Open

Systems Pharmacology

Hands-On Exercise: Pediatric Extrapolation

– Stepwise Solution –

Disclaimer:

Examples described herein have been designed to teach physiologically-based pharmacokinetic / pharmacodynamic (PBPK/PD) modeling with PK-Sim® and MoBi®. Cases may have been simplified to focus on relevant didactic aspects and may not necessarily describe the best model variant.

Exercise – Pediatric Extrapolation, Part 1.1

Part 1.1 - Establish a pediatric PBPK model

- Scale an adult model to a female child aged 1 year and simulate the pharmacokinetics of a hypothetical drug named "Drug" after 100 mg IV administration
  - *Adult PBPK model is already established and readily available (Session3_HandsOn_1.pksim5)*
- Compare the exposure simulated within the first 4 h (AUC_tEnd) with that simulated for an adult
  - *Use the option 'Compare Results' in 'Run & Analyze' to overlay the adult and pediatric simulation*

To start the exercise please open the file `Session2_HandsOn_1.pksim5`.

Objectives

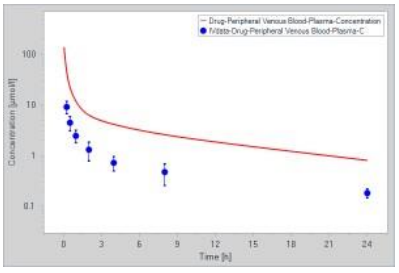
- Scale an adult PBPK model to a female child aged 1 year and simulate the pharmacokinetics of a hypothetical drug named "Drug" after 100 mg IV administration.
- Compare the exposure simulated within the first 24 h (AUC_tEnd) with the simulated adult exposure

Step-by-step guidance

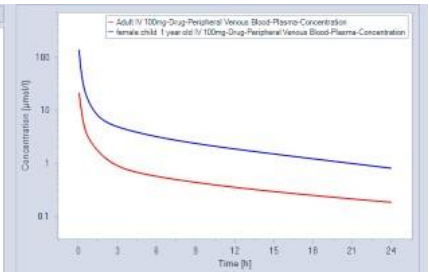
- Make yourself familiar with the given **Expression profiles, Individual**, **Compound** and **Administration Protocol** in the building block section
- Navigate to the Individual "Man30" in the Building Block section, open the context menu (right click) and select "Scale".
- In the pop-up window, define the following characteristics:
  - In the top field, change the name of the individual from "Man30" to "**female child 1 year old**" and keep all other parameters unchanged
  - Define the gender as **female** under population properties
  - Define the age as **1 year** under individual parameters
  - Keep the body weight and height as default values (if changed manually, reset them to the default values by clicking on "Mean")
  - Click on twice "**Next**" and then on "**OK**"
- A virtual female child aged 1 year has now been created and appears in the Individual

Building Block section. Double click on the individual to open it and make yourself familiar with the basic anatomical and physiological parameters under the tab "**Anatomy & Physiology**"

- Set up a simulation using the 1-year-old, female child as follows:
    - Open the context menu of the existing simulation for the adult by right clicking on **Adult IV 100mg** and select "**Clone**"
    - In the top field, change the name of the simulation from "Adult IV 100mg" to "**female child 1 year old IV 100 mg**"
    - In the section "individuals or Population" select the building block for the **female child 1 year old** from the drop-down menu. Keep all other parameters unchanged
    - Navigate through the subsequent tabs by clicking on "**Next**" (keep all parameters unchanged) and click on "**OK**" in the last step
- Have a look at the "**Settings"** in the appearing simulation (output intervals and time- point resolution) and verify that the end time is set to 24 h.
- Click on "**Run**" in the "**Simulation**" group of the "**Run & Analyze**" ribbon tab.
- Select the predefined "**Peripheral Venous Blood Plasma Ciprofloxacin Concentration**" and click "**OK**".
- The simulation is processed.
- Compare the simulation results with those of the adult simulation by clicking on "**Compare Results**" in the section "Individual Simulation" in the upper ribbon bar menu
- Drag and drop the adult and pediatric simulation in the grey area of the comparison window
- Display the simulated pharmacokinetic parameters (including AUC_tEnd) by clicking on "**Show PK Analysis**" below the window showing the simulated plasma concentration-time profile in the tab "**Simulation: female child 1 year old IV**"



