The Application of Systematic Analysis for Identifying and Addressing the Needs of the Pharmacometric Process

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ABSTRACT

Purpose. The current implementation of a pharmacometric process has, in most cases, grown from the *ad hoc* application of modeling and simulation activities to the drug-development process. This *ad hoc* implementation gives rise to a number of serious deficiencies that currently obstruct the optimal performance and application of pharmacometrics. The accelerating shift from empirical to model-based development strategies - and the growing reliance on modeling and simulation in decision-making will require the successful transformation of the pharmacometrics enterprise to a critical path service sufficiently provisioned to operate at the requisite level of efficiency, effectiveness, and reliability. We propose to use enterprise engineering methods and techniques to perform a systematic analysis of the current pharmacometrics operating environment in order to address critical unmet systematic, informatic, and processual needs of the pharmacometric process.

Objectives.
- Describe a process for performing forensic analyses of the challenges arising during modeling and simulation activities
- Formalize the pharmacometric process so that it can function at the requisite level of efficiency, effectiveness, and reliability to support model-based development

Methods. Ongoing forensic analyses of pharmacometric project team communications and work products during the performance of modeling and simulation activities will be performed. Specific programming instructions, such as the requirements for a NONMEM® analysis-ready dataset or instructions for a graphical display, coupled with team communications to resolve uncertainties and unanticipated complexities, along with subsequent deliverables will be used to develop a catalogue of the problems that arise. The nature of the gap between what was intended in the initial instructions and what was eventually defined via team communications to resolve uncertainties will be characterized and documented. The underlying entities and relationships that must be invoked for rigorous requirements definitions will be identified.

Results. Requirements definitions will serve as a basis for a series of interrelated enterprise definition efforts, including:
- refining the informatic elements required to fully inform programming efforts,
- providing feedback to upstream processes to improve deliverable effectiveness,
- informing subsequent pharmacometric enterprise design efforts,
- defining content and direction for training needs, and
- developing productivity tools.

Conclusions. By identifying and addressing the specific needs of the pharmacometrics process, the systematic analyses and accompanying training programs will directly impact the pharmacometric enterprise in three ways:
1.) They will improve the productivity, quality, and cost attributes of the existing pharmacometric process.
2.) These initiatives lay the groundwork for developing improved governance and operational management strategies for the pharmacometrics enterprise.
3.) They will point the way for the development of an idealized blueprint for a model-based drug development enterprise.

INTRODUCTION

The growing reliance on modeling and simulation in decision-making will increasingly tax the current *ad hoc* implementation of pharmacometrics. The successful transformation of the pharmacometrics enterprise to a critical path activity in development and regulatory decision-making requires that pharmacometrics be sufficiently provisioned to operate at the requisite level of efficiency and effectiveness. This transformation mandates that systematic, processual, and informatic needs - critical obstacles to meeting stakeholder needs for the timely delivery of pharmacometric services - be adequately and aptly addressed.[1]

We propose to use enterprise engineering methods and techniques to study the current pharmacometrics operating environment and develop strategies and tools to improve the processes and capabilities of the pharmacometric enterprise. The initiative described in this proposal has been pioneered and tested at Cognigen and demonstrated to successfully generate critical foundational knowledge with both short- and long-term benefits. This initiative will provision the pharmacometrics enterprise to reliably contribute to decision-making while fueling the transition to model-based development.

OBJECTIVES

- Describe a process for performing forensic analyses of the challenges arising during modeling and simulation activities
- Formalize the pharmacometric process so that it can function at the requisite level of efficiency, effectiveness, and reliability to support model-based development

NEEDS OF PHARMACOMETRICS

Informatic Needs

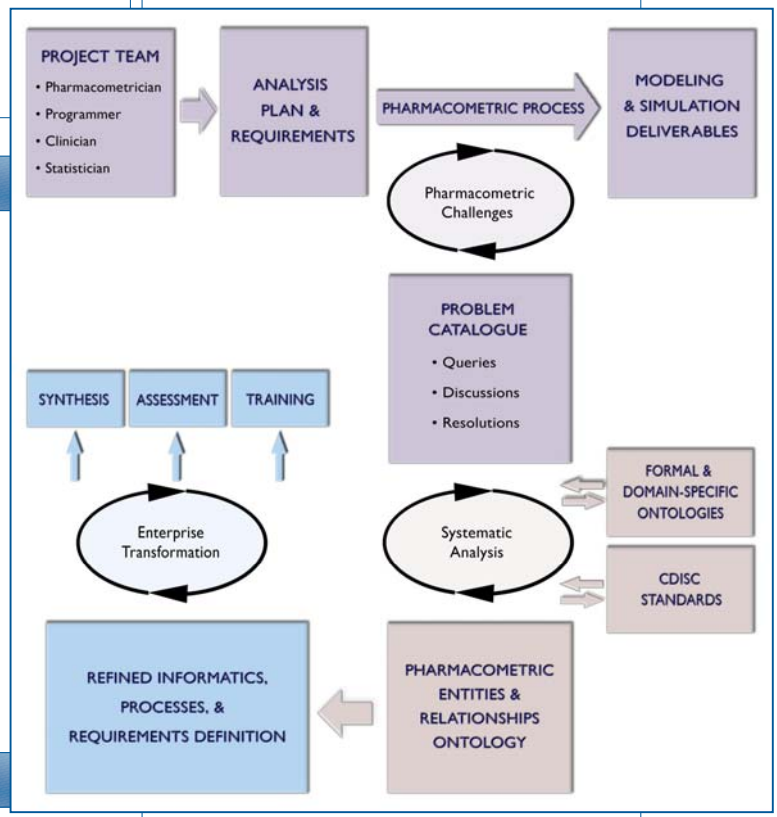
Informatics required for pharmacometric analysis encompasses information about the drug concentration-time data, covariates, pre-clinical and clinical biomarkers, and clinical outcome data used for modeling and simulation activities. Informatics in this regard includes, but is not limited to, metadata (e.g., the information about the structure and content of a dataset), prospectively defined data analysis plans and requirements, programming specifications for data assembly, archiving schema, validation requirements, and the information used for guiding the content and format of the presentation of results.[2]

