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**The Road to Pharma of the Future™**  
**The Transition to Model-Based Drug Discovery,  
Development, and Commercialization**



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## Background

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The pharmaceutical industry is undergoing major structural change in several dimensions simultaneously, and these changes will completely transform the industry's fundamental business models, core processes, and socio-technological infrastructures. The accelerating shift from empirical to formal (i.e. model-based) methods and the growing reliance on modeling and simulation (M & S) in decision-making is forcing important and urgent changes to occur in the nature of the work of drug discovery/development teams. Accordingly, what it takes to provide M & S support for these teams is also changing significantly from what it has required in the past. The current implementation of M & S activities must be properly provisioned and transformed into a fully-capable enterprise-wide process operating at the requisite level of efficiency and effectiveness. This transformation mandates that the systematic, processual, and informatic needs of the M & S process be addressed.

## The Rise of Model Based-Drug Discovery & Development

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While there is agreement on the challenges manifest in the ongoing Pharma R&D productivity crisis, consensus on the solution is much harder to achieve. Every sector in the drug development enterprise has engaged in a variety of initiatives to increase productivity and/or reduce costs. These initiatives range from deploying new technology and enhancing the information technology infrastructure to outsourcing and off-shoring. While many of these initiatives have merit, it is becoming clearer that more radical changes are necessary. In particular, the central process at the core of the drug discovery, development and commercialization paradigm, ie, the entire drug realization life-cycle, has come under scrutiny, along with the strategic and intellectual basis for devising study designs

and directing the corresponding data management and analysis activities.

The dominant paradigm for drug development is based on the conduct of empiric clinical trials and hypothesis testing against the null hypothesis as the primary method for evaluating the performance of new medicines. One idea that has surfaced as an alternative is model-based drug development (MBDD). In MBDD, mathematical equations are used to create computer-based models representing links between drug treatments and observed effects in what is now generally referred to as pharmacometric modeling and analysis. Pharmacometric modeling combines knowledge of a disease state, relevant biomarkers, and findings from pre-clinical and available clinical studies with knowledge of placebo responses and drop out rates to gain insights into the determinants of efficacy and safety outcomes. These models are then used in an attempt to improve the prediction of future events by simulating the outcomes of various alternative study designs and computing the probability of a successful trial.

### **The Challenge**

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Interest in modeling and simulation (M & S) to support drug discovery/development decision-making has grown markedly in the past 5 years. The effort to meet this demand with timely and relevant results has placed great pressure on people, process, and technology. Information technology and data programming groups have faced particular challenges in bringing support to the M & S process. In large measure these challenges stem

from the largely unmet, and often unrecognized, systematic, process, and informatic needs of the M & S process itself. Unlike the traditional empirical-based development process, the M & S process and its strategic and operational entailments have not yet been formalized to the extent of the more established, and integrated, functional areas.

Current attempts to define the M & S process often focus on the Modeler and M & S activities. The interrelationships with other functional areas, particularly the study design activities of the larger integrated drug discovery/development project team (IPT) and data capture and programming activities are often poorly defined. By default, the needs of the M & S process are presumed to be met by the established practices of these functional areas.

But the needs of the M & S process are different in important ways and it is critical to develop a formalization of the M & S process, and in particular the definition of the informatic elements required to properly support each of the subtasks of this process, so that the interrelationships with the larger drug discovery/development enterprise can be explicitly defined. Without this formalization, it would be as if the tools of the carpenter, rather than the plans of the architect, drive the design of your home.

### **Overview of the Pharma of the Future™ Initiative**

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The Pharma of the Future™ (PoF) initiative at Cognigen is focused on the identification and application of people, process, and technology enhancements in support of model-based discovery and development. The purpose of early PoF initiatives has been to examine, dissect and assess the essential functional elements required to successfully generate timely and relevant M & S results. The goals of these efforts have centered on reducing costs, increasing

productivity, and raising the standard of quality and effectiveness of M & S work products. Examples of early work include:

- Formalization of M & S process, including provisioning and execution workflows
- Improving the requirement specification process for data assembly
- Implementing a centralized interdisciplinary team communication system
- Developing strategies for addressing informatic deficiencies
- Creating tools for documenting and communicating the modeling process

The value of these tools and processes have been successfully demonstrated during the execution of numerous M & S projects for sponsors across the spectrum of large, medium and small Pharma and biotech companies.

