Introduction

1

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1.1 Scope of this Document

The term GxP indicates a collection of good practices, e.g., quality guidelines, to ensure that a product is safe and meets its intended use. The most important examples of GxP in biomedicine are Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). The GLP are curated by the Organisation for Economic Co-operation and Development (OECD); they provide "a managerial quality control system covering the organisational process and the conditions under which non-clinical health and environmental studies are planned, performed, monitored, recorded, reported, and retained (or archived)".[1] The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) curates the GCP. GCP provides an international ethical and scientific quality standard for clinical trials to facilitate the regulatory authorities' mutual acceptance of clinical evidence in the various ICH regions. GxP guidelines are available

[1] https://www.oecd.org/chemicalsafety/testing/overview-of-good-laboratory-practice.htm.

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for different industrial sectors, including foods, medical products, medical devices, and cosmetics. In some cases, the GxP simply expresses best practices within an industrial sector; in others, they are elevated to quasi-regulatory standards, which must be met to achieve specific regulatory approval.

The use of Computational Modelling and Simulation (CM&S) in clinical medicine is usually referred to as In Silico Medicine. The term was first used in PubMed in 2013 and has become popular since then. The academic research community loosely uses the term In silico Trials to indicate the use of CM&S to assess the safety and/or efficacy of new healthcare products, be they medical devices, medicinal products, or others. The term appeared in PubMed in 2002 (Ashelford et al., 2002). One of the issues with this term is that it uses the term "trial" loosely, whereas in the regulatory domain, the term is used in a much more specific way. To avoid such confusion, going forward, we will use the term In silico Trials only in a colloquial way. Instead, we will use the term **In Silico Methodology** to indicate any use of CM&S as, at any level, a regulatory decision support tool on new medical products for which a marketing authorisation is requested, whether medical devices, medicinal products, or others.

This position report on Good Simulation Practice (GSP) does not emerge from a vacuum. For example, since 2002, at least 21% of 565 original premarket approval (PMA) applications for medical devices included computational modelling efforts provided in the Summary of Safety and Effectiveness Data (SSED) (Morrison et al., 2019). Thus, our community of practice, in general, and major regulatory agencies, in particular, have been reflecting on using predictive models as a development and de-risking tool for medical products. In some cases, such reflections took the form of guidance documents or technical standards for specific uses. Annexe 1 reviews the existing regulatory guidance on the topic.

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While the regulatory community is actively engaged in developing a comprehensive regulatory framework that includes the use of computational simulations to support a medical decision with the introduction of the concept of "Software as a Medical Device" (SaMD), a similar level of engagement has been so far absent for the broader application of CM&S in regulatory decision-making processes. There is only one detailed resource for guiding the validation of In silico methodologies applied to medical devices: the American Society of Mechanical Engineers (ASME) Verification & Validation (V&V)-40 standard,[2] originally published in 2018, whose original scope was limited to medical devices (hereinafter referred to as VV-40:2018).

While the VV-40:2018 standard is a valuable resource, the authors of the present document believe there is a need for a document that summarises the good practices in using In silico methodologies to support the regulatory process for all kinds of medical products. Such a document could play a role similar to that of the Good Clinical Practice (GCP), the Good Laboratory Practice (GLP), or the Good Manufacturing Practice (GMP) guidelines. Thus, by analogy, it could be named "Good Modelling & Simulation Practice for medical products", and hopefully, it may be curated and/or adopted by the members of the International Medical Device Regulators Forum (IMDRF). A GxP may either remain a voluntary guideline or be elevated to a standard by standardisation bodies such as the International Council for Harmonisation (ICH) or the International Organization for Standardization (ISO). The compilation of Good Modelling & Simulation Practice for medical products is a challenging task. In silico methodologies have started to be adopted only recently, and the experience is limited. Also, the expertise required to write such a document is extremely multidisciplinary.

The VPH Institute[3] and the Avicenna Alliance[4] are two international not-for-profit organisations that represent all practitioners in the field of In silico Medicine: the first represents the academic community, and the second the industrial community. The EU-funded In Silico World project[5] operates an online forum, in collaboration with the VPH Institute and the Avicenna Alliance, called the In Silico World Community of Practice (ISW_CoP).[6] The over 500 experts participating in this ISW_CoP share a common professional or educational interest for In silico Medicine. Within this community, a consensus emerged on the opportunity to collaboratively compile a position report aimed to summarise the current thinking within the ISW_CoP on the good practices for In silico methodologies, so as to provide a basis for the future development of a formal standard on the Good Modelling & Simulation Practice for medical products.

