vs. investigational product
- Have the endpoints (and assays) been established?
  - Validated and clinically meaningful
  - In vitro/animal model providing proof-of-concept data?
- What is the appropriate trial design (size, statistical plan, endpoints, time points, etc.?
  - Encourage early engagement (e.g. pre-IND) with FDA
- Pediatric (including neonates) trials may be initiated, if
  - Supported after considerations of above points

Key Summary #3

For HIV cure research and product development in children:

1. **The basic science/immunology establishment helpful with trial design: extrapolation vs. full efficacy trial**
2. **Regardless of the trial design, the toxicity profile of the product and the overall risks/benefits should be considered prior to initiating pediatric trials.**

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