

Certara Nurture

Pediatric Drug Development

Pediatric drug development continues to be a vexing challenge, yet pediatric research is increasingly being mandated by regulators and patients alike. Traditional development methods can be problematic for ethical and logistical reasons. After all, children are not small adults. Most importantly, children are a heterogeneous population, especially neonates and infants, as organ maturation affects drug exposure and response.

Regulators Expect Results

In the past, pediatric drug development could be treated as a potential post-adult-marketing venture. Today, health authorities are demanding proactive, early, and thorough planning to address this population. Furthermore, there is a call to action for already marketed products to be specifically evaluated for tolerance and effects in pediatric patients.

Over the past few years, the major regulatory agencies have strongly encouraged the use of modeling and simulation (M&S) for pediatric drug development. In fact, US FDA guidance states that M&S, using all of the information available, should be an integral part of all pediatric development programs. M&S uses quantitative mathematical models that leverage all available and relevant sources of existing knowledge to inform on the pharmacokinetics, pharmacodynamics, efficacy, and safety of a drug. The usefulness of M&S in pediatric drug development includes clinical trial simulation, dose selection, choice and optimization of study design, endpoint selection, and extrapolation.

Understanding Drug Effects in Children

Growth, maturation and environmental factors, along with disease and genetic factors, directly affect drug performance in children, especially in those less than two years old. For example, a premature baby's body is composed of 80% water and 5% fat, while at one year old that composition changes to 61% water and 20% fat. Factors such as kidney function, brain volume, blood flow, and absorption, distribution, metabolism, and excretion (ADME) are non-linear during the neonate to small child period. This makes developing and prescribing drugs to children a scientific and logistical challenge.

Complicating pediatric drug development and contributing to the high percentage of failed pediatric trials are practical considerations, including study design, target populations, endpoint selection, timing of studies, risk/benefit (ethics), dose refinement, and formulation.