[2] https://www.asme.org/codes-standards/find-codes-standards/v-V-40-assessing-credibility-computational-modeling-verification-validation-application-medical-devices.

[3] https://www.vph-institute.org/.

[4] https://avicenna-alliance.com/.

[5] https://insilico.world/.

[6] https://insilico.world/community/.

Thus, the scope of this document is to provide a list of the best practices for using computer simulation to assess the safety and efficacy of medical products, which emerged through a consensus process within our ISW_CoP. The form we chose is a "Position Report"—a public document providing an expert opinion to orient policies or standards. In this sense, the present document is not binding and represents only the consensus among some field experts. However, we hope this document might provide a starting point for a future standardisation effort by an appropriate body. And while CM&S is used throughout the entire life cycle of medical products, including discovery and design, verification, development, optimisation, re-design, etc., this position report focuses only on their use to assess the safety and efficacy of medical products.

The first output that the ISW_CoP produced was a systematic analysis of all possible Contexts of Use (CoU) for In Silico Methodologies (Viceconti et al., 2021a). CoUs concisely describe how the new methodology will be used in the medical products' development and regulatory assessment process.

We used the taxonomy presented in Table 1.1 to organise the list of potential CoUs. The safety and efficacy of medical products are usually investigated using experimental methodologies: **in vitro and ex vivo** experiments, **in vivo animal** experimentation, or **in vivo human** experimentation. In silico Methodologies are a valid alternative to these experimental methodologies. Using terminology that was first used to categorise alternatives to animal experimentation, In Silico methodologies can be used to **reduce** the experiment (fewer bench tests, fewer animals enrolled, fewer patients enrolled), **refine** the experiment (reduce the suffering of animals, reduce risks for humans, improve the ability of pre-clinical studies to predict the clinical outcome, generalise the experimental finding, etc.), and **replace** the experiment (replace the experiment entirely). This produces a 3×3 taxonomy (Table 1.1), which will be used in the remainder of this document.

1.2 The Critical Elements of a Good Simulation Practice Standard

The critical elements that any reflection on the GSP should address are the theoretical foundations, the development and credibility assessment of the models, the possible regulatory and Health Technology Assessment (HTA) pathways, the ethical review process when In silico methodologies are involved, and the role of the sponsors and the investigators. These aspects will be addressed in the following chapters; here below, we provide a brief summary.

1.2.1 Theoretical Foundations of Good Simulation Practice

Regulatory science focuses on problems very close to clinical application. Thus, in general, its practitioners are not interested in the more fundamental aspects treated by

Table 1.1 Taxonomy of In silico methodologies

	Reduce	Refine	Replace
Preclinical In vitro/Ex vivo experiments	Reduce the number or duration of in vitro/ ex vivo experiments	Improve the predictive accuracy of safety and/or effectiveness provided by the in vitro or ex vivo experiment	Replace a portion or all the required in vitro or ex vivo experiments
Preclinical animal experiments	Reduce the number of animals involved in the experiment, or its duration (adoption of sustainability principles)	Alleviate the suffering of the animals involved, or improve the predictive accuracy of the safety and/or effectiveness provided by the animal experiment (solving or acknowledging animal protection issues)	Replace animal experiments used for the prediction of the expected safety and/or effectiveness of a new treatment during clinical experimentation
Clinical human experiments	Support the design of clinical experiments. Reduce the number of clinical studies, their duration, or the number of subjects involved. Solving scarcity on patients population related to rare diseases and where patients are children	Reduce the risks for the humans involved or improve the predictive accuracy of the safety and/or effectiveness provided by the human trials	Replace human experiments used for the prediction of the expected safety and/or effectiveness of a new treatment

mathematics, philosophy of science, and epistemology (study of human knowledge). However, the extreme interdisciplinarity involved with computational modelling and simulation in the development and de-risking of medical products makes it difficult for every single group of experts to use the epistemological guidelines accepted and established in the practice of their discipline. Having solid theoretical foundations helps in these cases to find common ground across different disciplines and epistemologies. The goal of Chap. 2 is to provide such foundations.

1.2.2 Model Development

A computer model is, first and foremost, a software artefact; as such, it must be developed and tested using the quality assurance principles in software engineering. While this is a relatively mature topic for regulatory science, which has been specialised for biomedical applications with the introduction of the so-called Software as a Medical Device category of medical devices, there are some specificities of providing quality assurance for software with predictive purposes that require specific treatments in a future GSP standard. In Chap. 3, we analyse this topic in full detail.

