PIII-56

Model Feasibility Assessment as a Driver for Model-Based Drug Development

B. Cirincione,[1] E. Blase,[2] M. Cummings,[1] M. S. Fineman,[2] T. H. Grasela,[1]
[1]Cognigen Corporation, Buffalo, NY and [2]Amylin Pharmaceuticals Incorporated, San Diego, CA

ABSTRACT

Background. Complex pharmacometric analyses raise concerns about cost, time, and reliability of the model-building process (MBP). The goal was to use a model feasibility assessment (MFA) process to improve the performance characteristics of the MBP.

Methods. Literature review provided a basis for a proposed mechanistic model of exenatide effects in type 2 diabetes. A study index database (SID) detailing design characteristics, interventions, and comparators of available studies was assembled and used to generate informatics to facilitate data pooling. Cross-study endpoint databases (CSED) for each endpoint were assembled and used to generate exploratory analyses (EA) of posited model relationships. A gap analysis (GA) performed during the assembly of SID and CSED identified issues regarding study design alignment, data adequacy, and the types and timing of interventions and endpoint measurements that impacted the MBP.

Results. 38 studies were reviewed and were included in the MBP. EA aided in determining functional form, providing initial parameter estimates, and specifying data programming requirements. GA was critical in choosing data for the MBP and generating design recommendations for future studies. The informatics generated during the GA and the discussions to resolve discrepancies enhanced data assembly and accelerated model-building efforts.

Conclusions. MFA provides a systematic approach to facilitate data selection and pooling and improves the performance characteristics of the MBP so that results are available for decision-making.

OBJECTIVES

- The objectives of this project were to:
  - develop a strategy to improve the efficiency and effectiveness of the model development process;
  - apply this strategy to the assessment of the feasibility of developing a mechanistic model that encompasses the pharmacologic effects of new selected drugs on the physiological factors underlying type 2 diabetes mellitus (T2DM); and
  - gain an understanding of the informatic elements required to support model-based drug development.

METHODS

- Perform a literature review to identify published variants of mechanistic models in T2DM and the physiologic interrelationships required to inform them
- Develop an inventory of published clinical trials and their content
- Develop a taxonomy of completed studies to characterize the subject populations, study conditions, interventions, and comparators
- Assess the informational content of the clinical trials and the usability of the existing data to address modeling issues
- Populate an SID to guide selection of studies for use in the modeling effort that will provide informatic and metadata elements to facilitate data pooling
- Create a cross-study endpoint database for each physiologic endpoint to be incorporated into the model
- Determine the challenges to data pooling and assembly for the analysis-ready datasets
- Perform a graphical and tabular analysis of the cross-study endpoint database to explore postulated model relationships
- Perform a GA on the desired model versus the available data

