VPH Institute
Building the Virtual Physiological Human

Call for evidence on Targeted revision of the EU rules for medical devices and in vitro diagnostics

Leveraging computer modelling and simulation methodologies including AI, to mitigate current challenges and prepare for future needs.

The VPH Institute (VPHi), an international scientific society representing experts in **in silico medicine** (use of computer modelling and simulation in health and care) from academia, research institutes, hospitals, and health technology assessment bodies, supports the European Commission's consultation on the evidence for revision of the Medical Device Regulation (MDR).

While the challenges inherent in the regulatory landscape of medical devices are widely discussed by many contributors from industry, clinical societies, SMEs, NGOs, etc., VPHi asserts that emerging Computer Modelling and Simulation (CM&S) technologies, including Artificial Intelligence (AI), are ideally positioned to address the **pressing concerns surrounding evidence generation for pre-market and post-market phases.** It can **address concerns on device safety** and the **increasing costs** that impact the availability of novel treatments for the European population.

As a non-profit scientific society, VPHi draws upon and shares the **learnings from EC-funded policy initiatives**, such as FP7, Horizon, and Digital Europe calls, along with **tangible scientific evidence** demonstrating how these in silico medicine technologies can be can be an enabling paradigm across the entire lifecycle of medical devices, from ideation and design to deployment and post-market surveillance.

We here present the evidence to leverage CM&S as a necessary enabler to address current bottlenecks and to act as an engine for competitiveness across the European healthcare sector.

We here present 6 areas for attention, with suitable solution and evidence:

i. A failure to recognize and address gaps in conventional clinical trials through emerging digital technologies like computer modelling and AI, leading to regulatory and adoption delays
ii. Impeding MDR clause and MDCG guidance on evidence from computer modelling and simulation testing
iii. Lack of unified authority, as well as qualified regulatory science tools / methodology for medical devices
iv. Latency in development and recognition of standards for regulatory and common specifications for MDR/IVDR compliance
v. Lack of channels for engagement with early innovators (e.g. academia, scientific consortium)
vi. Safety and Ethics in Human Testing Concern on safety and ethical aspects around responsible human testing

Yours sincerely,

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Summary of evidences

Feedback in the context of revising MDR and IVDR

1. Current challenges and possible solutions

1.1. A failure to recognize and address gaps in conventional clinical trials through emerging digital technologies, leading to regulatory and adoption delays

Current situation	**Solution(s)**
Advances in scientific and regulatory science, driven by the digital era, have introduced diverse, innovative evidence generation methods, such as digital twins, and in silico trials. These tools are crucial for augmenting conventional medical device testing and enabling next-generation clinical trials. However, the current EU Medical Device Regulation (MDR) and its implementation by organizations like the Medical Device Coordination Group and Notified Bodies, inadvertently restrict medical device assessment to reliance on conventional real-world randomized Clinical Trials (CTs).	**To advance medical product assessment, we must support and conduct all appropriate evidence generation methods, including (randomized) Clinical Trials, while simultaneously embracing novel technologies to augment them.** Specifically, the use of **in silico evidence** (computational modelling and simulation) must be considered **admissible across the entire product lifecycle and all clinical phases**. In a first instance, regulators should immediately begin by accepting in silico evidence – when proper credibility assessment of the evidence can be presented – for following applications: • **Recertifications** • **Post-Market Surveillance (PMS)** • **Orphan devices** • **Breakthrough devices** Restricting in silico methods solely to non-clinical testing will hinder technological progress and place regulatory science **"decades back from the technological strides."** This approach provides a practical, phased introduction before integrating in silico evidence into mainstream assessments.

Problem	Evidence
Randomized Controlled Trial (RCT) data, though highly valued for regulatory assessment, present significant challenges. RCTs focus on **predefined, restricted populations**, making clinical trial data **expensive, complex, and time-consuming to acquire**. This narrow focus introduces **residual uncertainty** for regulators and health technology assessors, resulting in **evidence gaps** that hinder a comprehensive assessment of a medical product's effectiveness in the broader patient population. On contrary, evidence from *in silico* technology allows digital representation of diseases, organs, interventions, populations while also objectively **quantifying the credibility and residual uncertainties**. Nevertheless, evidence from modelling and simulation are considered to be of low-quality or merely restricted to replacement of animal experiments, hence treated as non-clinical data.	While residual uncertainties in traditional evidence (animal, clinical data) are often difficult to objectively quantify, emerging digital evidence paradigms offer the potential of **extensively quantifying the predictive evidence** they generate. This is assured through V&V40 standard, a pioneering risk-based framework for credibility assessment of computational model, especially for use in medical devices.