Systematic Needs

There are two key sources of variability that impact the characteristics of a pharmacometric model and the content of associated work products. The first source of variability relates to inherent characteristics of the drug and the extent to which they are known, through previous experience with the compound itself or a class of similar compounds. The second source of variability relates to the fact that the current implementation of modeling and simulation is executed more as art than science. This latter source of work product variability stems from modeling approaches that are driven by modeler preference and experience rather than an objective science or industry standards.

Process Needs

The performance of modeling and simulation activities and the appropriate interpretation of the results requires the cooperation of a diverse group of scientists, data managers, statisticians, pharmacometricians, clinical pharmacologists, clinicians, and others. These groups have traditionally functioned independently and the current operating milieu is not geared for the synchronization of their activities in performing a pharmacometric analysis. This can result in duplication of effort or the lack of human, data, technical, and scientific resources at critical milestones.



FORMALIZING THE PHARMACOMETRICS PROCESS

A broad-based initiative to perform a systematic analysis of pharmacometric processes and work products is the critical first step in addressing the specific needs of pharmacometrics and formalizing the pharmacometrics enterprise. Building on the analytical and process definition work performed at Cognigen, the inputs, outputs, and deliverables of each of the subprocesses for providing pharmacometric analysis results can be rigorously defined. The systematic analysis we propose will provide the basis for identifying critical systematic, informatic, and processual elements that are either poorly developed – or completely lacking – in the current process. In this way, a rigorous and systematic assessment of the current pharmacometrics process can lead to the definition of a fully capable pharmacometric enterprise. The proposed strategy for implementing this systematic analysis in pharmacometrics is outlined in the figure above and described below.

Analysis Rationale

During the process of data assembly and dataset creation, the focus is on three main questions.

1.) What are the requirements of the analysis?
2.) What data are needed to perform an analysis that will meet these requirements?
3.) What data are actually available for inclusion in the analysis?

The challenge of answering these questions is compounded by the fact that the process must be iterative. This is to take account of the fact the requirements for an analysis will likely change over time, the development team or regulatory agency may raise new questions, new findings and understandings may emerge, and new data may become available as the development program matures.

In the process of developing answers to these questions, a series of more specific questions are formulated as the pharmacometrician and data programmer go back and forth to clarify issues and resolve uncertainties. The cycle of questioning, assessment, and discussion inherent in the current manual—and largely experiential—process is a valuable source of information about the fundamental entities and relationships invoked by pharmacometric analysis.

Systematics Study Group

A Systematics Study Group (SSG) will be formed to conduct forensic analyses of project team communications and work products generated during the effort to provide modeling and simulation (M&S) results to selected drug development programs. Specific programming instructions, such as the requirements for a NONMEM analysis-ready dataset or instructions for a graphical display, coupled with team communications to resolve uncertainties and unanticipated complexities, along with subsequent deliverables will be used to develop a catalogue of the problems that arise.

Integrated Project Team

An Integrated Project Team (IPT) will be constituted for each project. This team will initially focus on data assembly activities for selected drug development programs and then transition, if and when it is needed, to the provision of timely, comprehensive M&S results and interpretations to the drug development team. IPT membership will include one or more of the following individuals depending on the scope of the selected development program: IPT Leader, Pharmacometrician, Data Programmer, Clinical Pharmacologist, Statistician, Medical Writer, Administrative Assistant.

Communication Model

A web-based project communication toolkit, currently in use at Cognigen, will be deployed as a mechanism for all project communications to provide content for the systematic analysis. This toolkit consists of off-the-shelf software that has been customized for pharmacometric communications. The components include:

- PERSPECTIVE Hypertext Data Analysis Mapping Software,
- Confluence, professional Wiki for knowledge management, and
- Dotproject, open-source web-based project management software.

VALUE PROPOSITION

By identifying and addressing the current specific needs of the pharmacometrics process, the proposed systematic analyses will directly impact the pharmacometric enterprise in three ways:

1.) They will improve the productivity, quality, and cost attributes of the existing pharmacometric process work products, including:
   - analysis plans,
   - technical reports,
   - regulatory submissions, and
   - programming specifications.
2.) This initiative lays the groundwork for developing improved governance and operational management strategies for the pharmacometrics process, including:
   - measures of acceptability,
   - IPT performance specifications,
   - budgetary and staffing requirements, and
   - determinants of value.
3.) They will point the way for the development of an idealized blueprint for a model-based drug development enterprise, including:
   - future evolution of CDISC,
   - productivity tools,
   - new analysis algorithm development, and
   - regulatory and development transformation.

[1]Grasela, T.H. *et al.* Pharmacometrics and the Transition to Model-Based Development. *Clin Pharmacol Ther*. 2007; in press.
[2]Grasela, T.H. *et al*. Informatics and the future of pharmacometric analysis. *AAPS J*. (2007). http://www.aapsj.org/view.asp?art=aapsj0901008.

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