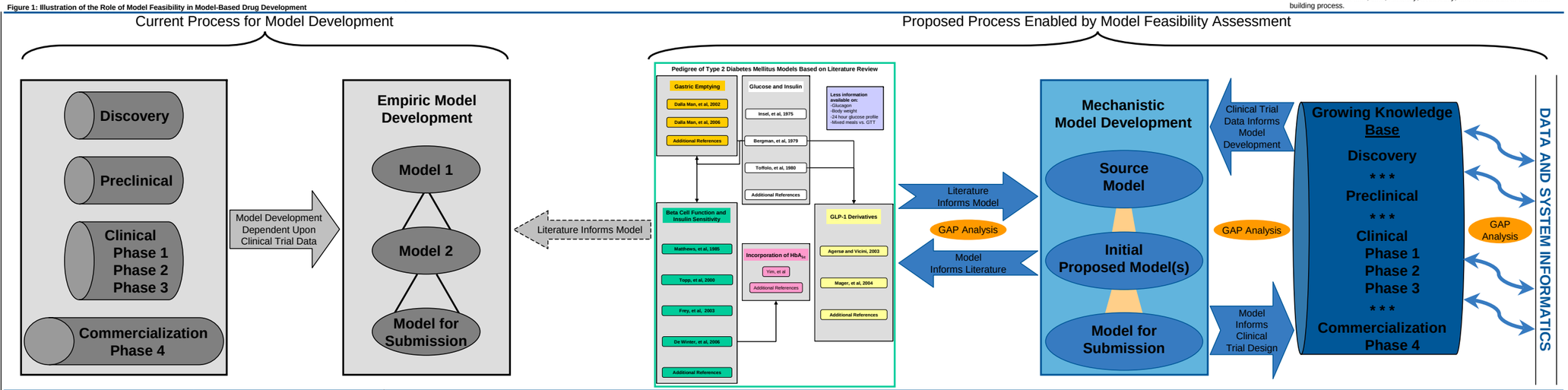
BACKGROUND: T2DM

- A number of classes of agents are available for the treatment of T2DM, including insulin, sulfonylureas, short-acting insulin secretagogues, biguanides, thiazolidinediones, α-glucosidase inhibitors, incretin mimetics, DPP IV inhibitors, and amylinomimetic agents.
- These drugs improve glycemic control to different degrees through varied, although sometimes overlapping, mechanisms of actions including:
  - Enhancement of glucose-dependent or independent insulin secretion
  - Restoration of first-phase insulin response
  - Improvement of insulin sensitivity
  - Reduction in hepatic glucose production
  - Delayed or decreased glucose absorption
  - Reduction in glucagon secretion
  - Slowing of gastric emptying
- Modeling of various aspects of T2DM has been going on for decades.
  - Predominantly, the literature has focused on:
    - glucose-insulin interactions;
    - glucose-HbA_{1c} interactions;
    - the influence of gastric emptying; and
    - beta cell function and insulin sensitivity.
  - The mechanistic components were handled in various ways.
    - This was due to differences in the available data which had an effect on the results of the model development process as well as the interpretation of the results.
  - There is less published information pertaining to:
    - 24-hour glucose profiles;
    - the incorporation of the effect of glucagon; and
    - the evaluation of different types of meals (low fat, high fat, liquid meal replacements).
  - See Figure 1 for Pedigree of T2DM.

BACKGROUND: PHARMACOMETRIC MODEL DEVELOPMENT

- The model-building process typically proceeds based on available data as well as literature review.
  - Information obtained from the literature is often specific for that published compound.
  - This leads to results that are difficult to interpret and apply to future modeling efforts with different data.
- There is an intricate relationship between the available data and the ability to develop a proposed model.
- Understanding this relationship requires assessment of the content of the data and a GA against the needs of the model.
- The GA requires the determination of the ability of the data structure to:
  - differentiate the informational content of datasets to quickly determine suitable data; and
  - assess the utility of specific data elements.
- The transition to model-based drug development is a paradigm shift:
  - away from building a model based on available data; and
  - towards pre-specified study design and data collection strategies based on the model requirements.
    - These requirements must encompass information on use, limitations on interpretation, and measures of acceptability for modeling needs.
- During the lifecycle of drug discovery and development, a model will become more complete and comprehensive and reflect the growing knowledge base for a drug.
- Facilitating this transition and managing the implications within the larger drug development infrastructure is a challenge.
- Such a transition may have other implications affecting:
  - study design, target population, and schedule of interventions;
  - data capture and management techniques;
  - informatic needs, including the metadata defining the structure and content of the dataset; and
  - concerns about the cost, time, reliability, availability, and robustness of the model-building process.

Figure 1: Illustration of the Role of Model Feasibility in Model-Based Drug Development



RESULTS

- **Study index database**
- A total of 38 clinical trials across 2 drug development programs were evaluated
  - 28 studies were conducted in subjects with T2DM
- The **cross-study endpoint database** was evaluated to determine which studies should be pooled to support the estimation of components of a mechanistic model and to facilitate the database creation process.
- Out of 38 studies evaluated:
  - 29 studies had information pertaining to glucose;
  - 20 studies had information on both glucose and insulin;
  - 10 studies had information on glucose, insulin, and glucagon;
  - 14 studies had information pertaining to glucose and HbA_{1c}; and
  - 10 studies evaluated gastric emptying.
- Glucose was administered through various methods including:
  - a standardized meal;
  - a liquid meal; and
  - IVGT.
- Dataset creation was targeted to begin with the subset of studies with the most comprehensive data on glucose, insulin, and glucagon.

