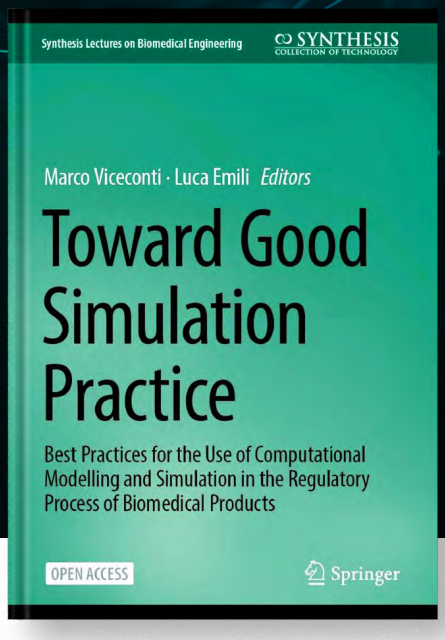
InSilicoTrials



In silico methodologies for regulatory approval:

Co-edited by InSilicoTrials' CEO Luca Emili, with contributions from 138 global experts, including 13 FDA Modeling & Simulation Working Group members.

Introduction to Good Simulation Practice

Good Simulation Practice (GSP) is a set of "good practices" designed to ensure the quality and reliability of computer modeling and simulation (CM&S) in the assessment of medical products. This concept draws parallels to established standards in biomedicine such as Good Clinical Practice (GCP) and Good Laboratory Practice (GLP), which are frameworks intended to ensure the safety, efficacy, and quality of medical products and interventions. While GCP and GLP are well-established under the guidance of international bodies like the Organisation for Economic Co-operation and Development (OECD) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), GSP is an emerging set of guidelines. It is aimed at leveraging CM&S for regulatory decision-making and supporting the development, optimization, and safety evaluation of medical products. GSP encompasses the use of "*In silico* Methodologies"—a term used to denote CM&S as tools in regulatory processes, particularly for medical devices and pharmaceuticals.

VPH Institute
Building the Virtual Physiological Human

INSILICO WORLD

Avicenna Alliance
Association for Predictive Medicine

History of Good Simulation Practice

Since 2002, computational modeling has been increasingly incorporated into premarket approval applications for medical devices, as evidenced by its inclusion in at least 21% of such applications by 2019. (Morrison et al., 2019) This integration signifies a broader acceptance and recognition of the importance of CM&S within the regulatory framework. The American Society of Mechanical Engineers (ASME) Verification & Validation (V&V)-40 standard, published initially in 2018 and specific to medical devices, marks a significant milestone in formalizing these practices. However, broader regulatory frameworks and guidance documents specific to the use of CM&S across various medical products were still underdeveloped as of the early 2020s.

FDA Mention of GSP in Their Regulatory Report

The push towards a standardized GSP was catalyzed by the collaborative efforts of communities like the Virtual Physiological Human (VPH) Institute and the Avicenna Alliance, which represent academic and industrial stakeholders in *in silico* medicine, respectively. These groups have been instrumental in gathering consensus and fostering discussions around the best practices for CM&S. The result was a position paper that emerged from the *In silico* World project and its associated Community of Practice (ISW_CoP), which comprises over 500 experts. This position report titled: **Toward Good Simulation Practice: Best Practices For The Use Of Computational Modelling & Simulation In The Regulatory Process Of Biomedical Products** proposed a systematic framework for using CM&S throughout the life cycle of medical products, focusing specifically on enhancing safety and efficacy assessments. It laid the groundwork for potential future standards and offered a structured approach to using *in silico* methodologies as alternatives or complements to traditional experimental methods. The paper, non-binding yet influential, serves as a foundational text aiming to orient future policies and standardization efforts in this rapidly evolving field.

"The implementation of Good Simulation Practice is seen as a key factor in ensuring the sustained success of M&S in the healthcare field."

Pras Pathmanathan
Office of Science and Engineering Laboratories
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Silver Spring, Maryland, USA

FDA U.S. FOOD & DRUG ADMINISTRATION

Insights from the chapters

01. Introduction

In silico methodologies can be categorised depending on how they are used as an alternative to experimental methodologies: **to refine, reduce, and replace in vitro, animal, or human experimentation.**

02. Theoretical Foundations of Good Simulation Practice

» The human mind can only understand reality through models. Models are finalised cognitive constructs of finite complexity that idealise an infinitely complex portion of reality. Their usefulness is measured by their ability to capture the functional aspects of interest of the portion of reality that we are investigating. This measure is called the Degree of Analogy.

» In each portion of reality, the functional aspects of interest can be observed experimentally or predicted through inductive or deductive reasoning. All these methods of investigation are models. However, the Degree of Analogy of experimental models can be directly inferred, whereas that of predictive models must be demonstrated by comparisons with controlled experiments. In other words, experiments are not necessarily more trustworthy than predictions, but their trustworthiness is easier to assess.

» Predictive models can be divided into predominantly data-driven models and predominantly mechanistic models. In predominantly mechanistic models, the Degree of Analogy can be established by decomposing the predictive errors in numerical, aleatoric, and epistemic errors through a process known as Verification, Validation, and Uncertainty Quantification. But in predominantly data-driven models, the Degree of Analogy can only be estimated by induction, using a total product lifecycle regulatory approach.

03. Model Development

» Establish your model's Context of Use - CoU(s), related risks and requirements in a model development plan before defining and implementing the model.

» Identify relevant industry standards for your model.

» When designing the model for your CoU(s), consider relevant domain-specific standards, parameter identifiability and options for software verification and validation. Document the decision-making process for the conceptual model and the resulting limitations in the model design document.