1.2. Impeding MDR clause and MDCG guidance on evidence from computer modelling and simulation testing

Current situation	Solution(s)
The core issue is a **lack of consistent and comprehensive reference** to in silico methods across all relevant MDR clauses. This ambiguity allows for **subjective interpretation** by notified bodies, competent authorities and MDCG WG: categorizing computer modelling and simulation as non-clinical data to be used primarily in the **pre-clinical phase, preventing its full and intended use across the entire medical device lifecycle, from design and clinical trials to post-market surveillance**	In silico evidence, derived from computer modelling and simulated use testing, is essential across the entire medical device lifecycle. **The revised MDR must integrate this critical evidence fully and cease its restrictive categorization as a purely 'non-clinical' component.**

Problem	**Evidence**

The MDR text and accompanying MDCG guidance, undermines the *in silico* technologies potential to de-risk medical device experimentation in humans.
- MDR allows consideration of biophysical or modelling evidence in two places, BUT
  o ONLY under Annex I GSPR Chapter II and later in Annex VII Section 4.5 (a) -line2. The latter is associating in silico evidence as part of "non-clinical" evidence.
- MDCG guidance document (**MDCG 2020-6 -clinical evidence; MDCG 2024-10 Orphan devices**) considers modelling and simulation results as part of evidence appraisal, BUT,
  o **MDCG 2020-6 Appendix III** ranks simulation evidence, as "non-clinical data" and appraises it at rank 11th out of 12 possible evidences. Leading to *in silico* evidence being referred to as "low-quality" evidence sources**Error! Bookmark not defined.**.
  o **MDCG 2024-10** enlists data from computer modelling and simulate use testing , including software-based models as a source of "non-clinical" data.
	Internationally, **Computational Modelling and Simulation (CM&S) data** are increasingly leveraged to **reduce, refine, or in some cases replace** traditional bench, animal, and human testing for medical products (both medicines and devices). This advancement has resulted in **reduced exposure of human subjects to harm**, facilitated **earlier access to life-saving medical devices**, and lowered device development costs.
	
	For example,
	- Conduct safety testing of imaging systems (e.g. MRI 7 Tesla scanner)[1]. The US FDA reviewed the safety of the radiofrequency subsystem through computational modelling, simulations and rigorous experimental validation.
	- The approval of cardiac pacemaker leads compatible with MRI scanners, thereby safeguarding human exposure[2].
	- The VICTRE trial: an in-silico replica of a clinical trial for evaluating digital breast tomosynthesis as a replacement for full-field digital mammography[3,4].

[1]US FDA clears first 7T magnetic resonance imaging device - https://www.fda.gov/news-events/press-announcements/fda-clears-first-7t-magnetic-resonance-imaging-device
[2] FDA - MDDT Summary of evidence and basis of qualification decision for Virtual MRI Safety Evaluations of Medical Devices - 2021 - https://www.fda.gov/media/154181/download?attachment
[3] VICTRE: *In silico* Breast Imaging Pipeline - The regulatory science tool is a set of computer models that allow for the generation of *in silico* breast radiographic images for the evaluation of digital mammography (DM) and digital breast tomosynthesis (DBT) devices. Accessed via: https://cdrh-rst.fda.gov/victre-silico-breast-imaging-pipeline
[4] Sharma D, Graff CG, Badal A, Zeng R, Sawant P, Sengupta A, Dahal E, Badano A. Technical Note: *In silico* imaging tools from the VICTRE clinical trial. Med Phys. 2019 Sep;46(9):3924-3928. doi: 10.1002/mp.13674. Epub 2019 Jul 17. PMID: 31228352

