

## Commentary

# Methodological Insights from Modeling and Simulation Informed Extrapolation for Sarilumab pcJIA Pediatric Development

Zhaoling Meng

Clinical Statistical Modeling, Sanofi, USA

*\*Corresponding author:* Zhaoling Meng, Clinical Statistical Modeling, Sanofi, USA

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## Abstract

Pediatric drug development frequently lags behind adult approvals. Adult-to-pediatric extrapolation frameworks leverage accumulated adult efficacy and safety data to streamline the development plan and reduce the required pediatric sample size. In this commentary, we use the pediatric polyarticular-course juvenile idiopathic arthritis (pcJIA) development program for sarilumab as a case example and discuss a model-informed pharmacokinetic-pharmacodynamic (PKPD) extrapolation approach based on exposure-response consistency between adult and pediatric populations. We contrast this strategy with a Bayesian historical control borrowing framework, which can be deployed under the assumption of disease similarity. Integrating these quantitative methodologies with innovative pediatric trial designs enables accelerated, scientifically and statistically rigorous pediatric drug development.

**Keywords:** Pediatric extrapolation, PKPD modeling, Statistical virtual trial simulation

## Introduction

Drug development typically spans 10 to 15 years with high attrition rates. The development in pediatric patients takes even longer as it frequently lags behind the development in adults. A review on pediatric oncology development cited additional average 6.5 years lag for approved drugs and with many drugs lacking any pediatric development record [1]. These long delays result in substantial unmet medical needs in pediatric population and drive off-label use without adequate efficacy and safety evidence [2]. Despite legislative mandates and incentives designed to expedite pediatric development, challenges remain. Beyond commercial considerations, pediatric population being a vulnerable population and with higher hurdle for recruitment are among the reasons for the lag. The pediatric clinical development often starts after the efficacy and safety profiles are established in adults. Therefore, when pediatric development starts to progress, the adult indication is usually approved or with enough benefit-risk evidence to inform pediatric development decisions. At the same time, even with specific pediatric needs being addressed in the study design and conduct, a pediatric study still faces more severe unwillingness or hesitation to participate due to many reasons including the potential exposure to placebo. Consequently, innovative development paradigms that leverage existing adult data to minimize pediatric patient burden are urgently needed to accelerate pediatric development and address the unmet medical needs in kids.

### Faster Pediatric Development Pathway Enabled by Adult-to-Pediatric Extrapolation

The ICH E11A “Guideline on pediatric extrapolation” (adopted

in August 2024 and became effective in January 2025) establishes a structured regulatory framework for leveraging adult data to streamline the pediatric drug development [3]. The adult-to-pediatric extrapolation is advocated to enable more efficient and faster pediatric development along with relevant innovative study designs. The approach takes advantage of the amount accumulated adult efficacy and safety data, frequently being sufficiently large and robust in supporting the adult indication approval. The leveraging of different types of extrapolations, i.e. full extrapolation or partial extrapolation, depends on physiology, metabolism, and disease progression similarity and difference between adult and pediatric patients. Historically available disease data (on both adults and pediatrics), specific treatment adult data (from the adult development) and treatment pediatric data (including planned in the future development) can be jointly assessed and then differentially leveraged according to targeted differential extrapolation pathways (i.e. full vs. partial). The extrapolation approach is also frequently combined with or enabled by various modeling and simulation approaches to realize robust and efficient decision making and drug approval.

Modeling & simulations are already routinely applied in pediatric development, for example to propose pediatric doses based on the adult dose(s) with scaling based on body weight, physiology etc. The proposed pediatric doses and its “adult-equivalent” exposure are then tested and confirmed in a clinical pediatric PK study. If the adult and pediatric similarity was well accepted, the so call full extrapolation from adults to pediatrics can be applied and the pediatric PK study demonstrating exposure similarity can serve as the primary approval evidence. On the other hand, if the similarity between adults and

pediatrics is heavily questioned, the gold standard of a pediatric development approach is still a fully powered, randomized, controlled clinical trial (RCT) to demonstrate treatment efficacy and safety. Many extrapolation scenarios fall in the middle under “partial extrapolation” and due to different degrees of adult to pediatric similarity evidence. Innovative approaches along with innovative study designs can be applied to generate and enhance robust evidence with scientific and statistical rigor as the pediatric program progresses.