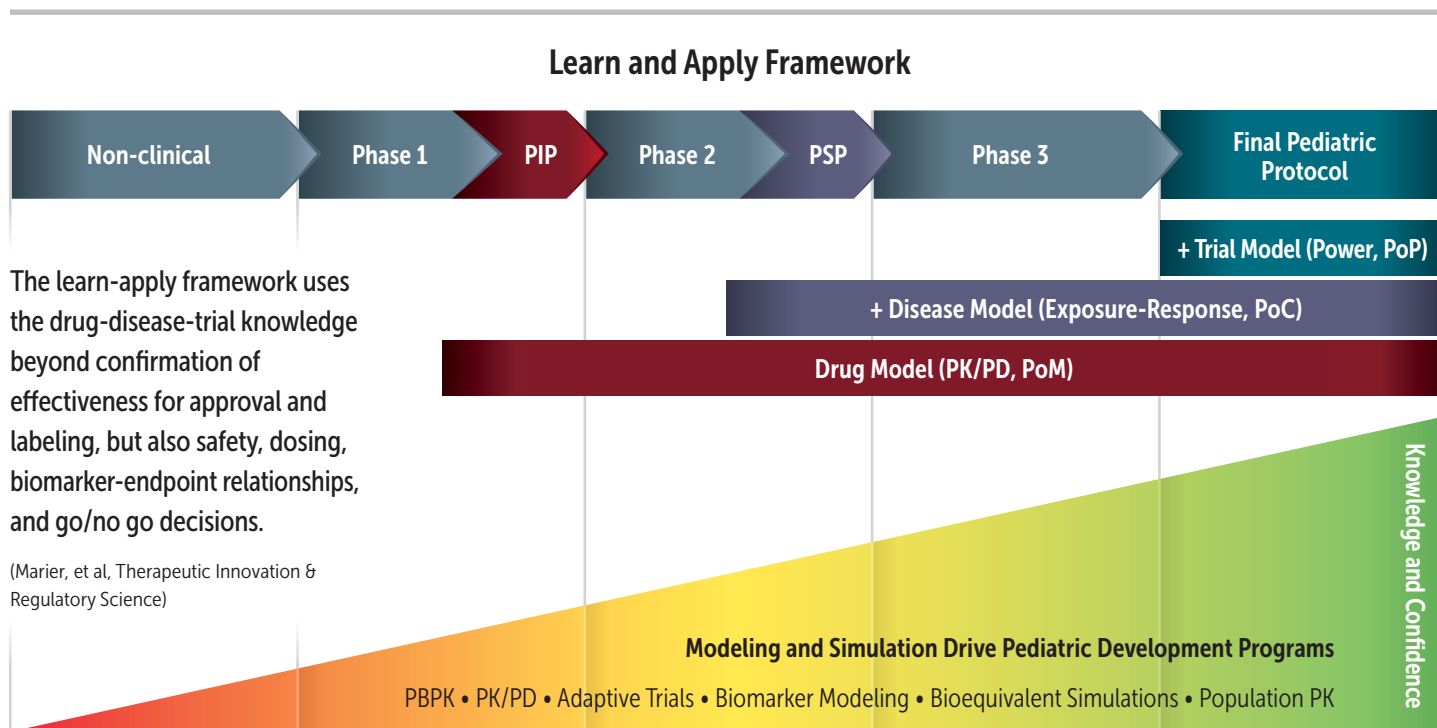
Benefits of Partnering with Certara

- Strategic and programmatic approach to pediatric programs maximize regulatory and commercial success
- Industry leadership in pediatric critical care, regulatory science, clinical pharmacology and model-informed drug development
- Largest volume of regulatory-approved PIPs and PSPs
- Unique technology for assessing drug performance in all ages, including neonates
- Quantitative modeling for determining the relationship between dosing and the safety/efficacy profile across all age groups
- Optimization of formulation and drug labels for pediatric patients

Unique Capabilities Focused on Pediatric Drug Development

Recognizing the great importance of serving pediatrics balanced against the inherent hurdles, Certara Nurture™ offers comprehensive pediatric drug development services focused on:

- Strategic planning of pediatric development plans
- Clinical pharmacology strategy and stewardship of complex pediatric programs
- Pediatric clinical trial study design
- Innovative modeling and simulation, characterizing PK, PD, disease progression, safety and efficacy
- Regulatory writing from IND through submittal and post-marketing
- Interactions with health authorities
- Pediatric formulations



Strategic Planning Improves Regulatory Outcomes

Certara applies a strategic and programmatic approach to pediatric drug development, underpinned by clinical pharmacology, regulatory expertise, and quantitative approaches. This approach is used for both pediatric diseases, which are oftentimes also rare diseases, and pediatric cases of previously characterized adult diseases. We view pediatric development as a team sport where we bring the domains of expertise and regulatory science innovation together toward working with vulnerable patients. The result, evidenced in our PIP and PSP work provides increased value and strategic differentiation versus merely satisfying a regulatory burden.

Modeling and Simulation in Pediatric Drug Development

Regulatory agencies worldwide encourage modeling and simulation to “get the dose right” and reduce risk in pediatric product development—beginning with translational science through clinical trial design to formulation development and post-marketing. As the knowledge leaders within the world’s largest quantitative modeling group, Certara scientists will meet the needs of the regulators, enhance feasibility of the studies, and increase safety for pediatrics. Certara’s methods leverage sparse data and prior information from pre-clinical studies, adult trials, literature data, and pediatric studies of related indications or drug actions. Building that knowledge into models of patient physiology, drug actions and trial characteristics enable us to develop and iterate clinical trial design, explore alternative dosing scenarios, *in silico* patient responses, drug-drug interactions, and whole trial outcomes.