1.3. Lack of unified authority, as well as qualified regulatory science tools / methodology for medical devices

Current situation	**Solution(s)**
The **absence of a unified medical device agency** in Europe contributes to a longstanding gap in recognized **regulatory science tools and methodologies**. In contrast, the United States has seen a significant boost in the **qualification of methodologies as regulatory science tools, for medical devices**. Europe continues to lag, hindered by a **lack of central oversight and consensus** on evidence generation paradigms, which results in the **siloed and fragmented adoption** of regulatory science advancements.	The medical device ecosystem in Europe requires a **unified medical device agency** to move past reliance on pilot programs and expert panels. By establishing a mechanism to **regularly review and qualify regulatory science tools** (such as Medical Device Development Tools) and their validation datasets, this agency could **systematically build mutual expertise** regarding evidence generation and review. This approach would be more efficient for all stakeholders and **significantly enhance regulatory confidence**.
Problem	**Evidence**
The trends in regulatory advancement clearly favour the US, which benefits from a dedicated qualification program for methodologies supporting the development and evaluation of both devices[5] and drugs[6]. **Europe continues to limits this pathway only to novel methodologies that support development and evaluation of medicines**[7]. For devices, it continues to rely on expert panels for high-risk devices.	- Medical Device Development Tool program - Center for devices and radiological Health (CDRH) - https://www.fda.gov/medical-devices/medical-device-development-tools-mddt - EMA's Qualification program for research and development of pharmaceuticals – 'Qualification of novel methodologies for medicine development' https://www.ema.europa.eu/en/qualification-novel-methodologies-medicine-development

[5] For Medical Device Development Tool program - Center for devices and radiological Health (CDRH) - https://www.fda.gov/medical-devices/medical-device-development-tools-mddt
[6] FDA's – Qualification program for Drug Development Tools https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-ddts
[7] EMA's Qualification program for research and development of pharmaceuticals – 'Qualification of novel methodologies for medicine development' - https://www.ema.europa.eu/en/qualification-novel-methodologies-medicine-development

1.4. *Latency in development and recognition of standards for regulatory and common specifications for MDR/IVDR compliance*

Current situation	**Solution(s)**
There is a **lack of recognition by Notified Bodies** of international or national standards concerning **emerging technologies**.	**International cooperation is essential, as this call for evidence advocates for.** In the domain of Computational Modelling and Simulation (CM&S) and Artificial Intelligence (AI), a substantial number of standards and guidance documents **have already been established or jointly developed** by the global scientific community.
Problem A regulatory paradox exists where standards for emerging technologies, such as CM&S, are **demanded as a prerequisite** for evidence acceptance, even as those standards are **non-existent or under active development**. Harmonization efforts with international bodies (like ISO/IEC) are complicated because: - Direct duplication of foreign standards (e.g., from the USA or South Korea) is prevented by copyright. - Developing equivalent standards in Europe is a lengthy process (**3-5 years**), resulting in a standard that is often obsolete by the time of publication, as the international version has already progressed. Therefore, Europe is hampered from leveraging global standards, despite contributing to their development.	**Evidence** List of standards and guidance in US, which are long published but remains under-recognised in Europe: - ASME V&V 40 (2018[8]); - FDA (2023[9])

[8] Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices V&V 40 – 2018. American Society of Mechanical Engineer ASME, 2018. 60p. ISBN: 9780791872048.
[9] US FDA - Credibility of Computational Models Program: Research on Computational Models and Simulation Associated with Medical Devices - LINK

1.5. Lack of channels for transparent engagement with early innovators

Current situation	Solution(s)
Disruptive medical device technology often originates in academic institutions and scientific research centres. Unfortunately, these early innovators **lack a clear and simple pathway** for engaging with regulators, Notified Bodies, and expert panels.	**Europe needs regulatory scientific forums for medical devices** that are equivalent to the EMA's Scientific and Methodological working parties for pharmaceuticals. Scientific consortia must have dedicated pathways for **early engagement with regulators** at the beginning of the device lifecycle. By utilizing mechanisms like **early feasibility studies** and **pre-competitive consultations** within the research and innovation (R&I) ecosystem, we can streamline European innovations to ensure they are better prepared for successful **translation into technology for our patients**.
Problem	**Evidence**
Despite being at the forefront of medical device innovation, EU-funded R&I consortia have **very limited interaction** with the regulatory community. This mutual disconnect is detrimental: regulatory actors are unable to **gain early exposure** to emerging technologies, while researchers lack a pathway for the **adoption and integration** of their innovative tools into the regulatory review process.	U.S. FDA's Pre-submission system is open for academics. Regulatory science tools and MDDT programs are open for scientific consortia.