	Drug	
	Adult IV 100mg-...	female child 1 ye...
AUC_inf [µmol*min/l]	1271.38	6188.45
AUC_inf_norm [µg*min/l]	3.73E+11	2.48E+11
AUC_tEnd [µmol*min/l]	1040.18	5475.17
AUC_tEnd_norm [µg*min/l]	3.04E+11	2.19E+11
C_max [µmol/l]	21.49	126.67
C_max_norm [mg/l]	6.27E+6	5.59E+6
C_tEnd [µmol/l]	0.18	0.81
Total body clearance,F [ml/min/kg]	2.63	4.04
% AUC (last->∞)	0.18	0.12
MRT [h]	12.56	9.08
t_max [h]	0.05	0.05
Half-life [h]	14.45	10.19
Vd (plasma),F [ml/kg]	3368.46	3863.01
Vss (plasma),F [ml/kg]	2029.88	2201.98



Exercise – Pediatric Extrapolation, Part 1.2

Part 1.2 - Establish a pediatric PBPK model

- Simulate a dose for a 1-year-old child that is equivalent to that of an adult of 73 kg receiving 100 mg IV
  - *The PBPK model used in the previous step can be used (Session3_HandsOn_2.pksim5)*
  - *Calculate the difference in exposure and simulate the fold difference in dose in the 1 year old child*
- Compare again the simulated exposure (AUC_tEnd) with that of the adult

In case you wish to start the exercise at this point and did not perform part 1.1 of the exercise described above, please open the file `Session2_HandsOn_2.pksim5`.

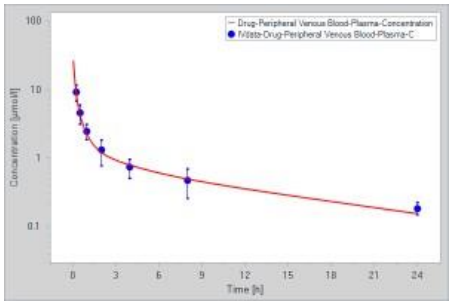
Objectives

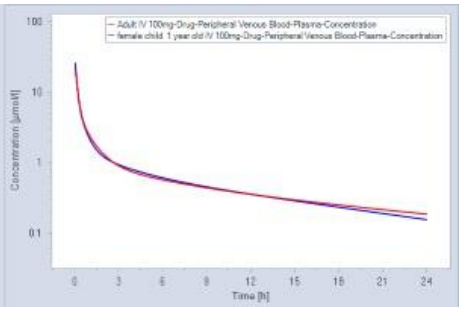
- Scale an adult PBPK model to a female child aged 1 year and simulate the pharmacokinetics of a hypothetical drug named "Drug" after 100 mg IV administration.
- Compare the exposure simulated within the first 24 h (AUC_tEnd) with the simulated adult exposure
- Simulate a dose for a 1-year-old child that is equivalent to that of an adult of 73 kg receiving 100 mg IV
- Compare again the simulated exposure (AUC_tEnd) with that of the adult

Step-by-step guidance

- Calculate the fold difference in exposure between the adult and 1-year-old child (1040 µmol min/L / 5437 µmol min/L) and apply this factor to the adult dose to estimate a new dose for the 1-year-old child (100 mg * 0.19 = 19 mg)
- Create a new **Administration Protocol** using this dose as follows:
  - Open the context menu by right clicking on **Administration Protocols**
  - Select "**Add Administration Protocol**"
  - Define a new administration named "**IV_19mg**" using the Administration Type "**Intravenous Bolus**", a dose of **19 mg**, and a **single dosing interval**
  - Click on **OK**

- Replace the Administration Protocol in the simulation "**female child 1 year old IV**" as follows:
    - Right click on the simulation name and select "**Configure**"
    - Navigate to the **Administration** tab and select the new Administration protocol "**IV_19mg**" from the drop-down menu
    - Click on **OK**
- Update the simulation results by rerunning the simulation through the button "**Run**" in the upper ribbon bar menu





Exercise – Pediatric Extrapolation, Part 2

Part 2 – Perform Population Simulation in Children

- Create a pediatric population with an age range of 6 – 12 years and simulate the geometric mean plasma concentration-time profile including the 5 th – 95th percentile range
  - *The PBPK model used in the previous step can be used (or alternatively `Session3_HandsOn_3.pksim5`)*
  - *Create a population of 100 children between 6 – 12 years old*
  - *Apply an IV dose of 1.37 mg/kg (100mg /73kg adult) for the pediatric population*
  - *Run a pediatric population simulation*

- Compare the exposure of the pediatric population (AUC_tEnd) with that of a simulated adult population
  - *Create first 100 adults between 20 – 40 years*
  - *Run a population simulation for the adults*

