PAGE

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Engineering the Pharmacometrics Enterprise

Ted Grasela, PharmD, PhD
President and CEO
Cognigen Corporation
&
Adjunct Professor of Pharmaceutics
Senior Fellow in Entrepreneurship
University at Buffalo
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Drug Development in the Future
Propositions

- A new drug development paradigm is essential for the survival of the pharmaceutical industry and its principal stakeholders
- This paradigm will be:
  - formal (e.g., model-based) rather than empirical,
  - iterative rather than sequential,
  - adaptive rather than programmatic
- Pharmacometrics is becoming a critical path process to support decision-making
- A properly provisioned pharmacometrics enterprise must be engineered for the successful transition to model-based development

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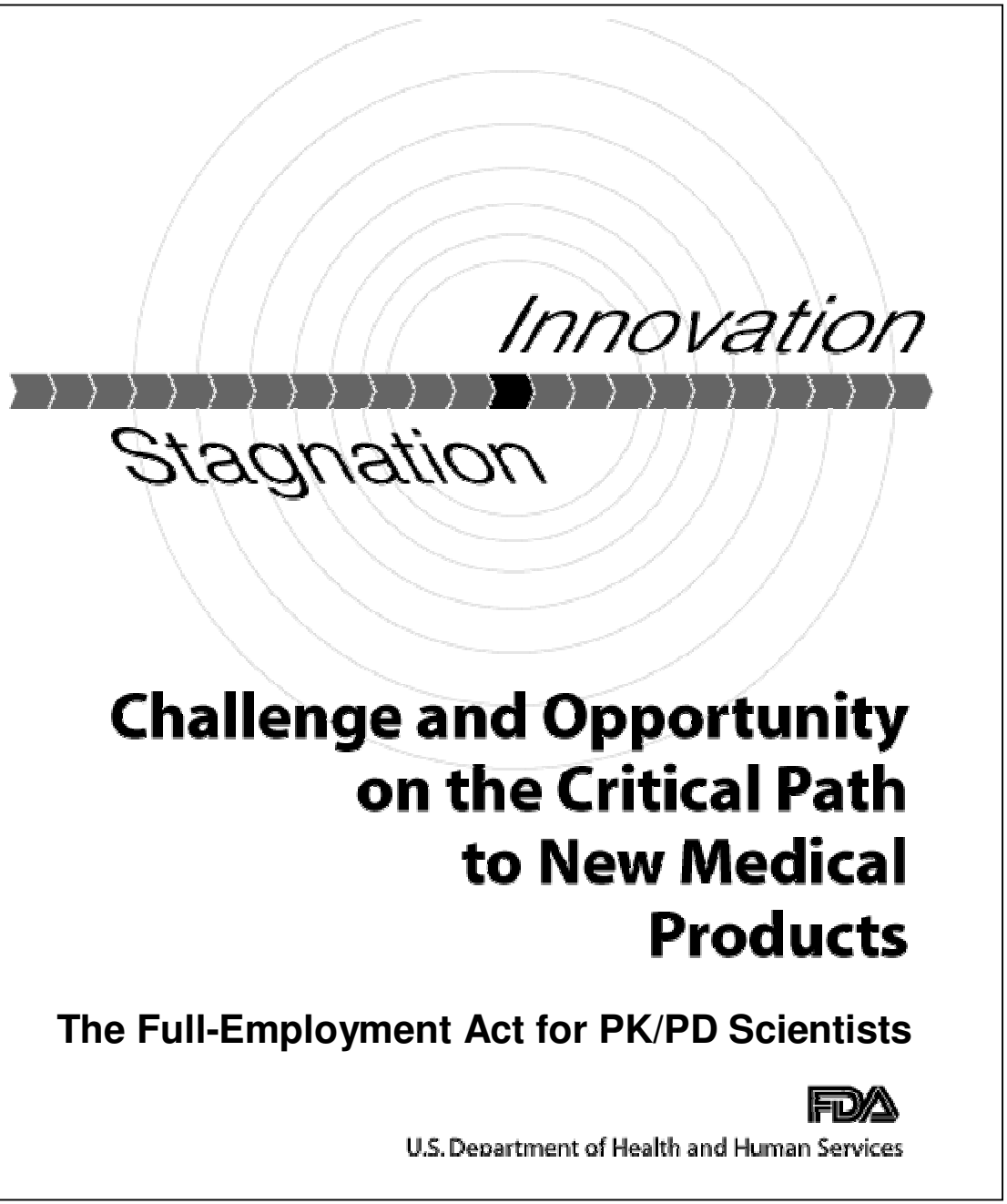
Innovation
Stagnation
Challenge and Opportunity on the Critical Path to New Medical Products
The Full-Employment Act for PK/PD Scientists
FDA
U.S. Department of Health and Human Services

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But…….

