# Drug Repurposing Guidebook

Building Block I456

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

| ITEM | DESCRIPTION |
|---|---|
| Building Block (BB) Title | PKPD (Pharmacokinetic and Pharmacodynamic) Modelling in children |
| References | https://www.certara.com/the-simcyp-consortium/<br>https://www.certara.com/software/simcyp-pediatric/<br><br>https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety-clinical-pharmacology-pharmacokinetics |
| Description | Pharmacodynamics (PD) refers to the action of a drug to the body, involving receptor binding, post-receptor effects, and chemical interactions. Pharmacokinetics (PK) determines the onset, duration, and intensity of drug action. Successful drug discovery relies on the selection of drug candidates with good in vivo PK properties, as well as appropriate preclinical efficacy and safety. In vivo PK profiling is often a bottleneck in the discovery process.<br><br>In order to prove effective, a drug delivered to the patient must reach the necessary concentration in the plasma and in relevant tissues (as measured by PK). This is necessary to effectively modulate the activity of the target protein (as measured by PD) in the body.<br><br>To minimize the exposure of children to new drug in development and to reduce the development timelines, the developers are offered with a set of PKPD platforms, softwares and tools for modelling and simulation which describe the drug concentration in different organs, behavior across different body tissues, and thus help to inform clinical trial design, first-in-human dosing, formulation design, dose differentiation for special populations, and predictions related to potential drug-drug interactions (DDI). |

| ITEM | DESCRIPTION |
|---|---|
| | While currently these tools are only private PK-PD tools, some of them are knowledgeable by the major regulatory bodies for their contribution to the success data package preparation of some approved drug.<br><br>The Simcyp™ division for example was founded in 2001 as a spin-out company from the University of Sheffield, UK. Simcyp was acquired by Certara in 2012. The SIMCYP Consortium is a pre-competitive group dedicated to teaching, using and progressing PBPK (physiologically based pharmacokinetics) in drug development. The members of the Simcyp Consortium collaborate with Simcyp scientists to guide the scientific development of the Simcyp Simulator, determining annual software development priorities, thus ensuring that the software continues to meet and exceed industry needs. Leading regulators, including the USA, European, Canadian and Japan Health Agencies, use Simcyp for research and drug review. |
| Category | Clinical development, including extrapolation of efficacy and safety data |
| Type of BB | Development practice |
| Geographical scope | International |
| Availability | For all stakeholders involved in drug development |
| Scope of use | Simcyp Pediatric provides insight into drug mechanisms while minimizing the exposure of children to experimental therapies.<br>It is a module within the Simcyp Simulator that allows for the modeling of pharmacokinetic behavior in neonates, infants and children. This provides valuable information relevant to dosing decisions, analysis of drug-drug interactions and other safety issues, design and formulation of drugs for children, and the design of pediatric clinical studies to minimize the number of required subjects. |
| Stakeholders involved | 35 of the world's leading biopharmaceutical companies are members of the Simcyp Consortium. |
| Enablers/ Requirements | The Simcyp Simulator includes a full PBPK model together with extensive libraries on demographics, developmental physiology and the ontogeny of drug elimination pathways. It links in vitro data to in |

| ITEM | DESCRIPTION |
|---|---|
| | vivo ADME and PK/PD outcomes to help explore potential clinical scenarios and support decision-making in drug development. |
| Output | - Determine and optimize dose selection for children, from neonates to age 2, 2-6 years, 6-12 years and adolescents;<br>- Predict pharmacokinetics based on *in vitro* drug data or from adult *in vivo* data by retrograde modeling;<br>- Quantify potential drug-drug interactions (DDIs) for any age range;<br>- Simulate pharmacokinetic variability over any pediatric age range.<br>- Inform clinical trial design for pediatrics. |
| Best time to apply and time window | Early in the development: Incorporating in vivo PK/PD efficacy studies at the early stages of drug development program can significantly accelerate the selection of the most promising compounds. |
| Expert tips | **Pros:**<br>- In-depth knowledge in peadiatric and orphan drug development: https://www.certara.com/software/simcyp-pbpk/simcyp-success-story/<br>- This tool is known by some regulatory authorities (i.e., EMA and FDA) which are aware that some developers may use it as a supporting tool of PBPK modeling for investigations in pediatric populations during drug development.<br>- This tool predicts what should actually happen into the human body and therefore provides information relevant to dosing decisions, analysis of DDI and other safety issues, design and formulation of drugs for children, and the design of pediatric clinical studies to minimize the number of required subjects.<br>**Cons**:<br>- Consultancy/private services – not PPP (Public-Private Partnership) initiative |

| ITEM | DESCRIPTION |
| --- | --- |
| | - As its implementation in the clinical development plan could be subject of interpretation, it is advisable to seek advice from the relevant Regulatory Authorities before using this tool into the drug development plan. |