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Application of Mechanistic Physiological Modeling in the Drug Development Process – Overview and Case Studies

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Abstract

Physiological mechanistic modeling offers a tool to generate insight into the biological interactions between pharmacological targets and health and disease. Over the last decade, Rosa has developed a powerful, quantitative physiological modeling approach to provide this mechanistic insight and support more informed decision making in the drug discovery and development process. This presentation will provide an overview of the Rosa modeling approach and illustrate this approach with case studies.

Rosa creates customized mechanistic models (PhysioPD™ models) focused on providing timely scientific insight and program impact. The models are systems of ordinary differential equations which provide biological insights by simulating disease pathophysiology, progression and response to therapeutic intervention. We have developed, tested and used these models with the participation of pharmaceutical and life science industry clients to ensure understanding, confidence, and actionable recommendations in virtually all major therapeutic areas, including metabolic disease, inflammation, oncology, and central nervous system disorders. Examples of drug development challenges we commonly address include: target identification and validation, translational medicine, clinical trial design and biomarker identification. An open-source modeling platform (JDesigner) and an extensive library of proprietary model components facilitate efficient and focused model development.

The process of creating a PhysioPD model begins with the creation of a PhysioMap®, the qualitative and graphical model architecture that represents the relationships between the multiple components of a biological system and documents the data and information used to guide each representation. Literature and other relevant content and data are used to: a) guide the development

of the PhysioMap and b) identify equation forms and parameters to convert the PhysioMap into a quantitative PhysioPD model capable performing the investigations of interest through scientific inquiry and simulation research. Each step of model development is guided by the Rosa Model Qualification Method (MQM), a comprehensive, systematic and transparent methodology that ensures the model is fit for purpose. The MQM addresses and documents the unique demands of a quantitative physiological model for relevance, management of biological uncertainty and variability, and consistency with experimental data. Once the PhysioPD Model has been qualified according to the MQM, simulation research is performed to address specific program objectives. Insights from the modeling research project are used to guide program decisions and to support more focused experimental approaches.

Case studies will be presented to illustrate this approach and provide examples of insights generated from various research projects.