INFORMATION INCLUDED IN THE STUDY INDEX DATABASE

- Type of study
  - Double blind vs. open label
- Dosing amounts and regimen
  - Placebo versus active drug
  - Single versus multiple dosing
- Healthy volunteers vs. patients
- Formulation
- Administration method
- Type of glucose administration
- Duration of treatment
- Sampling strategies
- Endpoints to be included in the cross-study endpoint databases
  - For example: insulin, glucagon, HbA_{1c}, glucose (pre-prandial, post-prandial, and fasting), GLP, gastric emptying times
- Timing of endpoint collection

GAP ANALYSIS

ISSUES ENCOUNTERED DURING DATA POOLING

- Differences in the units of measure reported
- Differences in assay used
- Differences in formulation
- Differences in study conditions
  - For example: food status at the time of dose administration

ISSUES ENCOUNTERED DURING ANALYSIS DATASET CREATION

- How many doses prior to a PK sample are needed to include the sample?
- How to handle non-steady-state visits?
- Are BLQs included?
- How will steady state be used?
- How should missing information be imputed?
- How should potential period effects be addressed?

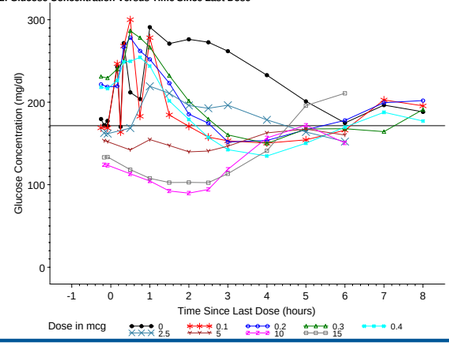
SCIENTIFIC REVIEW ISSUES

- What level of physiologic comprehensiveness is feasible given the available data and literature?
- How does the proposed model relate to the published literature?
- How will gaps in the data be handled?
- Which model components can be simplified if there is a lack of data?
- What are the consequences of the simplifications?
- What graphs are needed to decide on the functional form of the model?

EXPLORATORY ANALYSIS

- Exploratory analyses are performed to determine:
  - data adequacy and the need for literature estimates;
  - the initial functional form of the mathematical model; and
  - the scientific and data programming requirements.
- Figure 2
  - An exploratory graph used to determine initial parameter estimates and model structure

Figure 2: Glucose Concentration Versus Time Since Last Dose



MODEL FEASABILITY ASSESSMENT

	Glucose-Insulin	HbA_{1c}	Gastric Emptying	Glucagon	Overall
Prior Experience in Literature	5	3	2	1	
Data Availability	5	4	3	3	
Mathematical Model Tractable/Identifiable	4	5	2	2	
Overall Ranking	4.7	4	2.3	2	3.3

0 = Not feasible, 5 = Very feasible

- The availability of data from clinical studies, tentative identifiability of the model, and information from the literature were subjectively evaluated using a scale of 0 to 5 with 0 indicating no available data and 5 being an abundance of available data.
- The ranking for these 3 categories was averaged to determine an overall ranking, using a scale of 0 to 5.
- Based on current knowledge and data availability, the components of the model for glucose/insulin and glucose HbA_{1c} were ranked higher on the feasibility scale.
- More effort would be required to incorporate glucagon and gastric emptying as less knowledge is available for the modeling of these endpoints.

CONCLUSIONS

- Knowledge of the underlying physiologic relationships in a disease-state is a key starting point for model-based drug development.
- Systematic analysis of the challenges that arise during data assembly and the creation of analysis-ready datasets for modeling efforts is a critical tool for defining the informatic and infrastructure needs of the pharmacometrics process.
- MFA provides a systematic approach to facilitate data selection and pooling.
- Efficiency in drug development could be realized through informed trial design based on relevant models.
- The results of the GA and the MFA can serve as the basis for improving development programs in terms of strategic consideration of data collection, database design, study design, and technology deployment.

Presented at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) Annual Meeting, Orlando, Florida; April 2-5, 2008

For additional information, please contact Ted Grasela at Cognigen Corporation, 395 Youngs Road, Buffalo, NY 14221 (716) 633-3463 ext. 227 or ted.grasela@cognigencorp.com.