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In Silico Technologies

A STRATEGIC IMPERATIVE FOR ACCELERATING BREAKTHROUGHS AND MARKET LEADERSHIP FOR FDA-REGULATED PRODUCTS

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I. Executive Summary

The 21st century technology revolution has the power to reshape the way organizations manage, process, and harness data, drive innovation, and unlock new possibilities for consumers and patients across the globe. These innovations enable faster data processing, complex computations, and the ability to handle enormous datasets efficiently. Moreover, researchers and engineers can harness the advancements in causal (physics-based) modeling and complex systems representations to capture real-world phenomena. Other supporting technologies contributing to this convergence include artificial intelligence (AI) and machine learning (ML) for data analysis and automation, cybersecurity solutions to ensure data integrity and privacy, and advancements in networking infrastructure to enhance connectivity and communication between distributed systems.

However, the power of technology is available only when adopted. The time is now for companies with products that influence, impact, and improve human health and food safety to embrace *in silico technologies* (ISTs). ISTs encompass computer-based simulations and computational techniques used to model, analyze, and predict complex processes and systems, which include causal (e.g., mechanistic models, first-principle models) and data-driven inference models (e.g., ML). ISTs can be harnessed to transform human health by supporting the development and evaluation of all FDA-regulated products, including medical products, food safety, and digital health technologies.

This paper strives to bridge the gap between technical and business teams in the ecosystem of FDA-regulated products and the nation's food supply by building the business case for industry investment in ISTs as a strategic imperative for accelerating breakthroughs and market leadership in FDA-regulated products, thus transforming human health. The paper serves as a technology guide for business decision-makers, corporate leaders responsible for product development, company strategists, legal teams, venture capitalists, regulatory and quality teams within industry, and global jurisdictions.

Key points supporting the business case include:

- ISTs accelerate innovation—providing an environment for rapidly exploring promising ideas;
- ISTs are cost-effective—knowledge capture and transfer are streamlined;
- ISTs are a 'new normal' in product development life cycles in traditional engineering product development;
- ISTs are being accepted by the FDA in support of regulatory submissions;
- Global regulatory landscapes are also shifting to accept evidence generated from ISTs;
- ISTs strengthen the product safety profile of devices and drugs, and build a competitive advantage over the status-quo;
- ISTs enable progressive tangible next steps and structural changes for maximal transformation (leap in trust).

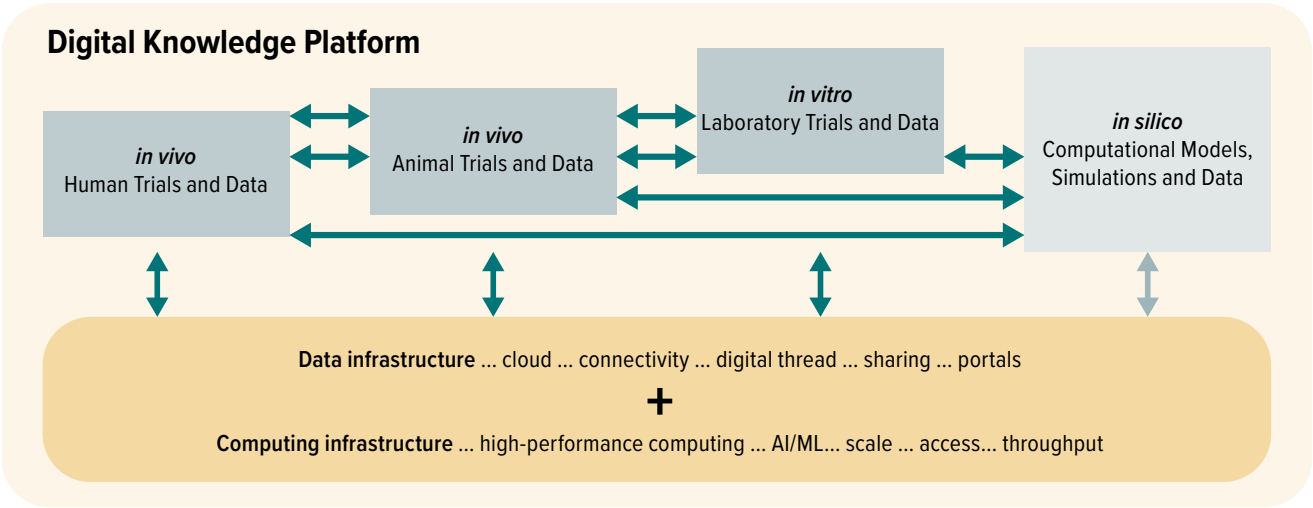
II. Introduction to In Silico Technologies (ISTs)

"In silico" processes occur on a computer rather than in a physical laboratory (in vitro)[1] or living organism (in vivo). ISTs complement or may replace traditional evidence generation methods by enhancing in vitro testing and in vivo studies through finer resolution, examination beyond the limits of physical testing, and elucidation of causal links. ISTs come in many forms, from traditional physics-based computational models and data-driven inference models to augmented or virtual reality headsets, and wireless connected edge-computing devices.

ISTs allow researchers to conduct experiments, test hypotheses, and predict outcomes beyond the scope of, and in addition to, experiments in the physical world (in vitro or in vivo) by tapping into technologies like augmented or virtual reality (AR/VR). This technology convergence provides innovative pathways to accelerate research, enhance precision, and optimize outcomes across a broad spectrum of applications.

Evidence and data used for efficient business practices and regulatory decision-making are contained in digital infrastructures. Due to their digital nature, ISTs can be easily connected to these existing infrastructures that then allows a more accessible, complete, and comprehensive evidence package for the healthcare technology under development. Imagine enhancing existing knowledge with digital knowledge throughout the lifecycle, as shown graphically in an example *Digital Knowledge Platform* (Figure 1). As depicted in the graphic, data and computing infrastructures serve as the foundation for harnessing digital knowledge from all model sources. Data management and governance are the foundation that will enable companies to fully harness existing data, create new data (e.g., to train AI/ML models), and support evidence strategies for FDA-regulated products. Businesses can deploy in silico technologies to fully harness existing data, create new data (e.g., to train AI/ML models), and support evidence strategies for FDA-regulated products.

Figure 1: Data to Evidence Landscape for Business and Regulatory Decisions



1 For purposes of this paper, in vitro also encompasses in chemico (i.e., biochemical cell-free screens).

Other safety-critical regulated industries consistently harness the power of ISTs (Figure 2) of this decades-tested resource. These mature technology sectors leverage ISTs to drive the design, risk reduction, evaluation, and manufacturability of their products.

Figure 2: Safety-Driven Regulated Industries that Rely on ISTs

AUTOMOTIVE

AVIATION

NUCLEAR

RAILROAD

SHIPPING

The "how" and "why" ISTs are used in the regulated, safety-driven industries shown in Figure 2 differ greatly. In the automotive and aviation industries, for example, physical prototypes are too large (and expensive) to build and test, so ISTs are the most cost-effective and instructive methods to guarantee safety. In other industries, e.g., nuclear and civil infrastructure, physical testing of failure scenarios is not possible (or ethical). In industries with tight margins that rely on logistical planning, such as railroad and shipping, rapid scenario investigation is critical to maintaining the logistical flow and minimizing disruptions. In healthcare technologies, ISTs are very cost-effective when used repeatedly, such as investigating the safety and effectiveness of a medical device or drug in a high-risk patient population.

But regulatory and industry inertia, cost, and the lack of familiarity or understanding of ISTs stall forward momentum in utilizing better, more human-relevant models[2] to develop products that support human health and where safety is robustly evaluated prior to human use. ISTs should be the core technology of an organization to better harness data from all evidence sources (in vivo human, in vivo animal, and in vitro)—thereby creating more comprehensive investigative and evidence-based strategies that drive improved product development, evaluation, acceptance, and maintenance. The remainder of this document illuminates how the benefits of embracing ISTs greatly outweigh the costs and risks.

The goal of this position paper is to encourage readers to embrace ISTs as a complement, enhancement, and where appropriate, replacement for methods of collecting data and thereby realize the product development benefits experienced in other safety-driven, regulated industries.