1.6. Concern on safety and ethical aspects around responsible human testing

Current situation	Solution(s)
	Advanced CM&S representations (e.g., in silico bench/animal/human testing paradigms, personalised digital twins) allow simulation of real-world pre-clinical, clinical and post-market scenarios. This helps **reduce the risk of exposing humans to unsafe or unethical clinical investigations** and can capture possible adverse reactions ahead of time.

Problem	Evidence
Need to reduce the risk of exposing humans to unsafe or unethical clinical investigations and can capture possible adverse reactions ahead of time.	Favre P, Bischoff J. Identifying the patient harms to include in an *in silico* clinical trial. Comput Methods Programs Biomed. 2023 Nov;241:107735. doi: 10.1016/j.cmpb.2023.107735.

2. Synthesis of current state of computer modelling and simulation - in Europe

Briefly, computer (*in silico*) modelling and simulation (CM&S) methodologies can be used throughout the entire lifecycle of medical products, be it for design, development, testing, assessment or post-market surveillance. Likewise, *in silico* methodologies may reduce, refine or replace diverse evidence sources, be it biophysical test, simulated tests, animal test as well as human testing. These CM&S technologies continue to advance and establish themselves **from being research methods to regulatory science tools**, thus becoming versatile for use in design, testing, pre-clinical, clinical or post-market phases.

European Commission driven innovation programs continue to recognize and value the progression of in silico methodologies, by supporting novel initiatives to support regulatory science for healthcare. This unique knowledge-treasure in Europe is standing by to address not only the challenges, but also uniquely power the medical device innovation and competitiveness of EU healthcare industry in global scale.

2.1. EU funded innovation within in silico medicine

Briefly, the output of **EC funding programs and R&I innovation projects**, supporting the regulatory value of in silico medicine:

- *In silico* trials for developing and assessing biomedical products[10], leading to projects[11]
- Accelerating the uptake of computer simulations for testing medicines and medical devices[12], leading to several EU-funded projects, including *In silico* World[13], SIMcor[14] and SimCardioTest[15], in which VPH Institute has been part of and played the ecosystem organisation role.
- Developing an ecosystem for digital twins in healthcare[16].

[10] H2020 – 2016-17 - In-silico trials for developing and assessing biomedical products - https://cordis.europa.eu/programme/id/H2020_SC1-PM-16-2017
[11] STriTuVaD In Silico Trial for Tuberculosis Vaccine Development, INSIST IN-Silico trials for treatment of acute Ischemic STroke,
[12] H2020 -2020 - Accelerating the uptake of computer simulations for testing medicines and medical devices - https://cordis.europa.eu/programme/id/H2020_SC1-DTH-06-2020
[13] https://insilico.world/
[14] https://www.simcor-h2020.eu/
[15] https://www.simcardiotest.eu/wordpress/
[16] DIGITAL -2021 - An ecosystem for digital twins in healthcare - https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/digital-2021-deploy-01-twins-health

- Personalised disease prediction and management using computational models[17].

Key position paper synthesizing the current state of knowledge in the field of in silico medicine

- *'Roadmap for in silico trials*[18] *(2016)',*
- *'Concept and early adoption of in silico trials*[19] *(2018)',*
- *'Regulatory pathway of in silico methods for medicinal products*[20,21] *(2020),*
- *'Possible Contexts of Use for In silico trials*[22] *(2021)',*
- *'Regulatory pathway for devices*[23] *(2022)', and*
- *'Advancing In silico Clinical Trials for Regulatory Adoption (2024)*[24]'.
- *'A moonshot vision From the digital twins in healthcare to the Virtual Human Twin(*2024)[25],
- Community-driven Good Simulation Practise book[26,27].