### **The Transformation to a New Decision-Making Paradigm**

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The pharmacometric analysis process is intended to address gaps in knowledge of relationships between determinants of drug effects and safety and efficacy outcomes in preclinical and clinical testing. The pharmacometric analysis process enables the synthesis of disjointed data, including pharmacokinetic and pharmacodynamic information into knowledge that can inform decision making milestones across the entire drug realization life cycle. The principle outputs of pharmacometric analysis typically include

characterizations of drug kinetics, drug dynamics and predictions or extrapolations concerning any of these attributes.

In MBDD, quantitative models and the information bases upon which they rest will likely play an increasingly dominant role. The models will become the principal instruments for the design and evaluation of preclinical and clinical studies and will be considered to be among the major deliverables of drug development programs. The primary mission of the pharmacometrics group executing the modeling and simulation process will be to efficiently develop, effectively disseminate, and reliably maintain verifiably accurate and complete explications of the determinants of drug effects.

In this context, the models become critical to drug development and regulatory decision-making as well as the foundation for attempts to ensure the safe and effective use of medicines in clinical applications. Consequently, the M & S process will become an integral part of the iterative drug discovery/development/delivery process, which will proceed via a design, test, capture data, model, simulate, redesign, retest, recapture data, remodel paradigm.

### **What MBDD is NOT About**

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- NONMEM – although Nonlinear Mixed Effect Modeling algorithms and other tools will be important to execution
- Grid Engines – although computational tools will be a critical support capability particularly as models grow in detail and complexity
- Hiring more modelers – although talented individuals will always be in high demand

- Heroic efforts to meet deadlines – although productivity will be an ongoing issue and strategies to achieve effective collaboration across interdisciplinary development teams must be addressed

The current implementation of pharmacometrics is more suggestive of *model-supported* drug development than *model-based* drug development. In this as-is implementation the strategy for collecting the information for pharmacometric analysis is typically overlaid onto traditional study designs. Often there is little opportunity to prospectively impact design characteristics to optimize the yield for M & S. Consequently, the results are mostly reactionary to the data collected and the knowledge gaps suddenly manifested as a decision-making milestone approaches. This ad hoc implementation of pharmacometrics and the “crisis” mode under which it frequently operates can obscure the important ways in which the growing use of modeling and simulation will impact the entire life-cycle of drug discovery, development and commercialization.

### **A Glimpse of the Future?**

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- The leveraging of M & S technology will be the basis for strategic competitiveness in the marketplace.

- Data and information, which is 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 develop intricate relations with 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 faulty “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.

### **Strategic Goals for a MBDD Enterprise**

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- Reduce the schedule span from First in Man to regulatory approval by 33%
- No late-stage clinical trial failures after Phase 2 completed
- The identification of a safety or efficacy issue in early stage development has one of two outcomes:
  - Recommendation to terminate program
  - Recommendation to modify program with defined implications for commercialization

## Operational Goals for a MBDD Enterprise

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- Informatic elements and data standards are defined during study planning and used to guide data capture and management strategies
- Integrated Project Team assignments, timelines, and incentives defined at the start of the program
- Modeling and simulation results routinely available within two weeks of study specific data lock

## Next Steps

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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 modeling and simulation process. The challenges stemming from the unmet process, informatic, and systematic needs of a mostly *ad hoc* M & S process represent critical obstacles to the realization of the value of modeling and simulation. Addressing these needs will require a series of interrelated initiatives to properly provision the M & S process and develop its relations with the larger drug discovery/development/commercialization enterprise.

### *Formalize the pharmacometric process*

No improvement can be expected if we simply increase demands on the existing *ad hoc* process. Importantly, the unmet needs also indicate that simple solutions borne from the

hiring of additional scientists and support staff are unlikely to yield successful and sustainable results. Successfully navigating around these issues will require a rigorous effort to transform pharmacometrics from an *ad hoc* process to a formal and fully integrated process.