By embracing ISTs as a complement to existing in vitro and in vivo models, decision-makers will arrive at a more informed, more broadly investigated product performance envelope with an improved quality, safety, and effectiveness profile.

2 The case can also be expanded for "species-relevant predictive models that support animal health."

III. Value Proposition for In Silico Technologies

ISTs are a proven key driver for product innovation and sustainability. Further developments in these areas will only help drive further advancements of ISTs, which have significant untapped potential. Without the use of ISTs, human clinical trials and animal models will remain limited by historical precedence, stifling innovation and delaying the availability of life-changing therapies. To summarize the value proposition of IST, Table 1 provides a non-exhaustive list of how organizations benefit by investing in ISTs.

Table 1: Value Proposition: Are You Capitalizing on These IST Benefits?

WHICH OF THESE COULD DRIVE CHANGE IN YOUR ORGANIZATION?
• First or shortened time to market with extended duration of exclusivity • Simultaneous entry into multiple markets • Smaller, more targeted, shorter (more successful) clinical trials* • Products that result in improved patient/consumer outcomes • Enhanced product safety (e.g., by significantly reducing recalls and providing savings on warranty expense) • Preserve/build brand reputation • Design for reliable/sustainable manufacturing • Provide method for devices, drugs, and food safety product evaluations when no other options exist (e.g., pediatrics, pregnancy, rare diseases, rare events) • Reduce/refine/replace in vivo testing * *ISTs may significantly influence the economics and performance of clinical trials*
In Silico Clinical Trials have demonstrated success in bringing a therapeutic treatment to market faster and at reduced cost:[3]
• **2 YEARS:** The product was released and first-to-market 2 years earlier than expected • **256:** Reduction in the number of patients required to power the clinical study • **$10M:** cost reduction due to reduced number of patients and 2 years of market dominance • **10k:** number of patients treated with the product in the 2 years of market dominance According to the FDA's Center for Devices and Radiological Health leadership "… stochastic engineering models [i.e., IST] may have the capability to simulate clinical outcomes for "virtual patients" by modeling a relationship between bench outcomes and clinical end points." And, "If it can be shown that these virtual patients are similar, in a precisely defined way, to real patients, future [clinical] trials may be able to rely partially on virtual-patient information, thus lessening the burden of enrolling additional real patients."[4]

Figure 3 depicts the comparison the four major data sources for the medical product industry: **Clinical** trials (in vivo human models), **Animal** (in vivo preclinical models), **Bench** (in vitro models), and **CM&S** (computational

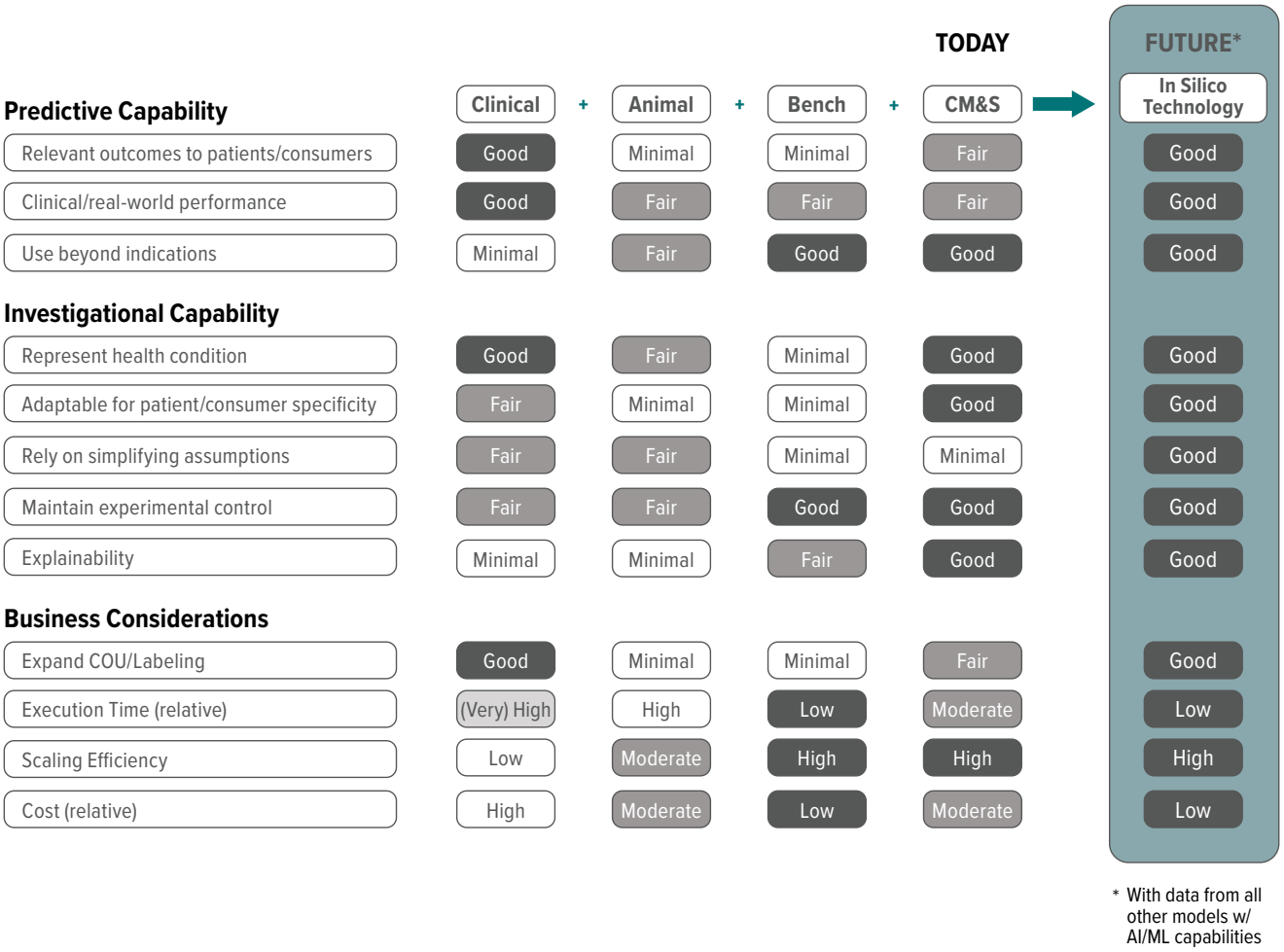
3 VPH Institute, Avicenna Alliance Association for Predictive Medicine. *IN VIVO, in VITRO, in SILICO: Why Computer Modelling Is the next Evolution of the Healthcare Sectorevolution*; 2018. Accessed May 2, 2024. https://www.vph-institute.org/upload/international-avicenna-alliance-conference-report-4-sept-2018-final_5bd9c5183292b.pdf

4 Faris O, Shuren J. An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials. N Engl J Med 2017;376:1350–1357 doi: 10.1056/NEJMra1512592

models and simulation, i.e., in silico models). Each model was assessed for its predictive capability, investigational capability, and for key business considerations. What is clear from the side-by-side comparisons, each model has its strengths and limitations. However, the most striking observation is that, as computing power and capabilities continue to evolve, especially alongside AI/ML, ISTs have the most potential for significant growth opportunity as compared to the other model types.

