UNIVERSITÀ DI TRENTO

Chiesi Farmaceutici S.p.A.

Borsa di studio/Scholarship

F	**Mathematical models in pharmacokinetics and pharmacodynamics to explore innovative biomarkers and optimize drug development**

Topic:

Application of Modeling and Simulation has become an essential tool in drug development and its use was described in the Model Informed Drug Discovery and Development (MID3) framework. MID3 is increasingly being integrated into regulatory guidelines to harmonize expectations regarding documentation standards, model development, and assessment criteria for regulatory submissions. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) recognize the value of MID3 in improving drug development efficiency and decision-making and encourage the use of modeling and simulation to support regulatory decisions, optimize clinical trial designs, and enhance drug approval processes. In this regard, pharmacometrics models can be used to calculate the Probability of Pharmacological Success (PoPS) as a metric to estimate the likelihood that a drug candidate will achieve its intended pharmacological effect in patients at a safe dose. Definition of PoPS through modeling integrates data on drug exposure, target engagement, and functional pharmacology to assess whether a compound meets efficacy and safety requirements. PoPS is particularly useful in early-stage drug development, helping researchers make informed decisions about compound progression, dose selection, and clinical trial design.

Project Manager: Cinzia Soresina (Università di Trento)

Contact: cinzia.soresina@unitn.it

Synthetic description of the activity and expected research outcome

The aim of this research is to explore, implement and evaluate new computational models, based on pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD), safety and efficacy readouts. The determination of the desired therapeutic window for each development program can take advantage of semi-empirical mathematical relationships based on the generated PK and PD data or more physiological approaches, such as physiology-based-PK (PB-PK) models or a combination of both. The combination of dynamic models of drug absorption (for instance, following route of administration as intranasal) with PK and PK/PD relationships using in animals and human data will also be explored. PK and PK/PD models will be developed and used as a simulation tool to support decision-making, optimize future study design and as a predictive tool for an optimal and safe treatment in a subpopulation of patients (such as pediatric patients). In addition, Modeling and Simulation techniques and, in particular, PK/PD models may benefit from emerging biomarkers (including imaging data) that, combined with clinical scores, can leverage the information available to support drug approval. Software as NONMEM, PKsim, R and Matlab will be exploited. The developed modeling framework is going to be employed within Chiesi as a strategy to be adopted in the different development phases for the definition of the PoPS.

References:

Mould, D. R., & Upton, R. N. (2013). Basic concepts in population modeling, simulation, and model-based drug development—part 2: introduction to pharmacokinetic modeling methods. CPT: pharmacometrics & systems pharmacology, 2(4), 1-14.

Krishnaswami, S., Austin, D., Della Pasqua, O., Gastonguay, M. R., Gobburu, J., Van der Graaf, P. H., Ouellet, D., Tannenbaum, S., & Visser, S. A. (2020). MID3: mission impossible or model-informed drug discovery and development? Point-counterpoint discussions on key challenges. Clinical Pharmacology and Therapeutics, 107(4), 762.

EFPIA MID3 Workgroup, Marshall, S. F., Burghaus, R., Cosson, V., Cheung, S. Y. A., Chenel, M.,…. & Visser, S. A. G. (2016). Good practices in model-informed drug discovery and development: practice, application, and documentation. CPT: pharmacometrics & systems pharmacology, 5(3), 93-122.

Marshall, S., Madabushi, R., Manolis, E., Krudys, K., Staab, A., Dykstra, K., & Visser, S. A. (2019). Model-informed drug discovery and development: current industry good practice and regulatory expectations and future perspectives. CPT: pharmacometrics & systems pharmacology, 8(2), 87-96.

Ideal candidate (skills and competencies)

Advanced knowledge in PK and PK/PD modelling, population PK models, statistics, NONMEM software and Matlab.