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## Use of Systems Biology in Clinical Development: Design and Prediction of a Type 2 Diabetes Clinical Trial

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**Systems biology** describes an approach aimed at understanding how integrated biological mechanisms regulate health; disease onset and progression; and patient responses to treatment. Entelos' approach to systems biology involves developing and applying **top-down, hypothesis-driven, mechanistic models**. These quantitative representations integrate and interpret biological (e.g., genomic, proteomic, physiological) and clinical data to reproduce a system's dynamic control principles. These computer-based models simulate a system's biological responses, a process termed **predictive biosimulation**.

At Entelos, these mechanistic models are managed within a virtual research environment – the PhysioLab<sup>®</sup> platform. Using this research platform, scientists have access to and can visualize all model variables over the time-course of the simulation, allowing dissection and quantification of the impact of therapies and their underlying mechanisms and to assess competing hypotheses. To date, researchers have applied this technology successfully in the areas of target validation, lead candidate selection, clinical trial optimization, biomarker research, and product differentiation<sup>1</sup>.

In this article we describe the application of the Entelos Metabolism PhysioLab platform in collaboration with Johnson & Johnson Pharmaceutical Research & Development, LLC (J&JPRD), where clinical trial simulations provided new information to inform decision making, reduced the number of patients required in a study, and decreased the time required to conduct the trial<sup>2</sup>.

### Biosimulation in Clinical Development

Clinical trials are the most expensive and time-consuming phase of the drug development process. Entelos rapidly simulates thousand of clinical trials, within the PhysioLab platform, using a high-performance, grid-based computing center (e.g., one 24-hour period can be simulated in roughly 20 seconds). These simulations involve three key elements: (1) virtual patients, (2) virtual patient cohorts, and (3) simulated clinical protocols.

**Virtual patients** are explicit, quantitative representations of known or hypothesized biology underlying both normal physiology and disease pathophysiology. Virtual patients can represent healthy phenotypes, different phenotypes with similar underlying pathophysiology, the same phenotype with different pathophysiologies, or patients at different stages of disease progression.

**Virtual patient cohorts** are a collection of individual virtual patients. Using classical statistical methods, Entelos applies these cohorts to evaluate optimum inclusion/exclusion criteria, establish the prevalence of virtual patients to subjects in the population, understand therapeutic response variability, and determine the distribution of responses experienced by a cohort when subjected to a simulated clinical protocol. This combination of biosimulation and statistical analysis predicts population-wide responses with high confidence.

**A simulated clinical protocol** is a series of instructions that inform the PhysioLab platform how to perform an *in silico* clinical trial. The protocol contains information about which virtual patients or virtual cohort to use in the simulation, a compound's pharmacokinetic (PK)/pharmacodynamic (PD) characteristics, dose and dose frequency, route of administration, diet, exercise, or concomitant therapies. Unlike an actual clinical protocol, however, no pre-specified data collection strategies are required as all model variables can be evaluated over the time course of the simulated clinical trial.

### Prediction and Design of a Type 2 Diabetes Clinical Trial

**Background:** J&JPRD was developing a first-in-class therapy for the treatment of type 2 diabetes. This candidate drug had a novel mechanism of action and had not been tested in humans. Following an initial toxicology evaluation, the safety and efficacy of the compound in humans still remained in question. Consequently, a broad dose-ranging plan was proposed to evaluate the safety of the compound in healthy subjects, followed by exploratory studies of efficacy in patients with diabetes.

**Goal:** Using the dose levels and dose administration schedules established by J&JPRD, use biosimulation to:

1. Predict subject responses to a proposed escalating dose Phase I clinical trial (results shown).
2. Predict the therapeutic response range in a broad population of virtual type 2 diabetic patients for a Phase II clinical trial and identify biomarkers predicting patient responsiveness (results not shown).