"Even though we have some knowledge of the human body and understand some of the variability, CM&S can complement other forms of regulatory evidence as computer models are based on causality. For instance, a digital twin based on CM&S can help us predict how the body should react and provide more sensitive insights when there is a deviation from normal, healthy patterns." Michael Hill, Vice-President Science, Technology and Clinical Affairs at Medtronic, 2018.[5]

Figure 3: A side-by-side comparison of models that are used to generate evidence for FDA-regulated Products, with IST holding the most promise for its predictive capability, investigational capability and business considerations.[6]

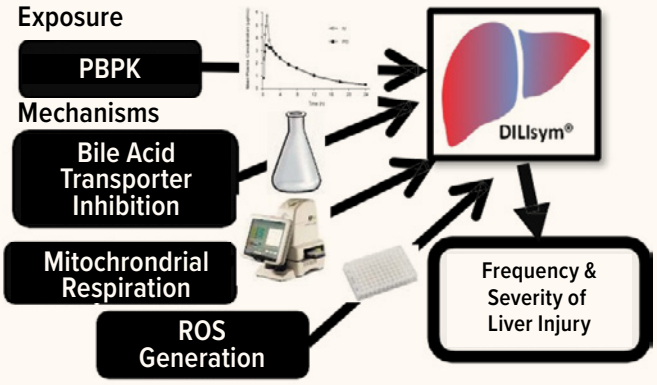


5 VPH Institute, Avicenna Alliance Association for Predictive Medicine. *IN VIVO, in VITRO, in SILICO: Why Computer Modelling Is the next Evolution of the Healthcare Sectorevolution;* 2018. Accessed May 2, 2024. https://www.vph-institute.org/upload/international-avicenna-alliance-conference-report-4-sept-2018-final_5bd9c5183292b.pdf

6 Graphic updated and modified from Table 1 of: Morrison TM, Dreher ML, Nagaraja S, et. al. The Role of Computational Modeling and Simulation in the Total Product Life Cycle of Peripheral Vascular Devices. J Med Device. 2017;11(2):024503. doi: 10.1115/1.4035866

The impact of ISTs is demonstrated by the success stories described below. Two are presented below, and additional examples can be found in the appendix.

EXAMPLE: Liver Safety Assessment of Chemicals[7]



- **PRODUCT:** Computer software for modeling liver interactions and responses to a chemical.
- **IN SILICO MODEL:** Quantitative system toxicology using physiologically-based pharmacokinetic model (PBPK), and toxicity modeling for assessing drug-induced liver injury.
- **EVIDENCE:** Data generated to assess the likelihood of drug-induced liver injury from various chemical stimulants.
- **OPPORTUNITY:** The company harnessed IST methodology, which enhanced its regulatory interaction and supported its approval.
- **BUSINESS IMPACT:** Rapid assessment of candidate drug formulations and dosages capable of causing hepatotoxicity facilitated quicker internal (business) decision making which led to reduced development costs and faster time to market while maintaining clinical safety and efficacy.

EXAMPLE: Tailored Osteotomy for Knee Alignment[8]

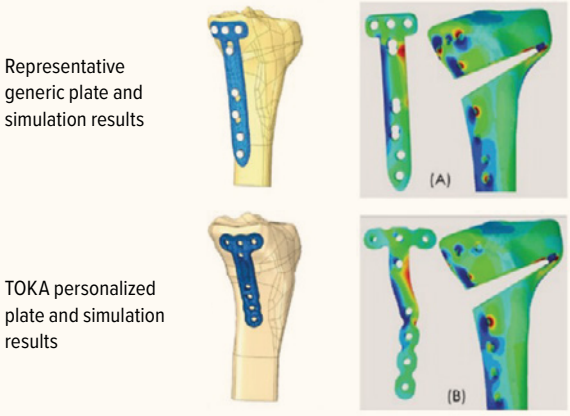


Illustration of virtual implantation of generic and TOKA plates for treatment of knee OA, and representative simulation results.

- **PRODUCT:** Personalized orthopedic medical device Implant
- **IN SILICO MODEL:** In silico patients using finite element analysis
- **EVIDENCE:** Demonstrated that the personalized high tibial osteotomy (HTO) plates had comparable safety to the gold standard prosthesis, with reduced stiffness that could promote improved bone healing.
- **OPPORTUNITY:** Positioned the in silico clinical trial in the same manner as a traditional clinical trial (registered on clinictrials.gov) to meet the expectations of clinical and regulatory evaluators.
- **BUSINESS IMPACT:** Device was cleared in several markets using in silico evidence as definitive clinical evaluation.

7 Watkins PB. Quantitative Systems Toxicology Approaches to Understand and Predict Drug-Induced Liver Injury. Clin Liver Dis. 2020 Feb;24(1):49–60. doi: 10.1016/j.cld.2019.09.003

8 MacLeod AR, Mandalia VI, Mathews JA, et. al. Personalised 3D Printed high tibial osteotomy achieves a high level of accuracy: 'IDEAL' preclinical stage evaluation of a novel patient specific system. Med Eng Phys. 2022 Oct;108:103875. doi: 10.1016/j.medengphy.2022.103875

IV. Drivers for Adoption

Most business and regulatory decisions about FDA-regulated products currently rely on evidence not from ISTs. However, ISTs hold the most promise for accelerating and improving product development and evaluation, as depicted by key drivers for adoption, which are presented in Table 2 along with a brief discussion of their advantages. In addition to the Table 2 drivers, ISTs afford opportunities to enhance the predictive capabilities of digital health tools, handle increased product complexity, and generate data for training and testing AI models through the use of computational modeling and simulation.

Table 2: Business Drivers for Adoption of ISTs

DRIVER	ADVANTAGE
De-risk time-consuming preclinical development	
	Critical path assessments of treatment development often hinge on complex long-duration tests, particularly in device development where a critical pillar of safety is the prediction of fatigue performance (e.g., for orthopedic or cardiovascular implants). Furthermore, unexpected failures can require both time- and money-intensive replacement studies and a costly failure analysis. ISTs can streamline critical paths through the careful development of these long duration tests. While durability tests of this nature are commonly supported by computational modeling, the real promise of ISTs is in the credible prediction and benchtop replication of in vivo conditions. Rather than relying on conservative assumptions based on legacy standards to define testing requirements, ISTs have the potential for credible recapitulation of in vivo conditions, potentially reducing the risk of device failure and subsequent risk to program timelines. A similar approach can be utilized during drug development. For example, molecular screening and identification of drug candidates is a time-consuming and high-risk endeavor in which significant resources are often spent to down-sample a pool of candidate molecules. ISTs have recently been developed to enhance molecular screening through the use of both first-principle models and AI approaches. These IST approaches can quickly sift through databases of known candidate materials or predict novel compounds based on specific target chemistry and biochemical interactions. The benefits of these approaches include both the identification of better candidates and the reduction of the number of false positives, thereby saving time and resources by enabling deeper assessment of more promising candidates.
Shorten/improve time to market	
	Time to market is a crucial driver for commercial success, particularly for new treatment modalities in which first-mover benefits can include significant market share advantages for years after approval. Being first to market presents significant commercial challenges, not least of which are developing appropriate protocols and endpoint assessments. ISTs can shorten the time to market by improving the efficiency of R&D efforts, streamlining preclinical assessments, and enhancing clinical trial design. ISTs can also enhance development efficiency with virtual prototyping in which computational models of a new device are rapidly iterated in a virtual environment, including assessments of safety and function, often before investing in physical prototyping and testing. Additionally, the use of ISTs for streamlining preclinical assessments can both increase testing efficiencies as well as improve knowledge gained through better test design and analysis, oftentimes limiting failures through more intelligent, more human-relevant design.

DRIVER	ADVANTAGE
Reduce/Refine/Replace for animal experimentation	
	Animal studies have long been a cornerstone of preclinical development, but their ability to predict human clinical efficacy and safety has increasingly been questioned. Additionally, ethical imperatives to refine, reduce, and replace animal experimentation have been gaining traction in commercial spaces with the rise of 'cruelty-free' products and in government spaces with initiatives like the US government Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM)[9] program. ISTs can drive more efficient development through reductions in animal testing, either through the replacement of animal studies or a reduction in required sample sizes (e.g., as in toxicology assessment; medical device studies). ISTs that leverage systems modeling to better represent human health and disease pathways can improve upon animal models to increase human relevance and identify superior therapeutics and treatment strategies.
Reduce clinical trial costs by reducing necessary enrollment	
	Virtual cohorts comprised of in silico patients can significantly reduce clinical trial-related costs. Innovative clinical trial designs based on an IST enrichment strategy[10] can reduce enrollment requirements by half or more while still achieving the necessary statistical power. Additional benefits include shorter enrollment and overall clinical trial durations.
Address unmet needs for rare conditions	
	Developing treatments for rare conditions presents multiple challenges, not least of which is developing clinical trial plans with sufficient participation and statistical power to overcome inherent patient variability and, too often, low confidence in biomarkers and trial endpoints. As a result, many promising treatments for rare conditions are not developed. ISTs can be developed to support research and development (R&D) and clinical trial processes by supplementing real-world populations with in silico cohorts. These in silico cohorts can be developed to capture the relevant physiology of physical patients, allowing the generation of large numbers of in silico patients on which to assess treatment safety and efficacy. These in silico cohorts can then be used to help design treatments and improve the statistical power of clinical trials, reducing the burden on rare populations and providing companies with a way forward on treatment development. Detailed analysis of highly variable clinical results using in silico retrospective analysis can also help to explain complicated trial results caused by variability in rare populations, greatly enhancing the information gained from early trials and facilitating the development of pivotal trials.