2.2. CE Marked Medical device products on in silico medicine technologies

Medical device products with successful FDA Certification and are on path to or already have CE Marking

- inHEART - France
  - inHEART™ - 2019
  - inHEART deliver **AI-enabled, digital twin of the heart** to advance the care of patients living with cardiac disease. The digital twin of the heart for image guided ablations.

[17] Horizon -2023 - Integrated, multi-scale computational models of patient patho-physiology ('virtual twins') for personalised disease management - https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-hlth-2023-tool-05-03
[18] 2016: Avicenna Alliance Roadmap: Viceconti, Marco & Henney, Adriano & Morley-Fletcher, Edwin. (2016). *in silico* Clinical Trials: How Computer Simulation will Transform the Biomedical Industry. https://doi.org/10.13140/RG.2.1.2756.6164.
[19] 2018: Francesco Pappalardo, Giulia Russo, Flora Musuamba Tshinanu, Marco Viceconti, *In silico* clinical trials: concepts and early adoptions, *Briefings in Bioinformatics*, Volume 20, Issue 5, September 2019, Pages 1699–1708, https://doi.org/10.1093/bib/bby043
[20] Musuamba Tshinanu, F., Bursi, R., Manolis, E., Karlsson, K., Kulesza, A., Courcelles, E., Boissel, J. P., Lesage, R., Crozatier, C., Voisin, E. M., Rousseau, C. F., Marchal, T., Alessandrello, R., & Geris, L. (2020). Verifying and Validating Quantitative Systems Pharmacology and *In silico* Models in Drug Development: Current Needs, Gaps, and Challenges. *CPT: Pharmacometrics and Systems Pharmacology*, *9*(4), 195-197. https://doi.org/10.1002/psp4.12504
[21] Musuamba FT, Skottheim, Rusten I, Lesage R, et al. Scientific and regulatory evaluation of mechanistic *in silico* drug and disease models in drug development: Building model credibility. *CPT Pharmacometrics Syst Pharmacol*. 2021;10:804–825. https://doi.org/10.1002/psp4.12669
[22] Viceconti M, Emili L, Afshari P, et al. Possible Contexts of Use for *In silico* Trials Methodologies: A Consensus-Based Review. *IEEE J Biomed Health Inform*. 2021;25(10):3977-3982. doi:10.1109/JBHI.2021.3090469
[23] Pappalardo F, Wilkinson J, Busquet F, et al. Toward A Regulatory Pathway for the Use of *in silico* Trials in the CE Marking of Medical Devices. *IEEE J Biomed Health Inform*. 2022;26(11):5282-5286. doi:10.1109/JBHI.2022.3198145
[24] Karanasiou, Georgia et al. "Advancing *In silico* Clinical Trials for Regulatory Adoption and Innovation." *IEEE journal of biomedical and health informatics*, vol. PP 10.1109/JBHI.2024.3486538. 8 Nov. 2024, doi:10.1109/JBHI.2024.3486538
[25] Viceconti M, De Vos M, Mellone S, Geris L. Position paper From the digital twins in healthcare to the Virtual Human Twin: a moon-shot project for digital health research. IEEE J Biomed Health Inform. 2023 Oct 11;PP. doi: 10.1109/JBHI.2023.3323688
[26] Viceconti, M., Luca, & Editors, E. (n.d.). Synthesis Lectures on Biomedical Engineering Toward Good Simulation Practice Best Practices for the Use of Computational Modelling and Simulation in the Regulatory Process of Biomedical Products.
[27] Viceconti, M. *In silico* World Online Community of Practice and GSP Consensus. Zenodo, 23 Dec. 2024, doi:10.5281/zenodo.14548377.