### Model-informed PKPD Extrapolation with Scientific and Statistical Rigor

Polyarticular-course juvenile idiopathic arthritis (pcJIA) manifests before the age of 16 years, with pathology similar to that of adult rheumatoid arthritis (RA). Sarilumab is an interleukin-6 receptor inhibitor approved for RA and pcJIA. In sarilumab pcJIA development case, the adult RA to pcJIA disease pathophysiology similarity to enable adult-to-pediatric extrapolation was not fully established before the pcJIA development [4]. However, the observed efficacy and safety data in the pcJIA pediatric dose finding study portion provided an opportunity to demonstrate the consistency of PKPD relationship in key efficacy and safety endpoints to those of the adult program. First, the existing adult key efficacy endpoints were reconstructed to align with pediatric meaningful endpoints. Therefore, the PKPD relationships between two populations can be compared using PKPD modeling approaches. Then, considering pediatric patient data variability in the current study size, a virtual trial simulation based on the established PKPD models was conducted to determine the sample size needed in supporting the PK/PD relationship consistency assessment. Based on the virtual trial results, the current Phase 2 dose ranging study was then expanded to ensure the final PK/PD consistency assessment with necessary statistical rigor.

The strength of this extrapolation approach is that it eliminates the need of assigning pediatric patients to a control arm and avoids a traditional RCT. It can minimize the study ethical consideration and increase the potential for enrollment operational feasibility, especially the control being the placebo. The final total study sample size could be potentially smaller depending on the expected treatment effect difference compared to the control arm. The requirement of this approach is demonstrating the treatment effect similarity between the adult and pediatric patients beyond disease similarity. The treatment effect similarity can be treatment mechanism of action (MOA) specific. Therefore, sufficient treatment specific data needs to be accumulated during the pediatric development to support this similarity claim. We can design an efficient pediatric development plan optimized by modeling and simulation approaches. The resulted pediatric plan is streamlined and greatly reduces the pediatric patient burden.

### Bayesian Borrowing as an Alternative Approach Under an Alternative Extrapolation Scenario

An alternative partial extrapolation approach is Bayesian borrowing of historical control arm to enable a smaller concurrent control in a pediatric RCT study design. The recent FDA draft guidance on “use of Bayesian Methodology in clinical trials of drug and biological products” outlined a clear path forward to enable this approach [5].

With the availability of historical pediatric trial control arm, the same drug adult trial control arm or relevant real-world data, the control arm borrowing can be carried out with statistical rigor if the marginal exchangeability of historical prior information and new study data can be assumed [6]. The validity of the borrowing approach further depends on the similarity of the borrowed control arm data sources (i.e. historical adult control or real-world data) and targeted pediatric population. If the assumption similarity uncertainty exists, a dynamic borrowing can be applied [7]. The dynamic borrowing automatically down-weights (or discards) historical priors if the current pediatric control is strongly different from the historical controls. However, if the marginal exchangeability cannot be assumed, for example, between current pediatric control and historical adult control arm to borrow from, a pharmacometrics-enhanced Bayesian borrowing (PEBB) was also proposed [8]. With this approach, a model predicted pediatric control can be used instead of observed historical control.

The strength of the control arm Bayesian borrowing approach is its applicability in a randomized control study design and only the similarity between the control arms (i.e. adult control vs. pediatric control) is required. The pediatric study sample size can be reduced to gain trial efficiency as a small control arm is needed. The approach limitation is it still requires a concurrent control arm (even though it is smaller than the original design). Including a concurrent control arm, especially a placebo or standard care arm, may still present an ethical issue (retain pediatric patients on placebo) and enrollment challenge. In addition, the operating characteristics and type I error inflation need to be understood and managed during the study design stage. Extensive virtual trial simulations with various scenario testing need to be carried out at the design stage to ensure the proper study power planning, especially in a dynamic borrowing setting.

### Conclusion and Outlook

To speed up the pediatric development and obtain robust evidence to support the decision, adult-to-pediatric extrapolation approaches serve as important methods. When partial extrapolations are needed due to lack of sufficient evidence for a full extrapolation, innovative study design and modeling & simulation approaches are critical to accumulate robust evidence and support a scientific and statistical rigorous decision. PK/PD model-based extrapolation and Bayesian borrowing with its corresponding innovative study design are two approaches that can be applied under different evidence scenarios to enhance the decision making. The data-driven quantitative evidence supported extrapolation speeds up the pediatric clinical development, addresses pediatric trial enrollment ethic concern and unmet pediatric needs for faster accessing efficacious medication.

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