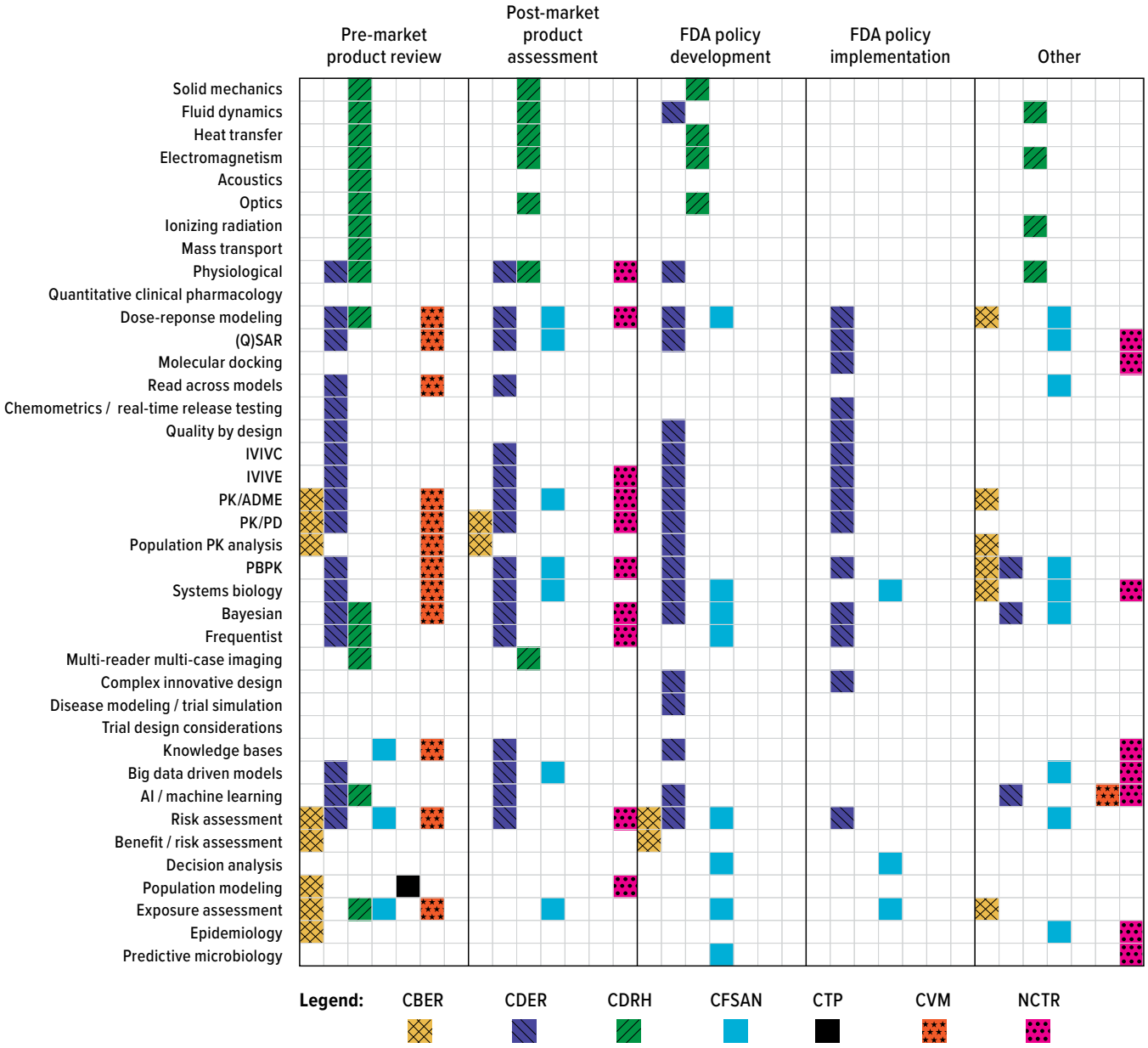
9 About ICCVAM. National Toxicology Program. Accessed May 23, 2024. https://ntp.niehs.nih.gov/go/iccvam

10 Medical Device Innovation Consortium. ENRICHMENT in Silico Clinical Trial Project (ENRICHMENT). MDIC. Accessed May 2, 2024. https://mdic.org/project/enrichment-in-silico-clinical-trial-project/

DRIVER	ADVANTAGE
Enhance clinical efficiency through pre-operative planning	
	Medical devices are increasingly complex, requiring careful surgical pre-planning, with clinical decisions that include choosing the appropriate device size, identifying strategies for device placement, and development of appropriate surgical guidelines. Efficiency in surgical pre-planning can therefore provide an important advantage to companies seeking to reduce clinician burden and enhance device efficacy. ISTs offer multiple paths to reducing clinical burden in pre-procedural planning. Companies investing in the digital infrastructure to promote pre-procedural planning can attract clinicians who want greater confidence in procedural plans, including those who take on more complicated cases requiring more complex procedures. ISTs can therefore provide companies with a way to differentiate their products in a crowded marketplace where device performance has limited clinical differentiation with competitors' adoption.

Figure 4 showcases how the FDA has adopted ISTs across the different aspects of the products' lifecycle and through its centers and functions.

Figure 4. Use of Modeling and Simulation by the FDA in Different Aspects of the Products' Lifecycle[11]



Use of modeling and simulation across FDA, organized by modeling discipline (rows), application area (outer columns) and FDA Center (inner columns, colors). CBER, CDER, CDRH, CFSAN, CTP, and CVM are regulatory product Centers and NCTR is a non-regulatory Center providing regulatory research support to product Centers. Acronyms: (Q)SAR: (quantitative) structure activity relationship; IVIVC/IVIVE: in vitro in vivo correlation/ extrapolation; PK: pharmacokinetics; ADME: absorption, distribution, metabolism, excretion; PK/PD: pharmacokinetics/pharmacodynamics; PBPK: physiologically-based pharmacokinetic; AI: artificial intelligence. Empty spaces should be interpreted as no information collected yet, rather than no work done in the area. Different Centers may have different interpretations of some of the modeling disciplines.

11 U.S. Food and Drug Administration. Modeling & Simulation at FDA. Published 2022. Accessed May 2, 2024. https://www.fda.gov/science-research/about-science-research-fda/modeling-simulation-fda

V. Myths Preventing the Adoption of In Silico Technologies

Risk can be expensive. Business leaders often support technology they trust, understand, and equate with lower risk. With the fast pace of business opportunities and technological advancements, it can seem easier and wiser to rely on approaches that do not shake the status quo, especially in the case of regulatory pathways and decision-making. It can feel risky to adopt new approaches, especially ones that might be perceived as adding uncertainty to the regulatory process. And without more public success stories or clear pathways for adoption, it is challenging to dispel myths. Which of these myths are holding you back? Table 3 lists myths about ISTs that may lead innovators to miss opportunities. Three common myths are discussed in detail (shown in bold below) and others can be found in Appendix B.