» Implement the model software based on established good practices for software engineering and development and follow a test-driven development paradigm.

» Consider the entire model life cycle in the model management plan and secure adequate resources for maintenance.

04. Model Credibility

» The credibility of *in silico* methodologies based on predominantly mechanistic models can be effectively demonstrated following the risk-based approach to model verification, validation and uncertainty quantification as detailed in the ASME VV-40:2018 technical standard. The credibility of methodologies based on predominantly data driven models should follow a Predetermined Change Control Plan, where the model's credibility is periodically retested using new test data.

» Where applicable, the validation of predominantly mechanistic models should be performed separately for the physiological modelling layer, the disease modelling layer, and the treatment modelling layers.

» Regulators qualifying *in silico* methodologies to be used as drug-development tools expect that prior knowledge is generally scarcely informative.

» Regulators currently require that *in silico* methodologies used as drug-development tools are qualified following the same regulatory framework used for experimental methodologies. In particular, the technical validation is expected to be separated from the clinical validation.

» In analogy to what is proposed to evaluate the applicability of the analytical validation activities for biomarkers, we recommend describing and assessing the collection/acquisition, preparation/processing, and storage of the comparator data used to validate *in silico* methodologies.

05. Possible Qualification Pathways for *In silico* Methodologies

» Regulatory agencies should increase the interdisciplinarity of scientific advisory panels and develop targeted staff re-training programs on the opportunities and risk those innovative technologies pose.

» Regulatory agencies should explore whether existing qualification pathways should be adapted to include *in silico* methodologies properly or if creating new qualification pathways for these methodologies is more prudent.

06. Possible Health Technology Assessment Pathways

In silico methodologies can provide evidence to be used in Health Technology Assessment for:

» Demonstrating value to payers by predicting the real-life benefit and the optimal target population for drugs or medical devices.

» Transposing Phase 3 trial results into virtual populations representative of specific geographies and context.

» Benchmarking competing health technologies by also considering the market access of new technologies and the achieved effectiveness in the real world.

07. Ethical Review of *In silico* Methodologies

In silico methodologies offer several potential ethical benefits:

» Refining human experimentation means reducing the risks to which the enrolled subjects are exposed but also increasing the benefit/risk ratio of the experimentation, maximising the regulatory utility of the information obtained by exposing the enrolled subjects to such risks.

» When an *in silico* methodology can reduce the number of subjects who need to be enrolled, and thus the number of persons exposed to the study's risks, this represents a direct ethical benefit.

» *In silico* methodologies can provide an ethical alternative where human experimentation is unethical.

» *In silico* methodologies can help in including in clinical studies the necessary diversity (e.g., of ethnicity, gender, age, physical conditions) that, for any reason, might be difficult to achieve experimentally.

» IEC/IRB should evaluate the ethical impact of *in silico* methodologies as they do for any other study methodology. With two special cases, both related to its use to replace human experimentation:

◊ For studies where the *in silico* methodologies are used to partially replace human experimentation, the ethical review of the study by the IEC/IRB is necessary. Still, it should be based on the regulatory qualification opinion on the *in silico* methodology.

◊ On the contrary, for studies that involve only *in silico* methodologies and no human experimentation, the IEC/IRB review is not necessary, with the notable exception of

the ethical management of clinical data to design, inform, or validate the *in silico* methodology.

» To properly assess the ethical implications of *in silico* methodologies, IEC/IRB also need technical expertise. Initially, the IEC/IRB may rely on the opinions of external experts. Still, in the long run, it is reasonable to expect the inclusion of technology experts in the IEC/IRB.

08. The Sponsor

» The Sponsor of an *in silico* clinical trial, as well as the CRO that manages it, should have in staff the necessary technical expertise.

» Computer modelling and simulation services required to support clinical development studies should be performed as per the recommendations provided in ICH E9 Statistical Principle for Clinical Trials and be in line with existing regulatory guidelines on the use of CM&S in drug/medical device development plan.

» All computerised systems used in *in silico* clinical studies should be GxP-compliant.

09. The Investigator: Modellers and Analysts

» Role and responsibilities of the Investigator are defined in relation to the sponsor and their mutual agreement, which should be documented.

» A record should be kept of eventual third parties contracted to assist in the CM&S activities and they should be adequately informed about the investigational product by the Investigator.

» The Investigator needs to ensure and convince stakeholders that all relevant qualifications are available in the team of experts involved in the study

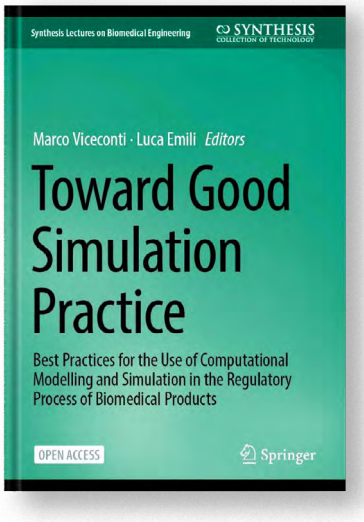
» The Investigator needs access to human resources, support, computing resources, and feedback necessary to accomplish the task as agreed with the Sponsor.

» All source documents, codes, results, and data should be adequately version controlled, recorded, maintained, and retained by the Investigator/institution, with the Sponsor's support, for the duration initially agreed with the Sponsor.

» The Investigator is responsible for providing regular and final written reports on the conduct of the study and its conclusions

by following appropriate reporting guidance.

» The Investigator and the Sponsor should implement proper data safety and security measures, complying with relevant regulations (GDPR, etc.).



Learn more on how to get started with Gen AI-powered *In silico* Data Modeling.

Download your free copy here:
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