- FeOps- Materialise, Belgium
  - TAVIguide™ - 2015
  - HeartGuide™ - 2019 / 2023
  - FEops is a recognized pioneer in the field of physics-based simulations for minimally invasive cardiovascular devices and procedures.
- TWINSIGHT MEDICAL, France
  - SurgiTwin 2025
  - SurgiTwin is a semi-automated **Software as a Medical Device (SaMD)** that assists health care professionals in the **pre-operative planning of total knee replacement surgery**. It uses algorithms to create segmented images, a 3D model, and measurements from the patient's medical images
- HeartFlow, USA
  - HeartFlow FFRCT Analysis creates a personalized three-dimensional model of the heart. Clinicians can use this model to evaluate the impact a blockage has on blood flow and determine the best treatment for patients.

2.3. In silico trial facilitated economic benefits – an example success story from cardiac pacemakers

A leading manufacturer's case study detailed the **benefits realized** after implementing **in silico augmented medical device testing**, including the following[28]:

- 2 years – The product was released 2 years earlier.
- 256 – reduction in the number of patients involved in the clinical trials.
- $10 million – cost reduction due to the reduced number of patients
- 10000 patients – number of patients treated during these two years with the product.

3. Outlook

With regard to the principles and implementation of MDR, we broadly acknowledge that MDR includes stringent pre- and post-market requirements to reduce safety issues in the EU. Despite the criticism regarding increased scrutiny, we believe that the principles and measures introduced by the MDR, when pragmatically implemented, aim to deliver patient safety, transparency and remain the right direction to achieve clinical benefit and effectiveness for patients. The main need for change arises because the MDR implementation is currently rooted in a conservative, siloed mindset and outdated "signal systems" that prevent the full leverage of emerging technologies, including computer modelling and AI systems.

[28] https://www.avicenna-alliance.com/application-brief/in-silico-trials.html

3.1. *The dilemma of quantifying uncertainties across all evidence sources*

In this context, we as a scientific community seek to clarify that **traditional evidence sources (including animal and clinical data) are accepted, as they have a long history of use** and "real-world testing". Conversely, **uncertainties of traditional evidence are even difficult to quantify and map with clinical endpoints or population level outcomes, objectively**. Emerging digital evidence paradigms, on the other hand, offer the potential of extensively quantifying the predictive evidence that they generate. **Ironically, the objective quantification of uncertainty itself seems to contribute to regulators' hesitation to embrace digital evidence**. As a result, guidance documents and regulatory practitioners **continue to rank *in silico* evidence as non-clinical data, as compared to human clinical data**.

3.2. *Emerging needs – digital twins in healthcare*

With advanced CM&S representations of human pathophysiology, one can simulate real-world clinical and post-market scenarios on personalised digital representations of organs, devices, and pathologies of individual patients. Thus **pave way to potentially reduce the risk of exposing humans to unsafe or unethical clinical investigations**, as well as capture adverse reactions ahead of time, saving lives, time, and money. Moreover, with the advent of CM&S powered **digital twins in healthcare**, multi-scale modelling of organs and human pathophysiology are starting to emerge[29,30]. On this note, consider the EC's vision and policy initiatives to foster digital twins in healthcare through the **European Virtual Human Twin initiative**[31]. It is imperative that the MDR remains relevant to these new technologies. Crucially, anticipate and shape regulatory science such that MDR evaluation sets the direction to transform the current stagnation of regulatory pathways. Only then can **publicly funded European innovation reach patients**, which, in turn would **enhance the competitiveness of the EU healthcare sector.**

Leveraging CM&S will not only address current bottlenecks in the EU health ecosystem but also act as an **engine for competitiveness across** the European healthcare sector. Recognising **in silico evidence as a complement to traditional physical experiments is paramount to accelerating innovation.**

[29] Viceconti M, De Vos M, Mellone S, Geris L. Position paper From the digital twins in healthcare to the Virtual Human Twin: a moon-shot project for digital health research. IEEE J Biomed Health Inform. 2023 Oct 11;PP. doi: 10.1109/JBHI.2023.3323688
[30] HORIZON-HEALTH-2023-TOOL-05-03: Integrated, multi-scale computational models of patient patho-physiology ('virtual twins') for personalised disease management
[31] European Virtual Human Twin Initiative - The European Virtual Human Twins Initiative is an EU framework supporting the emergence and adoption of the next generation of virtual human twins solutions in health and care. https://digital-strategy.ec.europa.eu/en/policies/virtual-human-twins