Table 3: Myths about ISTs and the Potential for Missed Opportunities

Myths you might be holding on to:	Missed opportunities by not using ISTs:
• **Business Impact** – Return on Investment (ROI) not high enough – ROI takes too long to realize • **Regulatory considerations** • **Modeling is not relevant or applicable across the product lifecycle** • Legacy/industry inertia • I'll make revenue with AI; I don't need ISTs • Lack of accurate input data (e.g., for tissue material properties) • ISTs lack relevance to clinical conditions • Validation is cumbersome	• Accelerate time to market • Improve product safety and efficacy profile • Reduce animal experimentation • Reduce the number of human subjects in clinical trials • Greater capacity to explore design space • Greater potential for scalability • Transition from in silico models for optimization to in silico models for evidence • Model reuse with minor tweaks for a similar product profile

(MYTH 1) Regulatory Consideration: (a) Regulatory processes to support the use of computational modeling do not exist,[12] there is too much uncertainty in the regulatory process. (b) If external regulatory processes exist to support modeling, they are overly selective or inaccessible for different company types.

(a) Why the myth is false: The global regulatory landscape is shifting to accept IST evidence with this evidence becoming more prevalent. A wide variety of uses of the existing programs have been shared across drug, diagnostic, and device industries and are shared on regulatory websites. Applicants/sponsors from both large and small companies have benefitted from the use of these new programs.

12 Modeled evidence is not accepted by regulators. Modeled evidence is not part of the required sections by regulators to complete the drug or device applications to the FDA/EMA There are no unique/clear regulatory processes or pathways for applicants to get regulatory feedback on their modeling or modeled evidence.

The FDA has provided resources highlighting the importance of modeling and simulation for use in applications.[13,14] Modeled evidence is often part of a standard submission package for drugs when a 505b2 application is used.[15,16] Simulation of modeled evidence (e.g., investigational drug on a biomarker) can be part of a standard drug or device application (e.g. new drug application (NDA), abbreviated new drug application (ANDA), biologics license applications (BLA)) and can be accepted by regulators as part of the submission to FDA. For drug applications, modeling or simulations can be submitted in the NDA/ANDA in Module 5.3.3.5. as part of the pharmacometric analysis.[17]

FDA has created a separate process/pathway for applicants to get feedback on their models and modeled evidence for use in drug applications via the model-informed drug development pathway.[18] The European Medicines Agency (EMA) has an early advice pathway for the review of modeling evidence and modeling or simulation plans.[19]

Approaches to address the myth: Regulators have highlighted examples to demonstrate how innovative companies have used modeled evidence to bring new technology to patients with high unmet medical needs. Thus, it improves the company profile by valuing the use of modeling as a mark of an innovative company. Regulators have also highlighted via multichannel media the benefits of modeling as part of patient-focused drug and device development.[20] Modeling used with safety data may permit a technology to reach patients sooner (e.g., rare disease drugs, unique medical devices, or diagnostic tests).

Regulators can continue to provide examples of best practices[21] and uses of modeling in drug and device applications, and provide supportive materials which highlight all the sections of drug and device applications where modeled evidence can be used by applicants. Regulatory organizations or modeling workgroups could provide open-source pitch decks that outline the regulatory processes for companies to use for internal cross-functional team education.

(b) Why the myth is false: Regulatory processes are available and applicable. A wide variety of uses of the existing programs have been shared across drug, diagnostic, and device industries and are shared on regulatory websites. Applicants/sponsors from both large and small companies have benefitted from the use of these new programs.

Approaches to address the myth: Regulators can continue to share information about which company types use these programs. Regulators may consider alternative forums for informal advice meetings such as dedicated time on critical path initiative meeting (CPIM) agendas or other open forums for IST drug, device, food, and personal product development questions.

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13 U.S. Food and Drug Administration. Modeling & Simulation at FDA. Published 2022. Accessed May 2, 2024. https://www.fda.gov/science-research/about-science-research-fda/modeling-simulation-fda

14 European Medicines Agency. Modelling and simulation: Questions and Answers. https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-and-pharmacokinetics/modelling-and-simulation-questions-and-answers

15 Center for Drug Evaluation and Research (CDER). Applications Covered by Section 505(b)(2). U.S. Food and Drug Administration. Published February 1, 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-covered-section-505b2

16 Premier Consulting. Use of PK Modeling & Steady-State Simulations in 505(b)(2) Drug Development | Premier Consulting. Published December 13, 2010. https://premierconsulting.com/resources/blog/pharmacokinetic-pk-modeling-steady-state-simulations-strategic-use-in-a-505b2-drug-development-program/#:~:text=Submit%20A%20Request-

17 Center for Drug Evaluation and Research (CDER). Model | Data Format. U.S. Food and Drug Administration. Published 2021. Accessed May 2, 2024. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format

18 Center for Drug Evaluation and Research (CDER). Model-Informed Drug Development Paired Meeting Program. U.S. Food and Drug Administration. Published October 31, 2022. Accessed May 2, 2024. https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program

19 Karlsson K. Regulatory Model-Informed Drug Development in EU. Published March 24, 2021. Accessed May 2, 2024. https://www.pmda.go.jp/files/000239914.pdf

20 U.S. Food and Drug Administration. Focus Area: Model-Informed Product Development. Focus Areas of Regulatory Science Report. Published 2022. Accessed May 2, 2024. https://www.fda.gov/science-research/focus-areas-regulatory-science-report/focus-area-model-informed-product-development#:~:text=Examples

21 U.S. Food and Drug Administration. Best Practices for Development and Application of Disease Progression Models - 11/19/2021. U.S. Food and Drug Administration. Published February 1, 2022. Accessed May 2, 2024. https://www.fda.gov/drugs/news-events-human-drugs/best-practices-development-and-application-disease-progression-models-11192021

(MYTH 2) Business Impact: ISTs are considered an additional/optional cost without a clear return on investment (ROI).

Investment estimates of the R&D costs for what is required to obtain evidence packages that get products to market often consider modeling as an "extra" activity; these estimates do not include short- or long-term financial benefits.

Why the myth is false: The company cost associated with developing and executing a modeling or simulation plan will be offset, as modeling can improve time-on or time-to-market. ISTs deliver results at scale, therefore increased model reuse improves model ROI.

Approaches to address the myth: Develop business cases for modeling uses that quantify ROI, impact, & cost benefits for time-to-market.[22,23] An open-source model made available by a professional organization which can demonstrate improvement in outcome metrics of interest with and without simulation to demonstrate scenarios of reduction on overall project timelines (e.g., time reduced from the drug or device lifecycle), reduced time to the filing of the application, or reduction in personal time, or a reduction in program expense, would be beneficial.

(MYTH 3) Modeling is not relevant or applicable to all types of decision-makers across the product lifecycle.

Why the myth is false: The research questions addressed by many models are useful for several phases of a product lifecycle. Modeling can estimate a drug or device benefit on a biomarker or outcome measure that is useful for minimizing the size of a clinical trial via simulation (e.g., phase 1–3), and is also useful for estimating treatment/device effect (e.g., phase 2- 4) for use in a drug/device application, and useful for estimating long term outcomes that could be infeasible to measure with prospective studies.

Approaches to address the myth: An open-source model could apply contemporary best practices in software development to computational model development. Within an open-source model, product lifecycle applications for modeling to be illustrated and more broadly can be shared within industry groups or across other communication channels. Joint efforts can be made to improve awareness of integrating modeling efforts in order to realize the value of modeling across organizations and company departments.[24]

22 Hill-McManus D, Hughes DA. Combining Model-Based Clinical Trial Simulation, Pharmacoeconomics, and Value of Information to Optimize Trial Design. CPT Pharmacometrics Syst Pharmacol. 2021 Jan;10(1):75–83. doi: 10.1002/psp4.12579

23 Ibid.

24 Caro JJ, Briggs AH, Siebert U, et al. Modeling good research practices—overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. Value Health. 2012;15(5):796–803.

VI. In Silico Technologies for Evidence Generation

Evidence to support FDA-regulated products traditionally comes from in vitro, in vivo animal and clinical trials. While these sources have been the traditional gold standard, there's been a surge of support for evidence from complementary sources such as ISTs. The integration of ISTs aligns with an evolving landscape demanding increased data linkages, data capacity, and advanced computing for evidence generation. Post-market assessment case studies in "Successes and Opportunities in Modeling & Simulation for FDA"[25] demonstrate how modeling and simulation fit into the regulatory environment.

