# Regulatory Challenges in Pediatric Drug Development

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# To Recap…

- Joe Horrigan: Where are we in 2020?
- Gahan Pandina: Timing of pediatric studies
- Christine McSherry: Outcome measures
- Alison Bateman-House: Ethics and IRBs

# A (Very) Brief History of Pediatric Drug Development in the US

- 1979: Pediatric Use subsection added to drug labeling
- 1994: Pediatric Labeling Rule
  - Required manufacturers to survey existing pediatric data and add to labeling
  - Pediatric extrapolation “introduced”
- 1997: Food and Drug Administration Modernization Act
  - First incentive program for conducting pediatric studies on drugs
- 1998: Pediatric Rule
  - First requirement for manufacturers to conduct pediatric studies in certain drugs
- 2002: Best Pharmaceuticals for Children Act (BPCA)
  - Provides a financial incentive to 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
- 2003: Pediatric Research Equity Act (PREA)
  - **Requires** companies to assess safety and effectiveness of certain products in pediatric patients
- 2012: BPCA and PREA permanently reauthorized with the Food and Drug Administration Safety and Innovation Act (FDASIA)

# Waivers and Deferrals

- Criteria for Full Waiver
  - Necessary studies are impossible or highly impracticable
  - The drug or biological product would be ineffective or unsafe in all pediatric age groups
  - The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients
- Criteria for Deferral
  - The drug or biological product is ready for approval for use in adults before pediatric studies are complete
  - Pediatric studies should be delayed until additional safety or effectiveness data have been collected

    OR
  - There is another appropriate reason for deferral

# Regulatory Challenges Remain

- BPCA and PREA effectively encourage pediatric trials of drugs already in development for adults
- Can we reduce the lag time between approval of adult and pediatric indications?
- What if drugs that are effective in adults don't have the same efficacy in children?
- How do we find the treatments that are effective mainly in the pediatric but not adult population?

# Extrapolation

- "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, ...pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies."

  – 21 U.S.C. § 355c

ARTICLE

# A Quantitative Justification of Similarity in Placebo Response Between Adults and Adolescents With Acute Exacerbation of Schizophrenia in Clinical Trials

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**Early-onset schizophrenia, or "adolescent schizophrenia," has a global incidence ranging up to 4% of all schizophrenia cases. Clinical data from antipsychotic programs were collected from new drug applications submitted to the US Food and Drug administration from 1993 to 2015. A placebo response–dropout model was developed to describe the time course of total positive and negative syndrome scale (PANSS) scores in adults and adolescents. The final model in both populations suggested that patients with higher baseline scores exhibited a greater absolute reduction from baseline. Higher baseline total PANSS, enrollment in US trials, and increases or small improvements in total PANSS were found to be predictors of dropout in both populations. Simulated adolescent data using the final adult placebo response model resembled the observed adolescent data. By confirming similar changes in disease symptomology during an acute exacerbation, efficient regulatory pathways for adolescents can be facilitated by using the extrapolation paradigm.**

## Study Highlights

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

☑ Conducting confirmatory pediatric trials to demonstrate safety and efficacy is time-consuming and costly. As a result, pediatric patients may not have available access to treatments with adequate dosing information. No quantitative knowledge exists on symptomatic changes in placebo-treated pediatric patients with schizophrenia after an acute exacerbation.

**WHAT QUESTION DID THIS STUDY ADDRESS?**

☑ The objective of this study is to leverage placebo data from short-term adult and adolescent schizophrenia trials to assess similarity in symptomatic changes after an acute exacerbation and to potentially streamline future clinical development for adolescents.

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

☑ This analysis provides the first model-based evaluation of symptomatic change in pediatric patients receiving placebo and the quantitative basis to compare the similarity between adults and adolescents. The results confirmed similarity in changes in total PANSS scores and predictors for dropouts between the two populations.

**HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**

☑ This work will potentially allow the community to bring innovation into pediatric development programs and reshape the current practices in antipsychotic drug development.

Early-onset schizophrenia (EOS), or "adolescent schizophrenia," has been recognized more frequently over the past decade.[1] Although the typical onset of schizophrenia occurs in young adulthood between the ages of 18 and 25 years old, adolescent-onset makes up 4% of all cases of schizophrenia, with an incidence rate of 9.1 cases per 100,000 person-years.[1,2] The symptomology

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*Drug Names*: To maintain confidentiality with sponsors who have submitted new drug applications for an antipsychotic claim regardless of approval status, individual drug names are not reported.