1.2.3 Model Credibility

Even if a model has been developed with the highest possible quality standard, this does not guarantee that the predictions this model provides can be trusted per se. The problem of assessing the credibility of a model's prediction is a problem that has been addressed in the regulatory science of high-risk products such as nuclear power plants or passenger aircrafts. Yet, in the biomedical domain, this is a very recent topic.

Annexe 1 provides an overview of all regulatory documents that address this problem. Still, even the most recent efforts, such as the ASME VV-40:2018, leave an ample portion of the territory untouched. VV-40:2018 targets the development of medical devices, leaving out drug development and the development of Advanced Therapeutic Medicinal Products (ATMPs). The classic VVUQ approach the VV-40:2018 refers to is robustly defined for purely mechanistic models, i.e., models built exclusively from widely accepted theories; however, many predictors are now built using data-driven methodologies, where no theory is involved. Furthermore, in practice, most models are called *grey-box models* because they are built by combining mechanistic and empirical knowledge. In Chap. 4, we provide a systematic discussion of the topic.

1.2.4 Possible Regulatory Pathways

The regulatory assessment of In silico methodologies does not fit well with the traditional separation between drugs and medical devices. It must include elements of technical validation more common in the regulatory pathways of medical devices, but also elements of clinical validation more common in the regulatory pathways of medicinal products. In Chap. 5, we explore the issue of which regulatory pathway is most suitable to qualify In silico methodologies to be used in the regulatory assessment of new medical products. We describe four possible pathways and discuss their pros and cons.

1.2.5 Possible Health Technology Assessment Pathways

In silico methodologies can play an essential role in the marketing authorisation of new medical products, their cost–benefit assessment, the definition of prescriptive appropriateness, and post-marketing surveillance. In Chap. 6, all these aspects are considered and discussed with concrete examples.

1.2.6 Ethical Review of In Silico Methodologies

Before it starts, every experimental study on humans must be reviewed by an independent organisation known in Europe as Independent Ethics Committee and in the USA as Institutional Review Board. Chap. 7 explores if and how such a review process needs to change when In silico methodologies are involved.

1.2.7 The Role of the Sponsor in In Silico Methodologies

The sponsor is "an individual, company, institution, or organisation which takes responsibility for initiating, managing, and/or financing a clinical trial".[7] The sponsor plays a vital role in conventional trials, codified in detail in various standards and guidelines, such as the Good Clinical Practice. Chap. 8 explores how such a role needs to be extended when In silico methodologies are involved.

1.2.8 The Role of the Investigator in In Silico Methodologies

The investigator is another role that needs to be partially redefined when the clinical evaluation of a new medical product involves In silico methodologies. In a clinical study, the Investigator is the person involved in running the study. The Investigator may help prepare and carry out the study, monitor the study safety, collect and analyse the data, and report study results. When In silico methodologies are involved, the Investigator is also responsible for carrying out the modelling tasks and generating the In silico evidence. Chap. 9 explores how these additional responsibilities change the Investigator's profile and role.

[7] https://toolkit.ncats.nih.gov/glossary/clinical-study-sponsor/.

1.3 Essential Good Simulation Practice Recommendations

– 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.

References

Ashelford, K. E., Weightman, A. J., & Fry, J. C. (2002). PRIMROSE: A computer program for generating and estimating the phylogenetic range of 16S rRNA oligonucleotide probes and primers in conjunction with the RDP-II database. *Nucleic Acids Research, 30*, 3481–3489. https://doi.org/10.1093/nar/gkf450

Morrison, T. M., Hariharan, P., Funkhouser, C. M., Afshari, P., Goodin, M., & Horner, M. (2019). Assessing computational model credibility using a risk-based framework: application to hemolysis in centrifugal blood pumps. *ASAIO Journal, 65*, 349–360. https://doi.org/10.1097/MAT.0000000000000996

Viceconti, M., Emili, L., Afshari, P., Courcelles, E., Curreli, C., Famaey, N., Geris, L., Horner, M., Jori, M. C., Kulesza, A., Loewe, A., Neidlin, M., Reiterer, M., Rousseau, C. F., Russo, G., Sontag, S. J., Voisin, E. M., & Pappalardo, F. (2021). Possible contexts of use for in silico trials methodologies: a consensus-based review. *IEEE Journal of Biomedical and Health Informatics, 25*, 3977–3982. https://doi.org/10.1109/JBHI.2021.3090469