**Results:** Following the incorporation of proprietary compound data into the PhysioLab platform, the proposed Phase I protocol was simulated. This protocol

included the administration of an oral glucose tolerance test (OGTT) in healthy subjects following single escalating doses of the compound. The results indicated that the effects on plasma glucose would be minimal (Figure 1). In fact, the maximum effect at the highest compound dose was only a 15 mg/dl reduction in peak glucose concentration.

Given variations in patient responsiveness and the infrequent sampling times proposed in the original clinical trial design, it was concluded that these differences would be difficult to observe in a real clinical population. Furthermore, it was suggested that differences would not be observable at the lower proposed doses. After detailed discussion with the clinical team, the original trial design was modified to include only the placebo and the highest tolerable dose, and the trial was run.

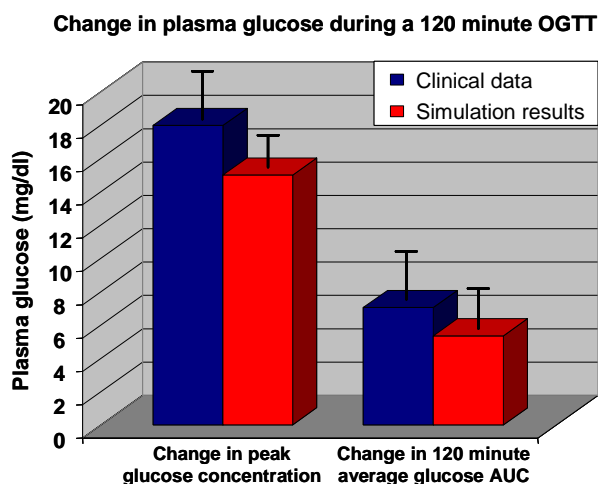


Figure 1: Change in plasma glucose concentrations during a 120 minute oral glucose tolerance test (OGTT) in a clinical population (blue) and virtual patient cohort (red).

Clinical results using the modified protocol showed only moderate efficacy at the highest dose and were in agreement with the simulation results (Figure 1). Based on both the *in vivo* results and biosimulation data, it was concluded that the single highest dose yielded the same information that would have been otherwise obtained had the original escalating trial design been performed.

Next, Entelos prospectively evaluated a complex, six-month Phase II clinical trial protocol in a diverse population of virtual type 2 diabetic patients to provide an indication of the expected response variability. Although

numerous aspects of the Phase II trial design had already been determined by J&JPRD clinical scientists (e.g., dosing schedules and trial duration), simulation of the proposed clinical trial protocol led to the identification of those compound properties which would be most efficacious in the patient population under consideration, thus potentially allowing earlier optimization of a backup compound based on those properties.

**Metrics:** By modifying the Phase 1 clinical trial design to include fewer patients and trial arms, biosimulation provided information that led to substantial time and cost savings, while at the same time increasing confidence in decision-making. In this example, J&JPRD recognized the following direct savings:

- Elimination of four dosing arms from the protocol, reducing the total number of patients recruited.
- Reduction of the clinical trial duration from fourteen to eight weeks.

and utilized the following information to support decision-making:

- Biomarkers of patient response, new sampling times, and frequencies for a clinical trial in type 2 diabetes patients.
- Ideal PK/PD properties to optimize a backup compound.

**Conclusions:** Predictive biosimulation applied to clinical development by trained and knowledgeable biosimulation researchers can improve efficiency and information yield, even when the compound acts through a novel mechanism or profile. Here we demonstrate a **40% reduction in time** and a **66% reduction in the number of patients** required in a Phase I trial. Additionally, predicting the Phase II dosing and efficacy supported J&J PRD's decision-making in the development of this novel treatment for type 2 diabetes.

Similar benefits have been achieved with the Entelos technology and approach by other pharmaceutical partners working in discovery, preclinical, clinical development, and post-launch.

- (1) PAREXEL's Pharmaceutical R&D Sourcebook 2003/2004, p. 128-9.
- (2) Presented by Camille Wallwork at Beyond Genome *In Silico* Biology, San Diego (2002).

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