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The Transition to Model-Based Drug Development Phase 1: Formalizing the Pharmacometric Process



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Contents

Synopsis	2
Introduction	2
Purpose	3
Formalization Work Plan	3
Challenges	3
Value Proposition	4
ABOUT COGNIGEN	6

Synopsis

We describe a strategy for formalizing the pharmacometric process and developing conceptual process maps for critical subtasks.

Introduction

There has been a growing interest in performing modeling and simulation of efficacy and safety endpoints in order to select and justify dosing regimens and optimize trial designs in both preclinical and clinical venues. Examples of the application of modeling and simulation can be found throughout the drug realization life cycle and there has been growing regulatory demand for, and reliance on, modeling and simulation results to guide regulatory decision-making. Consequently, the development and implementation of an efficient and effective process to support modeling and simulation activities is emerging as a critical enabling step in ensuring the timely availability of relevant results.

The current implementation of pharmacometrics is mostly reactionary to the data collected and the knowledge gaps recognized by the drug development team as they approach a decision-making milestone. This ad hoc implementation of pharmacometrics and the “crisis” mode under which it frequently operates can obscure the important ways in which modeling and simulation can impact the entire life cycle of drug discovery, development and commercialization. As the evolution to model-based development continues to unfold, the pharmacometric analysis process must make the important transition from a sidebar activity to an official critical path activity, ie, a requisite part of the drug development and regulatory decision-making program timeline.

Purpose

Two of the key tasks of the pharmacometric process are (1) the development of pharmacokinetic and pharmacodynamic models that serve as a mathematical representation of physiologic or pharmacologic phenomena and (2) the exploratory data analysis efforts that should be performed prior to, and in conjunction with, the model-building effort. In this context, exploratory data analysis serves as a rapid prototyping effort to assess the feasibility of the desired model and provide diagnostic information to identify and address modeling difficulties.

Both these critical and interrelated activities are amenable to formalization and the process maps that are developed as a result of the formalization process provide management tools to significantly improve the efficiency, effectiveness, and quality characteristics of the pharmacometric process, as follows:

- They provide management with an objective toolkit for governing what is currently considered an ad hoc art form rather than a standards-based scientific endeavor
- They define the requirements at the interface with upstream and downstream stakeholders in the larger drug discovery/development enterprise
- They provide a basis for identifying critical milestones and developing associated performance metrics

- They serve as heuristics for scientists engaged in a model-building effort and provide a community standard for approaching model complexities and decision-making

Formalization Work Plan

The process of formalization involves the identification of all the subtasks required for completing the exploratory data analysis and model-building activities in a prototypical drug development project. The complete list of subtasks is then arranged in a hierarchical relationship to identify the high level subtasks and their associated lower level intermediate steps. Each of these intermediate steps is then considered with respect to their inputs, outputs, and deliverables. The inputs are the entities required for the completion of the tasks, the outputs are intermediate results of the subtasks used as inputs for downstream subtasks, and the deliverables are the work products that demonstrate successful completion of the subtasks. Iteration loops are also defined. Once these entities and their interrelationships are identified, project development timeline relationships and critical process steps can be determined. Measures of acceptability, performance metrics, and proposed governance strategies are then defined for each of these critical milestones.

Challenges

Formalization of these components of the pharmacometric process present several interesting challenges. First, there can be resistance to the idea that these activities can be formalized, since this process is usually viewed as an art form rather than a science. Second, the development of measures of acceptability is a difficult task that will require developing an ontology of models and components so that the applicability of various components and

criteria for use in commonly encountered settings can be discerned. Third, while many of the inputs for various subtasks can be explicitly defined, it is often difficult to rationalize the data definitions and format with the upstream and downstream processes. The difficulty of this communication is one reason why scientists frequently work alone and much of this communication is not documented. Encouraging and documenting this communication is one way of learning about the necessary attributes and content that will be important for the effective functioning of Integrated Project Teams.

Value Proposition

The growing reliance on modeling and simulation in decision-making is forcing important and urgent changes to occur in the nature of the work of the drug development teams, including the pharmacometricians. There are several emerging factors that point to the evolving demands on the pharmacometrics group and the important changes that will affect the people, process, and technology currently invoked in performing a modeling and simulation project:

- Stakeholders will become increasingly sophisticated and cognizant of their needs as they continue to gain experience using modeling and simulation in decision-making
- Stakeholder demand for timely and relevant results will continue to increase

- The rigor with which models must be justified and defended will increase as the use of pharmacometric models in regulatory decision-making becomes standardized

While a more proactive strategy is emerging in a number of pharmaceutical companies that have most aggressively implemented model-supported development, there is still a lack of formalization of the pharmacometric modeling and simulation process, and the informatic, systematic, and processual needs of modeling and simulation activities are largely unrecognized. The activities described in this initiative are intended to address these issues and bring about a new paradigm of model-based decision-making in which:

- The leveraging of M & S technology will be the basis for strategic competitiveness in the marketplace
- Data and information, which are consistent and widely shared within the company, will significantly improve productivity, substantially reduce errors and development missteps, and allow the effective integration of all primary stakeholders into the process
- A more diverse group of stakeholders will become directly involved in the M & S process ensuring wider applicability of the results. The M & S process will become an integral part of the larger drug discovery/development/commercialization enterprise
- The data analysis and simulation cycle time will be substantially reduced and the application of model-based development will result in more formal definition and standardization of the drug development process, avoiding errors induced by ad hoc “one of a kind” development plans

- Data analysis process standardization will result in high-quality, consistent results across disciplines allowing new discoveries through interdisciplinary synergy

ABOUT COGNIGEN

Cognigen is a state-of-the-art scientific, technical, and strategic partner for our clients in the pharmaceutical and biotechnology industry. Our focus is on providing scientific support for dose selection and justification at all drug development and regulatory milestones.

Our vision

To advance the science and engineer the systems for model-based drug development.

Our mission

- To help our clients understand the determinants of safety and efficacy of new medicines in order to:
 - Increase stakeholder confidence at decision-making milestones
 - Improve the chances for success with innovative therapies
 - Enhance the value of new medicines for patients and providers
- To provide a challenging and rewarding work environment for the professional growth and development of our scientists and staff.

We provide pharmacometric services for approximately 20 to 30 drugs per year. In 2007, 4 of the 17 NDAs submitted to the FDA incorporated our work as a basis for dose selection and justification. We have had experience in most therapeutic areas and have worked on projects in all phases of drug development from

pre-clinical to clinical development, from discovery to commercialization and post-marketing surveillance. We have a well-established reputation for the credibility of our work and track record of successfully utilizing pharmacokinetic and pharmacodynamic modeling and simulations to influence regulatory and clinical decision-making.



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