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ACCP

# Assessment of Similarity in Antipsychotic Exposure-Response Relationships in Clinical Trials Between Adults and Adolescents With Acute Exacerbation of Schizophrenia

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**Abstract**

Despite agreement that early-onset schizophrenia is continuous with the adult-onset form, quantitative relationships between antipsychotic exposure and clinical response are relatively unexplored in adolescents, compared to adults. Clinical efficacy data from second-generation antipsychotic development programs (N = 5951 adults and N = 1035 adolescents ranging from 12 to 17 years old) were collected from available new drug applications submitted to the US Food and Drug Administration from 1993 to 2017. The developed disease–drug trial models adequately predicted the longitudinal trend in total positive and negative syndrome scale scores in both adults and adolescents using a Weibull placebo response, time-delayed drug effect, and a Weibull structural dropout model. Maximum drug effect was similar between the two populations and was estimated to be between a range of 5% to 11% in adults and 5% to 7% in adolescents. Half maximal effective concentration parameter estimates also indicated similar exposure-response relationships in adults and adolescents across all 4 antipsychotics. Simulated adolescent data using final model parameter estimates from the adult model were in agreement with adolescent observations. This analysis confirms similarity in exposure-response for efficacy and could expedite the development of second-generation antipsychotics for adolescents.

**Keywords**

drug efficacy, early-onset schizophrenia, exposure-response, positive and negative symptom scale, second-generation antipsychotics

Early-onset schizophrenia is commonly reported to be neurobiologically and phenotypically continuous with the psychiatric disorder observed in adults.[1] Although the prevalence of early-onset schizophrenia is low, there has been an increase in the use of antipsychotics for the treatment of schizophrenia in adolescents.[2] Several studies indicate that patients with early-onset schizophrenia may have a worse prognosis compared to those with adult-onset schizophrenia. While adults with schizophrenia typically experience exacerbations of psychotic symptoms between periods of relative normalcy, adolescents with schizophrenia may never achieve full remission after the initial episode.[3] Timely intervention in adolescents is therefore of the utmost importance to ensure improvement in long-term outcomes and to avoid future treatment resistance.[4] Due to the increased risk of extrapyramidal symptoms observed with first-generation antipsychotics in adolescents, second-generation antipsychotics have become the mainstay of treatment. However, managing adolescents with schizophrenia can be challenging due to their increased sensitivity to side effects of second-generation antipsychotics, particularly with respect to metabolic changes.[5,6] Currently, there are 6 second-generation antipsychotics approved by the US Food and Drug Administration (FDA) for adolescents and adults: olanzapine, risperidone, quetiapine,

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# Required for Extrapolation

- Mechanism: D2-receptor antagonism or partial agonism, 5-HT1A partial agonism, and/or 5-HT2A antagonism
- Approved indication in adults
- Pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposures (at levels demonstrated to be effective in adults) in pediatric and adult patients. This analysis will require pharmacokinetic data from both the adult and pediatric populations.
- Long-term open label safety study(ies) in pediatric patients
- Juvenile animal study to support an indication for the treatment of bipolar I disorder in pediatric patients less than 13 years age

# Accelerating Medicines Partnership–Schizophrenia (AMP SCZ)

- First neuropsychiatric project of the Accelerating Medicines Partnership (AMP)
- Managed by the Foundation for the National Institutes of Health (FNIH)
- Public-private partnership
- Intended to address critical need for more effective treatments for people with schizophrenia
- Mission: Discover promising biological markers of risk, track progression of symptoms and other outcomes, and define targets for treatment development

# When to Initiate Studies in Children: General Considerations

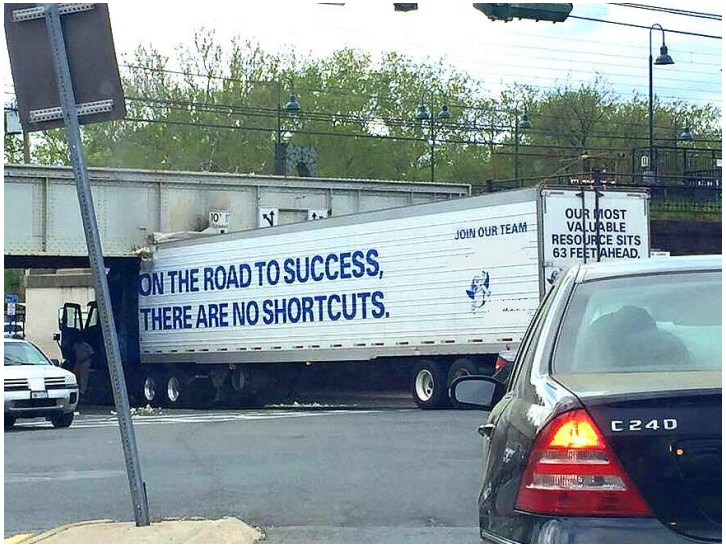
- Disease onset
- Clinical manifestations
- Course of illness
- Nature of intervention

# 21 CFR 50 Subpart D

- Research involving children either
  - must be restricted to either "minimal" or a "minor increase over minimal" risk absent a potential for direct benefit to the child, or
    - 21 CFR 50.51/53
  - must present risks that are 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

# Fit-for-Purpose Endpoints

- "What has worked, what has not" slide
- Qualitative work is important
  - Endpoint development
  - Defining clinically meaningful within patient change
- Talk to us



# One More Challenge…

- Differences in timing and requirements for FDA and EMA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