Simon Buatois Date de soutenance : 26/11/2018

Titre : Novel pharmacometric methods to improve clinical drug development in progressive diseases

Résumé: In the mid-1990, model-based approaches were mainly used as supporting tools for drug development. Restricted to the “rescue mode” in situations of drug development failure, the impact of model-based approaches was relatively limited. Nowadays, the merits of these approaches are widely recognised by stakeholders in healthcare and have a crucial role in drug development for progressive diseases.

Despite their numerous advantages, model-based approaches present important drawbacks limiting their use in confirmatory trials. Traditional pharmacometric (PMX) analyses relies on model selection, and consequently ignores model structure uncertainty when generating statistical inference. The problem of model selection is potentially leading to overoptimistic confidence intervals and resulting in a type I error inflation. Two projects of this thesis aimed at investigating the value of innovative PMX approaches to address part of these shortcomings in a hypothetical dose-finding study for a progressive disorder. The model averaging approach coupled to a combined likelihood ratio test showed promising results and represents an additional step towards the use of PMX for primary analysis in dose-finding studies.

In the learning phase, PMX is a key discipline with applications at every stage of drug development to gain insight into drug, mechanism and disease characteristics with the ultimate goal to aid efficient drug development. In this thesis, the merits of PMX analysis were evaluated, in the context of Parkinson’s disease. An item-response theory longitudinal model was successfully developed to precisely describe the disease progression of Parkinson’s disease patients while acknowledging the composite nature of a patient-reported outcome. To conclude, this thesis enhances the use of PMX to aid efficient drug development and/or regulatory decisions in drug development.

Mots clefs : Pharmacometrics, Disease progression, Nonlinear mixed effect models, Model selection, Model averaging, Item-response theory