Objectives

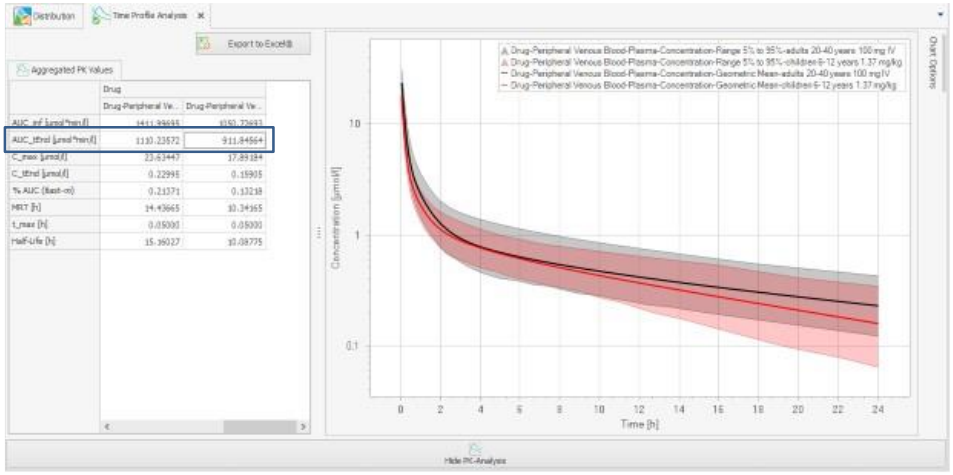
- Create a pediatric population with an age range of 6 – 12 years and simulate the geometric mean plasma concentration-time profile including the 5th – 95th percentile range
- Compare the exposure of the pediatric population (AUC_tEnd) with that of a simulated adult population

Step-by-step guidance

- Create a population of adult by right clicking on the Populations building block and select "**Add Population**"
- Define the population as follows:
  - Name "**Adults 20-40 years IV 100 mg**"
  - Based on individual: "**Man30**"
  - Number of Individuals: 100
  - Proportion of females: 50%
  - Age range from 20 to 40 years
  - No ranges specified other the other parameters (Weight, Height, BMI)
- Create another population as described above with the following characteristics:
  - Name "**school children 6-12 years**"
  - Based on individual: "**female child 1 year old**"
  - Number of Individuals: 100
  - Proportion of females: 50%
  - Age range from 6 to 12 years
  - No ranges specified other the other parameters (Weight, Height, BMI)
- Calculate the body-weight normalized dose for adults (100 mg / 73 kg) and create a

new **Administration Protocol** as follows:
    - Open the context menu by right clicking on **Administration Protocols**
    - Select "**Add Administration Protocol**"
    - Define a new administration named "**IV_1.37mg/kg**" using the Administration Type "**Intravenous Bolus**", a dose of **1.37 mg/kg**, and a **single dosing interval**
    - Click on **OK**
- Create a population simulation for adults and children each as follows:
    - Clone the individual simulation by right-clicking on the simulation name and select "**Clone**"
    - In the pop-up window, rename the simulation (e.g., "**adults 20-40 years 100 mg IV**" or "**children 6-12 years 1.37 mg/kg**"
    - In the section "**Individual or Population**", replace the individual with the corresponding population in the drop-down menu ("**Adults 20-40 years IV 100 mg**" or "**school children 6-12 years**"**)**
    - In case of the population for children, switch to the tab "**Administration**" and replace the existing Protocol "IV_19mg" with the new protocol "**IV_1.37mg/kg**"
    - Click on "**OK**"
- Create a comparison chart for the population simulation as follows:
    - Navigate to the tab "**Population Simulation**" in the upper ribbon bar
    - Click on "**Compare Results**"
    - In the pop-up window, select the adult and pediatric population simulation ("**Adults 20-40 years IV 100 mg**" and "**school children 6-12 years**") and click on "**OK**"
    - In the next pop-up window, navigate to "**Scaling**" of the drug concentration in the upper right panel and select "**Log**" from the drop-down menu
    - In the lower right panel ("**Output: Select distribution statistics for display**"), untick "**Arithmetic Mean**" and select "**Geometric mean**" and "**Range 5% to 95%**"
    - Switch to the tab "**Time Profile Analysis**" by clicking on "**Next**"
    - Click on "**OK**"
- In the comparison window, switch to the tab "Time Profile Analysis" and click on "**Show PK-Analysis**" below the chart
- In the table showing the simulated PK parameter values, navigate to columns listing the **geometric mean values** on the right (the full column titles can be displayed by mouseover or by increasing the column width)

Comparison Exposure children versus adults using the same mg/kg dose



In case you wish see the end of this exercise and you did not perform the steps described above, please open file `Session2_HandsOn_4.pksim5`