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A Guide to *In Silico* Modeling and Simulation

As a prerequisite for marketing approval, regulatory agencies typically require that a sponsor conduct a randomized controlled trial, where the control group is either a placebo, an active control, or a standard of care control arm. There are, however, situations in which a placebo control may be unethical or where neither an active control nor standard of care exists. In these scenarios, potential solutions include constructing a historical control arm using real-world data (RWD) or using an *in silico* method to construct a virtual patient control arm.

In *in silico* trials, investigational drugs are tested in virtual patients using sophisticated computational modeling and simulation techniques. *In silico* approaches may be used to evaluate drug candidates prior to testing in humans or to serve as an external synthetic control arm in single-arm prospective human trials.

Defining virtual patients and synthetic data

In pharmacological evaluations, a virtual patient is a computational model with parameters selected so that model outcomes represent a biological, physiological, pathophysiological, pharmacokinetic (PK), pharmacodynamic, or other process of a realistic human subject. There are two approaches to utilizing virtual patients:

- **Virtual populations.** In *in silico* trials, variations in model parameters are used to generate a cohort of virtual patients, or a virtual population. Simulations are then performed on this virtual population to predict clinical measurements that are relevant for assessing the safety or efficacy of a medical intervention.
- **Personalized virtual patients**. This approach inputs patient-specific data into the computational model to create a personalized virtual patient, which can be used to inform diagnoses, treatment decisions, and personal prognosis.

Synthetic data are patient data generated from advanced computations methods, such as mechanistic modelling or approaches based on machine leaning and artificial intelligence. A cohort of synthetic patients, when properly validated, can be used to replace or augment a control arm in a clinical trial.

Figure 1.

Understanding the regulatory perspective on *in silico* methods

Before any method is deemed acceptable for regulatory submission, the method's overall credibility in providing evidence for a given regulatory procedure must be assessed and qualified.[1] The U.S. Food and Drug Administration (FDA) has released several guidance documents on modeling approaches that can be used in different phases or for specific types of analysis in the research and development of new products, including:

- *Population PK*, which offers recommendations on the use of population PK to help identify differences in drug safety and efficacy among population subgroups
- *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*, which describes the strategy for analyzing data in the exposure-response modeling process
- *Physiologically Based PK Analyses*, which outlines the recommended format and content for physiologically based PK analyses to support regulatory submissions

In December 2021, the FDA released a draft guidance document titled Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions, signaling that the agency is open to *in silico* methods. In this document, the FDA acknowledges that the use of *in silico* methods in regulatory submissions, whether to generate information supporting safety and efficacy or to complement real-world clinical trials, is well-established and increasing rapidly.[2]

The agency also provides a generalized framework for assessing the credibility of *in silico* modeling in medical device regulatory submissions. This framework comprises nine steps (*Figure 1*):[1]

1. Stating the question of interest
2. Stating the context of use
3. Assessing model risk
4. Identifying credibility evidence to be collected
5. Stating credibility factors and goals
6. Performing a prospective adequacy assessment
7. Executing studies and/or analyzing previously collected data
8. Performing a post-study adequacy assessment
9. Preparing a final Credibility Assessment Report

The framework also includes an option to submit a pre-submission meeting request to the FDA to receive feedback on the proposed plan, demonstrating the agency's willingness to partner with developers to incorporate *in silico* methods into product evaluation. Moreover, the FDA's new budget indicates that the agency will start to accelerate—and be more receptive to—*in silico* modeling.

Constructing an *in silico* design

There are three general steps for constructing an *in silico* design:

1. **Understanding the pathophysiology of the disease.** This involves constructing either a disease model or models that characterize the disease areas of interest
2. **Constructing sub-models of the drug candidate.** This involves generating mechanistic models by breaking down the pathophysiology into sub-models that more effectively characterize the disease.
3. **Generating virtual patients.** This involves converting the mechanistic models into mathematical models that can be used to simulate virtual patients.

Ensuring applicability of *in silico* methods

The success of *in silico* methods and virtual patient controls relies heavily on the creation of a robust and clinically meaningful disease model, which may not always be possible. For pediatric subpopulations or rare diseases, where natural history is poorly understood and patients are scarce, *in silico* modeling may be instrumental in moving clinical programs forward. The FDA has started to demonstrate increased flexibility in terms of understanding how *in silico* testing can be implemented in less well-defined disease models. Engaging in a pre-submission or Q-submission meeting gives developers an opportunity to educate regulators on how computational methods and simulations could be used in these circumstances.

Sample construct of an *in silico* design

In studies of non-alcoholic steatohepatitis (NASH), it may be unethical to include a placebo arm due to the severity of the disease. Thus, a synthetic control arm may be useful. The first step in constructing an *in silico* design might be breaking down the pathophysiology of NASH into disease areas such as cholesterol and bile acids, apoptosis and endoplasmic reticulum stress, fibrosis, fatty acids and lipotoxicity, and the immune system. Then, sub-models would be created within each disease area by extracting data from literature or earlier studies to help characterize the underlying mechanisms of disease. Close interaction among physicians, pharmacologists, and statisticians is required for defining, calibrating, and validating these mechanistic models. Once validated, the mechanistic models are converted into mathematical equations using available raw data from previous studies to simulate virtual patients.

Conclusion

Mechanistic *in silico* modeling has emerged as a valuable tool in both preclinical and clinical evaluations of new medical products. Regulatory agencies are increasingly open to accepting evidence generated by *in silico* methods in submissions, and certain types of studies—including PK-related drug-drug interactions, therapeutic trials for small populations, cardiac safety studies, and dose-finding studies—are routinely replaced by modeling and simulation under well-defined conditions.[1] Mature, validated models may also be used to supplement human clinical trials and may help to reduce human experimentation and accelerate development.

At Premier Consulting, we can help researchers and developers assess the feasibility of *in silico* methods and integrate them into development programs for drugs, biologics, and medical devices. Premier Consulting is a strategic product development and global regulatory consulting group dedicated to helping biotech innovators transform their life-changing ideas and breakthrough science into new medical treatments. Our end-to-end solutions in strategy; regulatory; nonclinical; chemistry, manufacturing, and controls (CMC); quality; and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results.

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[1] *Viceconti M, et al.* In silico *trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. Methods. 2021;185:120-127.*[2] *Eurordis.*

[2] *U.S. Food and Drug Administration. Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions, December 23, 2021. Available at https://www.fda.gov/media/154985/download.*

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Premier Consulting is a strategic product development and global regulatory consulting company dedicated to helping biotech innovators transform their life-changing ideas and breakthrough science into new medical treatments.

Our end-to-end solutions in strategy, regulatory, nonclinical, clinical, CMC, quality, and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results for sponsors and the patients they serve.

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