The use of ISTs requires the generation (or curation) of experimental evidence that can be used to build credibility. This evidence generation may already be part of the development plan, but in some circumstances, additional data or evidence will be required to specifically to support IST model development and validation. While a key benefit of modeling includes a reduction in overall experimental expense, the costs to generate experimental evidence required to support such modeling should also be considered.

In silico models developed from available data and sets of assumptions are valuable in several ways. When looking at various opportunities across a portfolio, models can be used to assess the probability of technical success (PTS), which can then be used with the expected rate of return to facilitate investment choices. Projects with low PTS can be discontinued and the resources redeployed to technologies that are more likely to bring value. Within a project, when uncertainty surrounding some of the model assumptions exist, the impact of assumptions can be assessed to find those that are most influential and efforts may then be directed to obtain more certainty surrounding those key assumptions. Eventually, this allows a more precise estimate of PTS and portfolio decisions can be made with greater confidence.

At a project level, ISTs can bring more efficiency to development programs by optimizing development strategies, resulting in companies accelerating the introduction of new products to patients and consumers. With regard to pre-clinical and clinical trials, ISTs can be used to evaluate various study scenarios (e.g., study length, timing of assessments, number of treatments) to prioritize the most efficient trial designs.

In the short term, the adoption of in silico technology yields immediate benefits such as improved data management, streamlined workflows, and enhanced decision-making processes where digital transformation facilitates seamless integration with computational modeling and simulation tools. Midterm gains may include accelerated discovery and development timelines, reduced costs associated with experimental research, and enhanced predictive modeling for patient outcomes. In the long term, companies and institutions can expect significant returns on investment, including improved patient care, personalized treatment approaches, and groundbreaking medical discoveries driven by in silico technologies.

25 Food and Drug Administration, Modeling & Simulation Working Group of the Senior Science Council. Successes and Opportunities in Modeling & Simulation for FDA.; 2022. https://www.fda.gov/media/163156/download

VII. Economic Considerations

The internal and external pressures to reduce product production costs exist for all industries. The Inflation Reduction Act (IRA) of 2022[26] introduces another external driver to reduce costs in the healthcare industry. Fortunately for the healthcare industry, ISTs are an available and invaluable tool to tackle these cost pressures by providing understanding and information at a scale and resolution that is often unparalleled by physical testing.

ISTs like many, if not all, computational methods require sizable initial investments. In other industries (e.g., automotive, aerospace) where physical testing can be prohibitively expensive, this initial investment is trivially small. In the healthcare industry, the initial investment is large compared to physical bench testing. However, once an IST has been validated it can be used at will for minimal increment cost, and the more the ISTs are used, the more cost-effective they become.

The economic benefit for a new product first to market usually results in market exclusivity for 2.8 to 3.8 years,[27] so utilizing ISTs to accelerate the delivery of transformative products into the market can yield tremendous financial benefits. Relative to other industry sectors, the health care industry is slow moving: new products often require five to seven years to become publicly available.[28] The first mover advantage persists for ten years after launching a new drug, despite the unique complexities in the pharmaceutical industry, such as prescribing characteristics and competitive dynamics.[29]

ISTs, as with all models (e.g., in vitro, in vivo animal, clinical trials) used to develop, evaluate, sustain and improve a product, incur direct and indirect costs. Direct costs are typically associated with more tangible items and data security, while indirect costs are associated with gathering the necessary validation data and other factors (Table 4). Indirect costs may be more difficult to quantify. The technical capabilities to perform the necessary simulations may require building a team of modeling experts and associated supporting personnel. In addition to the skills required of the simulation practitioners, additional expertise may be required to generate the associated experimental data (both in vitro and preclinical/clinical). These personnel must understand the type and quality of data necessary to support each computational study. Additional expertise may also be required in regulatory-facing departments, including those familiar with non-traditional clinical trials and the associated statistical methods required to incorporate different types of evidence. Many companies utilize external resources with requisite expertise to conduct analyses and provide associated guidance on experimental methods and regulatory considerations.

26 H.R. 5376 - 117th Congress (2021-2022): Inflation Reduction Act of 2022 | Congress.gov | Library of Congress.

27 Stern AD. Innovation under Regulatory Uncertainty: Evidence from Medical Technology. J Public Econ. 2017 Jan;145:181–200. doi: 10.1016/j.jpubeco.2016.11.010

28 Goldfarb A, Teodoridis F. Why Is AI Adoption in Health Care lagging? Brookings. Published March 9, 2022. Accessed May 2, 2024. https://www.brookings.edu/articles/why-is-ai-adoption-in-health-care-lagging/#:~:text=With%20especially%20strong%20privacy%20concerns

29 Cha M, Yu F. Pharma's first-to-market Advantage | McKinsey. www.mckinsey.com. Published September 1, 2014. Accessed May 2, 2024. https://www.mckinsey.com/industries/life-sciences/our-insights/pharmas-first-to-market-advantage

Table 4: Potential Costs Associated with ISTs

Direct Costs	Indirect Costs
Software (chosen to be interoperable) • Simulations (e.g., PKPD, finite element analysis (FEA), computational fluid dynamics (CFD)) • Model generation (e.g., computer aided design (CAD), clinical imaging analysis) • Statistical packages **Hardware** • Local computer cluster • Cloud-based systems **Data Security** • Confidentiality of intellectual property and trade secrets **Data storage** • Analysis/compute time	**Expertise** • Skill sets • Education & training **Evidence Generation** • Benchtop tests • Pre-clinical and/or clinical studies • Curation of evidence (e.g., systematic reviews) **Scaling Factors** • Scope of analyses (e.g., simple idealized analyses vs. large-scale in silico clinical trials)

ROI is achieved once ISTs have been accredited for use within an organization, received qualification as a tool (e.g., for medical[30] or drug[31] development tools programs) or demonstrated success in supporting a regulatory application.[32,33] This sentiment is captured in Figure 5, which shows that costs stemming from design changes are at least an order of magnitude less costly to absorb if the changes are made earlier in the product lifecycle.[34] Improved profitability can only be fully realized with the early adoption of IST-driven product development and evaluation. Other safety-driven industry sectors heavily rely on ISTs (Section II, Figure 2). The push for ISTs in these sectors is motivated by the high-cost of developing and failing prototypes. While prototyping costs for medical technology remain relatively low as compared to other safety-driven industry sectors, other factors will likely contribute to an increased cost of materials (or lack of availability), supply-chain disruptions, healthcare demands, and the call for more robust evidence generation health systems, as highlighted in Section VI.

30 Center for Devices and Radiological Health. Qualification of Medical Device Development Tools. U.S. Food and Drug Administration. Published July 17, 2023. Accessed May 2, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualification-medical-device-development-tools

