**Objectives and introduction**

There are hardly customized posology programs that can be used in clinical scenarios to optimize and monitor doses and administration times of drugs for patients with special requirements. However, PK/PD models have shown success in monitoring and describing distribution and elimination of drugs in clinical trials during drug development, as well as to quantify therapeutic effects. More recently, the addition of physiological knowledge by means of PBPK models is showing the ability to detect drug-drug interactions (DDI) and the influence of different pathologies in the therapeutic and adverse effect of drugs, thanks to their better predictive capability.

The success of pharmacokinetic and physiological modelling and simulation in drug discovery is pushing the definition of updated guidelines and recommendations to use this methodology for improving drug security and efficacy in this area.

However, there are not widely accepted software systems that facilitate the translation of the knowledge implicit in PK/PBPK/PD models to clinical practice. This work is a preliminary study that addresses this lack with a proof of concept. We have developed a personalized posology software for Tacrolimus immunosuppressors drug, using a new M&S advanced software, PhysPK®. The study shows briefly a seamless process, that starts from the building of the PK and PBPK models, performs the fitting and validation following usual methods, focused on our target population, and finally with the use of the validated models as knowledge engines into a personalized posology software that can be run standalone in any personal computer.

The software will be tested in a next stage in a University Hospital, to validate and optimize both posology recommendations and interfaces.

**Methods: PK and PBPK models building on PhysPK**

- **PK/PD building procedure**
  - Drug and route of administrations
  - Main parameters that affect
  - PK/PD base model: 2 compartment model with linear absorption and first order elimination
  - PBPK base model: three main flow limited tissues (Fat, Liver, Kidney)
  - PBPK organs model: rat organs model (toxicity)
  - PBPK pharmacodynamic model: Michaelis Menten model
  - PBPK target model: three main flow limited tissue in PK, Liver, Lung
    - PBPK model of Tacrolimus drug in patients with renal transplant as knowledge engines for personalized knowledge engines
    - PBPK® development and preliminary results

**Population study and selection of the best model at each category PK / PBPK to be used as knowledge engines**

- **PhysPK models** provide pre-built validated models with sets of parameters, which can be extended by the user.
- **Models** can be modified using PBPK® (PBPK/PD) extended elements (library) to included levels of aggregation (from systems to cells, including trafficking and biochemical networks).
- **Optimal** and extendable modules will be able to extract standard parameters from available data.
- **Animal** and **human models** can be linked with devices model.
- **New mechanisms** can be easily added to facilitate evolution of knowledge.
- **Advanced** non-PBPK physiologically-based elements are also available (pressure dynamics, etc.)

**Summary**

- **PK and PBPK models** for Tacrolimus drug have been built using a new advanced multi-level physiological modelling and simulation software, PhysPK®.
- The building process was guided by a graphic user interface with unlimited aggregation levels and without the necessity of mathematical skills.
- Models have been analysed, explored, fitted and validated using standard and flexible modules inside PhysPK® focused on our target population, and finally adjusted to individual patients.
- Preliminary outcomes show a better predictive capability in PBPK model, as expected, but there are not procedural differences in their use as knowledge engines for the posology program.
- We have shown the reliance of PhysPK® to generate a customized posology software based on any PRECISE-PBPK model as knowledge engine, using the DECK technology and the Posology optimization module of PhysPK®.
- This developed customized posology software runs on Excel, and included a graphic interface with plots and standards Windows controls.
- However, textual console is also a valid alternative when no graphic details are required by the physician or clinical pharmacologist.
- The possology software integrates a workflow of the pharmacological treatment, from the patient register up to the posology computation to fulfill with the desired target (e.g. AUC 12 h) and other requirements (toxicity levels, ...). It also includes what-if scenarios.