”I’m feeling a little anxious.”

Beetlejuice, 1988

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Transition to Model-Based Development
Symptoms of Deeper Problems?

- Data required for PK/PD analysis often not available until primary safety and efficacy analyses completed
- Data assembly and scrubbing are remarkably time-consuming and result in high discard rates and delays
- Generally accepted measures of acceptability are not available
- Resistance to use results of M&S in decision-making
  - M&S results are not reducible to p-values
  - opportunities for collaboration, creative thinking and synthesis of knowledge may be sacrificed because of urgent timelines
- Lost opportunities to impact on development and regulatory decision-making

Transition to Model-Based Development

The Obstacles to a New Paradigm

There are enormous strategic, logistical, tactical, and architectural obstacles that must be overcome if pharmacometrics is to be a reliable, effective, and efficient element of a new paradigm for drug development and commercialization.

A enterprise engineering approach will be required to bridge:

1. Translational Gaps
2. Technological Gaps
3. Architectural Gaps

From an Architectural Perspective…

…Empirically based development is:

- Predictable in cost and schedule
  - informatic elements straightforward and relatively easy to acquire
- Reliable, repeatable, and determinable
  - programmatic – “recipe driven” development
- Outcome adequate for major stakeholders
  - p-value – driven concept of efficacy and safety

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From an Architectural Perspective…

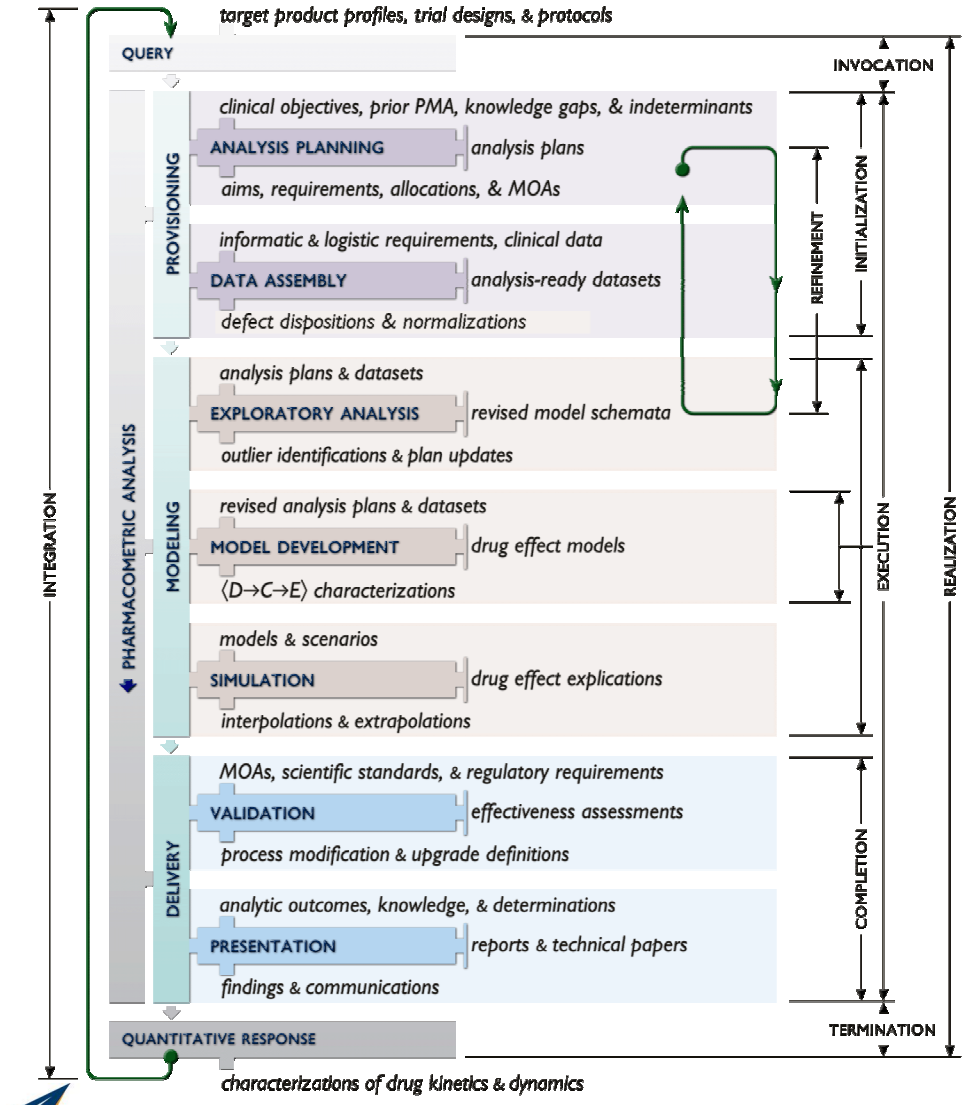
… Model-based development is:

- Highly cost/schedule variable
  - data availability and quality problems
- Model dependent, analyst dependent, and multiply interpretable
  - non-programmatic – MBD is both a 'hypothesis generator' and a confirmator
- Outcome is overly complex for historical stakeholder purposes
  - principal stakeholders must consciously want and accept the need for complex characterizations of efficacy and safety

Two Ways to Improve Drug Development Process Performance

- First – do the same thing better and faster - that is, deploy new methods and technologies that will enable the existing process to be more efficient
  - Adaptive trial techniques
  - Informatic standards
- Second – re-invent the process itself – that is, to deliberately architect a new drug development process
  - Deploy an industrialized model-driven process coupled with restructured regulatory policy and practice
  - This will require a new synthesis of disciplines known as Enterprise Engineering
  - We have only begun to appreciate the needs and requirements of pharmacometrics in a truly model-based development paradigm

The Pharmacometrics Enterprise



- Process invoked to address gaps in knowledge of the determinants of drug effects
- Inputs: Target product profiles, designs for clinical trials, prior knowledge
- Outputs: Characterization of determinants of drug effects
- Critical to define the interfaces with drug realization enterprise

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The Pharmacometrics Enterprise
Elements of Any Complete Solution

- Infrastructure – Where are the data definitions that would:
  - Allow pooling of data across trials? Across programs?
  - Support global development programs?
  - Enable rapid and effective assessment of data set content?
- Process – How do we:
  - Decide when and where M&S should be applied?
  - Assess the performance and impact of M&S?
  - Talk about results that are not reducible to a p-value?
- Organization and Culture – How do we:
  - Incentivize establishment of truly integrated, multi-organizational teams?
  - Articulate value of M&S-based conceptualization of safety and efficacy to all principal stakeholders, including sponsors, regulators, providers, etc.

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Pharmacometrics Enterprise

Needs Identification – Systematic Needs

- PHM analyses typically viewed as one-off, unique creations
- Two sources of variability
  - Differences in drug effects across therapeutic categories
  - Differences in process execution, capabilities and preference
- Systematics – The scientific study of the kinds and diversity of biological organisms and of any and all relationships among them
- Systematic analysis in PHM provides a rigorous basis for minimizing the effects of unnecessary variability in work processes and products

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Pharmacometrics Enterprise
Needs Identification – Process Needs

- PHM analyses depend on the cooperation and talents of traditionally independent groups not geared to the synchronization of tasks specifically required for PHM
- Challenging logistics – Find the data, manage the data, analyze the data, govern the process, use the results
- Performance expectations will continue to increase
- A conceptualization of PHM, situated in the larger drug realization enterprise, provides the context for:
  - developing provisioning and utilization protocols,
  - defining performance and reliability measures,
  - specifying assurance process
  - defining career paths

Pharmacometrics Enterprise
Needs Identification – Informatic Needs

- Data pooling and complex characterizations of efficacy and safety are hallmarks of PHM analysis
- These require heretofore unavailable definition data, i.e., the informatics to specifically support pharmacometrics
- Converse sides of the same coin:
  - Data management problems stem from deficiencies in data collection and management – schematic gaps in definition data management
  - Report production and configuration management problems stem from implementation deficiencies – shortcomings in existing software systems that preclude deployment of canonical documents

Engineering a PHM Enterprise
Conclusions

- PHM is faced with a significant, but ephemeral, opportunity
- The tools of PHM are sufficiently understood at the same time that the limitations of empiric-based development are becoming more widely appreciated
- 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
- Only by envisioning and engineering a comprehensive PHM enterprise can the full promise of MBD be realized

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Thank You

For more information contact:

Thaddeus Grasela, PharmD, PhD
President and CEO
ted.grasela@cognigencorp.com
Phone: 716-633-3463 ext. 227

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