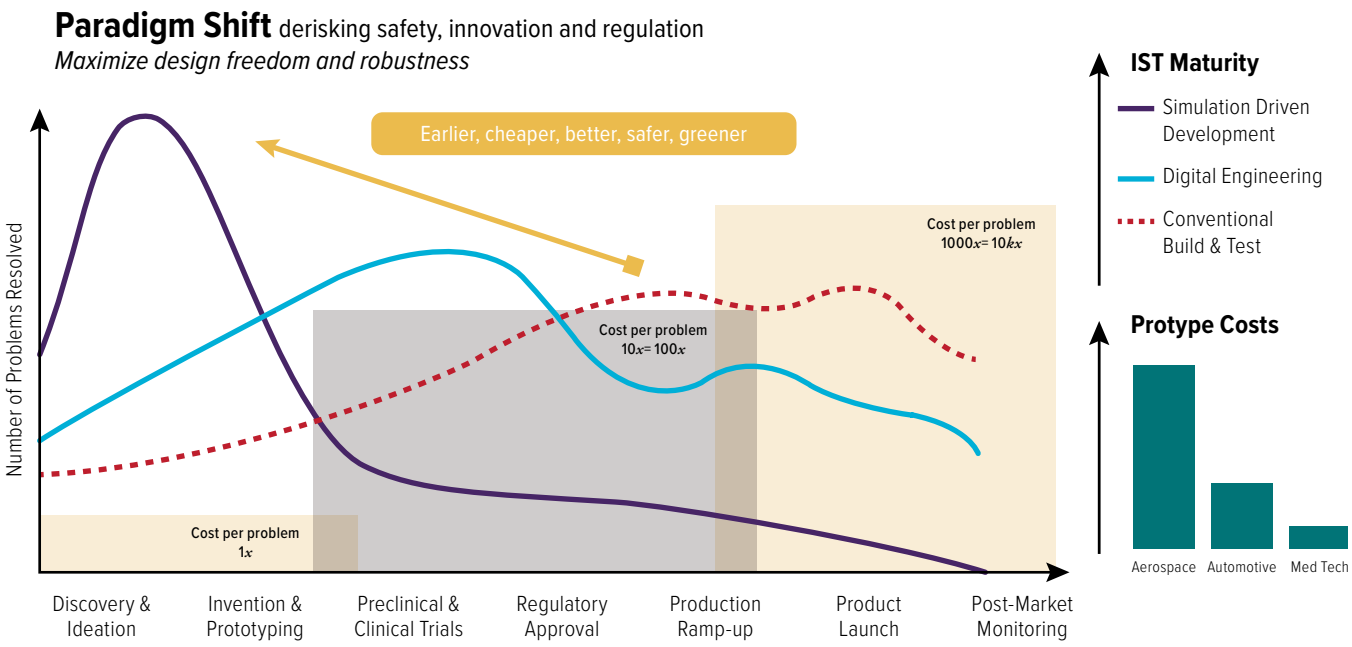
31 Center for Drug Evaluation and Research (CDER). Drug Development Tool (DDT) Qualification Programs. U.S. Food and Drug Administration. Published April 6, 2023. Accessed May 2, 2024. https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs

32 VPH Institute, Avicenna Alliance Association for Predictive Medicine. *IN VIVO, in VITRO, in SILICO: Why Computer Modelling Is the next Evolution of the Healthcare Sectorevolution*; 2018. Accessed May 2, 2024. https://www.vph-institute.org/upload/international-avicenna-alliance-conference-report-4-sept-2018-final_5bd9c5183292b.pdf

33 Faris O, Shuren J. An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials. N Engl J Med 2017;376:1350–1357 doi: 10.1056/NEJMra1512592.

34 International TechneGroup Incorporated (ITI). Improve Profitability by Managing Engineering Escapes ITI White Paper. www.iti-global.com. Published May 26, 2016. Accessed May 9, 2024. https://www.iti-global.com/improve-profitability-by-managing-engineering-escapes-iti-white-paper

Figure 5: Demonstrating the ROI of ISTs[35]



Source: J Lennon, ITI Global, adapted by Mark Palmer and Alejandro Frangi

Another motivating factor for other industry sectors is lower profit margins. These drive the need to improve efficiencies in all aspects of the product lifecycle. Proctor & Gamble also understand this point, and they intentionally harness ISTs to grow and create value for their products.[36] The paradigm shift will help to derisk safety, innovation and regulation for FDA-regulated products.

A. COST AND TIME BENEFITS GAINED BY ADOPTING REGULATORY GUIDANCE

The expected cost to develop a new drug—including capital costs and expenditures on drugs that fail to reach the market (90% failure rate in translating from pre-clinical to clinical)[37]—has been estimated to range from less than $1 billion to more than $2 billion.[38] In 2018, four drug development programs had previously-unstudied dose regimens approved based on in silico evidence in lieu of additional clinical trials. Combined, these companies saved an estimated $80 million in development costs and 54 months of development time.[39]

In 2021, sixteen companies participating in the FDA's model-informed drug development (MIDD) paired meeting pilot program estimated that their participation in the program collectively saved $201.5 million in development costs, and 279 months of development time. This translates to a total estimated savings of $54.7 billion.[40]

35 Ibid.

36 Ibid.

37 Dowden H, Munro J. Trends in clinical success rates and therapeutic focus. Nat Rev Drug Discov 2019;18:495e6. doi: https://doi.org/10.1038/d41573-019-00074-z

38 Congressional Budget Office. Research and Development in the Pharmaceutical Industry. www.cbo.gov. Published April 8, 2021. Accessed May 2, 2024. https://www.cbo.gov/publication/57126#:~:text=The%20expected%20cost%20to%20develop

39 Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20(2):273–286. doi: 10.1093/biostatistics/kxx069. Erratum in: Biostatistics. 2019 Apr 1;20(2):366.

40 Galluppi GR, Brar S, Caro L, et. al. Industrial Perspective on the Benefits Realized From the FDA's Model-Informed Drug Development Paired Meeting Pilot Program. Clin Pharmacol Ther 2021;110:1172–1175. doi: 10.1002/cpt.2265

It should be noted that all of these are essentially anecdotes reported by sponsors and the FDA. As such, they grossly underestimate the actual impact of ISTs on drug development, because only a small percentage of such case studies are reported in the literature.

B. COST OF NOT HARNESSING ISTs NOW

Costs associated with only limited adoption of ISTs include:

- Using a traditional design-build-test model requiring slow physical iteration time, even with the advent of rapid prototyping tools;
- Relying on costly standard animal models for preclinical development with uncertain scientific gain, as animal models often exhibit differences to human physiology that are challenging to interpret;
- Preclinical testing that is uninformed by predictive modeling, resulting in unwelcome surprises such as failed long-duration studies thus requiring subsequent root cause analysis efforts and re-testing;
- Failing to leverage innovative trial designs, including augmentation with virtual patients, resulting in clinical trials that require more participants with longer enrollment periods; and
- Designs of subsequent generations of a product are limited if models are not available to interpret and contextualize learnings from the development and results of existing product generations.

VIII. Resources

In the rapidly evolving landscape of healthcare and food science, the adoption of ISTs has emerged as a transformative approach with the potential to revolutionize scientific research, drug discovery, medical device development, and overall patient care. While many organizations may choose to develop complete IST resources in-house, the modeling and simulation ecosystem currently offers many resources to quickly implement ISTs with lower long-term investments. Table 5 provides some of the resources currently available. Additional resources are provided in Appendix C.

Table 5: IST Resources

RESOURCE	DESCRIPTION
In silico (simulation) platforms	• Simulation platforms that include patient models and therapeutic effect prediction developed for use in a variety of clinical areas • Can be full-service resources with minimal need for in-house simulation expertise
Cloud computing platforms	• Resources that allow licensing of software packages on an as-needed basis • Requires in-house expertise to build and manage CM&S models
Consultancies	• Resources with technical knowledge and computing resources (both hardware and software) who can build models and execute simulations directly for businesses • Does not require in-house expertise to build and manage CM&S models • Simulation as a service
Anatomical model generation	• Software companies with expertise in generating computational models of anatomical scans for use in development of virtual patients • Leveraged as a tool to streamline aspects of internal model development
Government agency resources: The NTP (National Toxicology Program) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)	• Provides guidance on the development of alternative regulatory approach methodologies in toxicology with a formal purpose of using these methodologies to accomplish the 3Rs (replace, reduce, refine) in relation to animal testing, including computational toxicology resources[41]
Government agency resources: FDA Medical Device Development Tools	• Computational resources that are developed for specific applications and qualified for use in regulatory submissions with an aim towards streamlining regulatory acceptance through the use of known approaches and tools[42]

41 National Toxicology Program. Computational Toxicology Projects. U.S. Department of Health and Human Services. https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox

42 Center for Devices and Radiological Health. Medical Device Development Tools (MDDT). U.S. Food and Drug Administration. Published September 19, 2022. https://www.fda.gov/medical-devices/medical-device-development-tools-mddt

IX. Conclusion

In silico technologies are revolutionizing the way we approach the development and evaluation of pharmaceuticals, medical devices, digital health technologies, personal care products, and food. By leveraging computational power to simulate real-world, human-centric outcomes, these technologies offer a cost-effective, efficient, and highly predictive toolset for innovation and safety assessment. As computational methods continue to advance, their role in supporting the lifecycle of products from design through regulatory approval and market surveillance will only grow, heralding a new era of precision in health and wellness industries.

First and foremost, successful adoption of in silico technology requires a cultural shift within organizations. This shift involves fostering an environment of openness, a culture of curiosity, and acceptance of innovative approaches where the value of ISTs in augmenting traditional experimental methods is embraced.