### *Strengthen the informatic infrastructure*

Informatics will eventually come to be recognized as a critical determinant of the effectiveness and productivity of the M & S process. Informatics required for pharmacometric analysis includes, but is not limited to, metadata for drug concentration-time data, covariates, pre-clinical and clinical biomarkers, and clinical outcome data. High quality metadata, which summarize data content, context, structure, inter-relationships are critical to successful information management, annotation, integration and analysis.

### *Implement a Requirements Definition and Management program*

The overall efficiency and quality of a modeling and simulation effort can be improved by systematizing the requirements definition process. The objective is to define the information required for unambiguous communications between and among IPT members and their support staff. The common sources of miscommunication between team members must be identified and formalized programming specifications must be developed. A strategy and feedback loop for continually refining and expanding the scope of these programming specifications is warranted, along with efforts to identify targets for automation.

### *Adopt a Scientific Workflow strategy as a basis for model documentation, reporting and communication*

Throughout the data assembly and M & S processes, data may undergo many transformations at a variety of distributed locations and may be analyzed and

processed by a number of collaborators. In most M & S projects the complex computational processes are often generated, managed, and described with manual and *ad-hoc* approaches. Such approaches are problematic in practice for several reasons, perhaps most importantly because of the difficulty in re-generating the results. Reproducibility requires rich process information, so that researchers can repeat techniques and analysis methods to obtain scientifically similar results. Today, reproducibility is virtually impossible even for relatively simple M & S results; and without it large-scale M & S results may be questioned in terms of scientific soundness and integrity.

#### *Develop training programs for Integrated Project Team scientists and support staff*

The M & S process is growing increasingly sophisticated, and stakeholders are placing an increased emphasis on the results as a basis for decision-making. The ability to perform these analyses with the requisite level of timeliness, quality, and sophistication creates the need for personnel who have appropriate levels of scientific, technical, and business skills. Training for the IPT scientists and support staff must encompass not only the technical and scientific aspects of M & S, but also begin to inculcate the skills required for assessing and balancing risk, performance, schedule, and cost considerations in specifying development program designs and analysis procedures.

#### *Adopt a Lean Six Sigma approach to process improvement*

A systematic analysis of the challenges in performing modeling and simulation activities can yield a rich catalogue of the problems currently faced by IPTs working in a model-supported environment. A formal, systematic analysis of this catalogue, coupled with a critical consideration of the CDISC and other standards, would provide a basis to improve the performance of various M & S subtasks, provide needed insight into future CDISC improvements for M & S, and create functional specifications for future software and process based productivity enhancements.

#### **Summary**

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The current application of M & S in drug discovery/development decision-making is faced with a significant, but ephemeral, opportunity. The tools of M & S are sufficiently understood at the same time that the limitations of empiric-based development are becoming more widely appreciated. However, tools do not an enterprise make and *ad hoc* solutions incur a high risk of failure in the face of cost, quality and schedule constraints.

The development of an effective M & S infrastructure can serve as a “bow wave” or change agent for the transformation to a model-based discovery/development paradigm. The current implementation of M & S activities must be properly provisioned and transformed into a fully-capable enterprise-wide process operating at the requisite level of efficiency and effectiveness. This transformation mandates that the needs of the M & S process – systematic, processual, and informatic – be adequately and aptly addressed.

## Additional Reading

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1. Grasela TH, Dement CW, Kolterman OG, et al. Pharmacometrics and the transition to model-based development. *Clin Pharmacol Ther.* 2007;82:137-42.  
Requests for reprints may be sent to Thaddeus H. Grasela at [Ted.Grasela@cognigencorp.com](mailto:Ted.Grasela@cognigencorp.com).
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4. Grasela TH, Fiedler-Kelly J, Walawander CA, et al. Challenges in the transition to model-based development. *AAPS J.* 2005;7(2):on-line.  
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## ABOUT COGNIGEN

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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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