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What's Next for Fit-for-Purpose (F4P) Models?

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Blog

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Nearly a decade ago, Gobburu and Lesko* described three categories of models – empirical, semi-mechanistic and mechanistic. They recognized a continuum of models representing varying degrees of available knowledge on the pharmacology of a new drug candidate. Today, models on this continuum are sometimes referred to as fit-for-purpose (F4P) models to acknowledge that they may only achieve a certain level of model completeness based on current experience, but are adequate for decision-making purposes.

Most of the pharmacometric (PMx) models we develop can be defined as F4P, with "purpose" determined by the sponsor. The purpose only occasionally goes beyond addressing the very particular decision at hand. Once the modeling project is complete, the bits and pieces of assembled knowledge that were not incorporated into the F4P version of the model, may be lost as we move on to the next F4P modeling effort. Only occasionally do these F4P models further develop and evolve into "platform models" with potential applicability beyond the current drug development program.

There are many reasons why F4P modeling stops at a decision-making milestone. Sponsors may be reluctant to pay for further model development once their most pressing needs are addressed. Pharmaceutical R&D itself is fit-for-purpose across departmental divides because regulatory requirements necessarily focus development programs on demonstrating acceptable formulation, efficacy and safety characteristics of drugs. Drug candidates move into late-stage clinical development and completing the phase 3 trials becomes paramount. We use the data coming from these development programs to build our models and generally, the data come first, then the models use what data are available.

To increase the efficiency in model-informed decision making, the F4P modeling approach needs to evolve to maximize knowledge retention and the integration of prior learning. Such evolution is exemplified by mechanistic modeling platforms such as the PBPK modeling and simulation computer software, **GastroPlus®**, and the quantitative systems pharmacology software for predicting drug-induced liver injury, **DILIsym®**. These platforms integrate well-established and emerging preclinical and clinical knowledge across development programs in the form of predictive models wherein new information about pharmacology and toxicology is used to improve the models. The incorporation of new knowledge requires the close collaboration between

scientists and software designers to continuously improve predictive performance and enable innovative applications in new settings and research contexts.

The semi-mechanistic and empirical models we use in drug development can follow this evolutionary process, but we need to view these F4P models as iterative steps towards greater understanding. Model building in this context is an intensive exercise in knowledge synthesis during an on-going R&D program. Over the course of a typical development program, **Cognigen** develops F4P models based on the current facts and available data to inform drug development decision making, address regulatory milestones, and aid in the design of subsequent trials. These F4P models represent an important repository of knowledge which can be expanded into platform models with applicability beyond the current drug development program. The cloud-based **KIWI™** platform serves a key role in this process by tracking the model refinement process and capturing development team insights and suggested improvements.

The ability to incorporate new knowledge and improve the predictability and usefulness of tools will be a hallmark of companies embracing model-informed drug discovery and development. At **Simulations Plus**, we believe that the tools and techniques we develop are transforming the R&D process as we transform data into knowledge to inform drug development decisions.

* Gobburu, J. V. & Lesko, L. J. Quantitative disease, drug, and trial models. *Annu Rev Pharmacol Toxicol*. **49**, 291-301 (2009).