Oftentimes, Certara will support the PIP/PSP development plan by creating a PopPK(PD) model using adult data scaled to pediatrics. That model will integrate a range of maturation and disease factors with allometric scaling to set the best dose for the first pediatric trial cohort. The “learn and apply” approach is repeated for each cohort, with additional M&D technologies used throughout the cycle.

Our consultants also leverage the Simcyp® Pediatric Simulator, the industry’s most sophisticated physiologically-based pharmacokinetic (PBPK) technology for modeling drug performance and assessing drug-drug interactions in neonates, infants, and children. The Simcyp Pediatric Simulator contains extensive libraries on demographics, developmental physiology, and the ontogeny of drug elimination pathways. It is used by all of the industry’s leading pharma companies.

Regulatory Writing, Publishing and Submission – PIP and PSP

The Synchrogenix® division of Certara is the largest, global regulatory/medical writing consultancy, employing more than 200 professionals. Its expertise in pediatrics spans more than 15 therapeutic areas, including oncology, infectious diseases, and cardiovascular disorders. Core competencies include consulting, writing, preparing and managing documents, including PIPs and PSPs through global regulatory processes, and authoring scientific and commercial documents. The recent addition of GlobalSubmit™ clinical trial operations technology now facilitates the eCTD submittal process, providing scalability and consistency for sponsors.

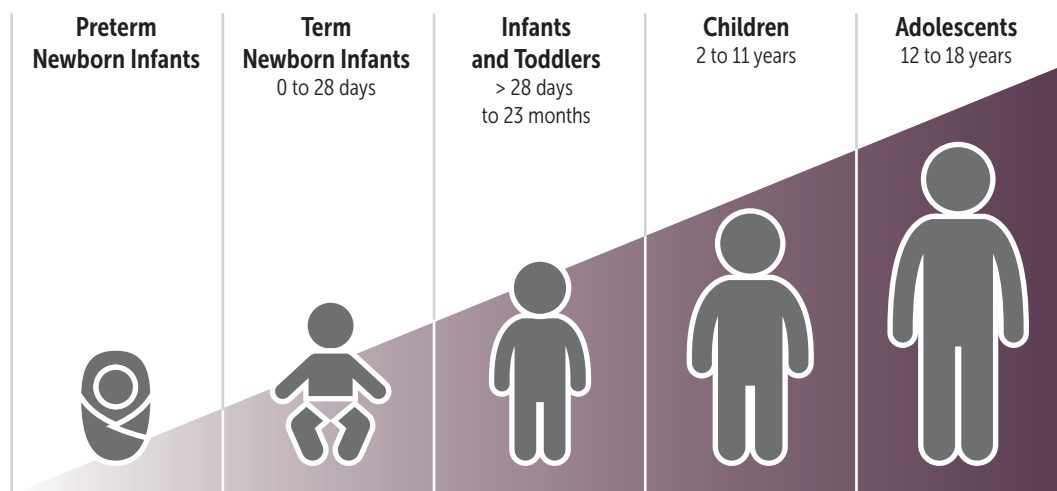


Certara is changing the way we bring therapies to children.

Under Certara Nurture, pediatric development programs can benefit from targeted solutions or comprehensive oversight from Certara’s scientific consulting team.

Rely on a Team of Pediatric Experts

The Certara team includes drug development and regulatory strategists with significant experience in designing and stewarding complex pediatric programs from concept to approval. We have pediatricians, epidemiologists, regulatory scientists, clinical pharmacologists, modeling and simulation experts, and others, working together to inform pivotal decisions to bring safe therapies to children. To that end, the Certara team has contributed to more than 100 PIPs/PSPs as subject matter experts in all areas of regulatory science. Regardless of size or complexity, your pediatric drug development program will benefit from working with Certara.



(courtesy of National Institutes of Health)

Children may need different doses of medicine, different sizes of devices, or different types of therapy at each stage of growth.

Certara Nurture harnesses the company's unique experience and expertise to address that need.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

For more information visit www.certara.com or email sales@certara.com.