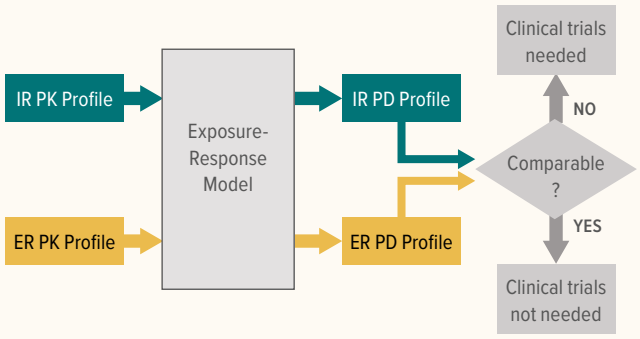
Moreover, healthcare companies must be their own drivers of change, and distinguish between simply transferring paper-based processes to electronic systems and true digital *transformation*. True digital restructuring or transformation involves rethinking and redesigning organizational processes to ensure that all aspects of the product through its life cycle are on a digital platform. This alignment with digital restructuring is essential for leveraging the full potential of in silico technology and maximizing its impact on healthcare innovation.

The ability to adapt quickly to the incoming digital revolution, embracing emerging technologies and innovative approaches, is essential to stay ahead, competitively. Proactive acceptance of ISTs can accelerate innovation in new ways that ultimately drives positive outcomes for both organizations and patients alike.

Appendices

APPENDIX A: EXAMPLES

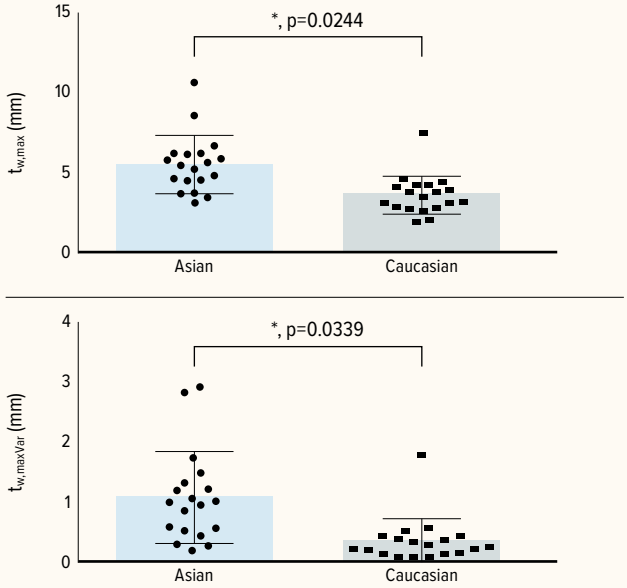
1. Model-Informed Drug Development (MIDD) – Reduced Drug Development Time and Cost Savings[43]



MIDD Approach for Bridging Efficacy from Immediate-release (IR) to Extended-release (XR) Drug Formulation

- **PRODUCT:** Drug development for targeted therapeutic use
- **IN SILICO MODEL:** Extended vs. immediate release formulations, reduced target toxicities
- **EVIDENCE: D**ata on candidate drug formulations can be successfully assessed computationally to predict a clinical effect
- **BUSINESS IMPACT:** Rapid candidate drug formulations facilitated quicker internal decision making leading to reduced development costs (no clinical efficacy and safety studies were needed for approval) and time to market while maintaining clinical safety and efficacy
- **OPPORTUNITY:** Leverage methodology to enhance regulatory interaction and approval

2. Cardiovascular device applicability—Morphological Differences Correlated Target Population Race[44]

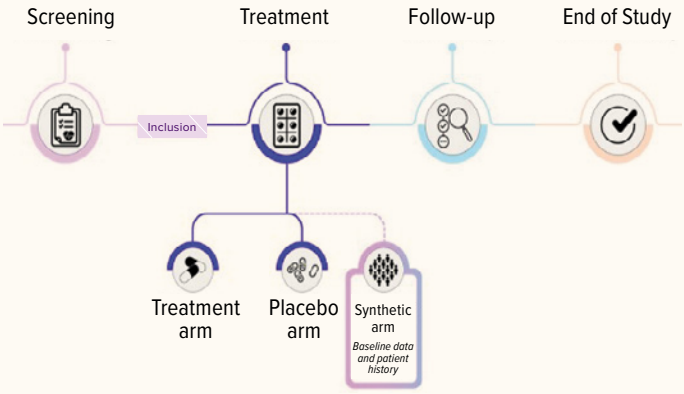


- **PRODUCT:** Population targeted cardiovascular medical device design
- **IN SILICO MODEL:** Finite element analysis and statistical shape modeling for interrogating sub-population differences
- **EVIDENCE:** Geometric and morphological measurements used for describing sub-population differences. Structural quantities to assess anatomical responses to device implantation
- **BUSINESS IMPACT:** Leveraged current clinical data to extend and optimize a current product offering of implant sizes for improved efficiency
- **OPPORTUNITY:** Leverage methodology to enhance regulatory interaction and approval

43 Mukherjee A, Tsuchiwata S, Chang C, Bridging Efficacy of Tafacitinib Immediate-Release to Extended-Release Formulations for Treatment of Ulcerative Colitis: Application of a Model-Informed Drug Development Approach. Clin Pharmacol Drug Dev 2022;11(8):976–986. doi: 10.1002/cpdd.1106

44 Canchi T, Patnaik SS, Nguyen HN, et. al. A Comparative Study of Biomechanical and Geometrical Attributes of Abdominal Aortic Aneurysms in the Asian and Caucasian Populations. J Biomech Eng. 2020;142(6):061003. doi: 10.1115/1.4045268

3. Dose Regimen Adjustment for Phase II ALS Study[45]



Phase II study design of NX201c in ALS patients

- **PRODUCT:** A cyclic peptide with promising properties for neurodegenerative diseases.
- **IN SILICO MODEL: T**wo parts: (1) A PKPD model was used to design a Phase II study. A synthetic control arm augmented the sample size of the control group; (2) the peptide's mechanism of action was incorporated in a quantitative systems pharmacology (QSP) model.
- **EVIDENCE:** The Phase II study is powered to detect statistically significant effects in the real and synthetic patient populations with doses selected for accurate dose-response characterization.
- **BUSINESS IMPACT:** optimize the dose regimen for a Phase II study in ALS patients, drawing on Phase I model-based results that correlated NX210c drug concentrations with efficacy biomarkers observed in healthy subjects.
- **OPPORTUNITY:** As the model describes the potential of NX210c to repair disruption of the blood brain-barrier, it may be a tool for bridging the efficacy of the drug from the ALS populations to other indications, such as Multiple Sclerosis, Alzheimer's disease, and Parkinson's disease.

45 Lovern MR. Population Pharmacokinetics (PK) and Pharmacodynamic (PD) Analyses of Multiple Intravenous Infusions of NX210C Peptide in Healthy Elderly Volunteers presented at: The American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2024 Annual Meeting; March 27, 2024; Colorado Springs, CO.

APPENDIX B: MYTHS

DESCRIPTION OF MYTH AND/OR EXAMPLE OF MYTH	WHY THE MYTH IS FALSE	SUGGESTED APPROACH TO ADDRESS THE MYTH Includes approaches relevant to a specific audience
Myth: Institutional legacy inertia—infeasible internal company processes or circumstances exist within the company/product sponsor to facilitate the use of modeling; thus, a misconception about when modeled evidence is useful.		
Investing in a simulation modeling plan (e.g., MIDD) is considered by the company at a time when it's too late to impact drug/device development stages.	A modeling and simulation plan can be developed at any stage of the product lifecycle (e.g., for phase 1–3 drug studies) and phase 3 is among the most common time to include modeling/simulation in development plans. Simulation plans can be included as amendments to the existing pharmacokinetic statistical analytic plans/protocols which are part of the usual drug development process. As listed in the new FDA credibility assessment guidance,[46] there are many evidence categories that facilitate the use of CM&S across the total product life cycle.	**CEO audience:** ROI examples associated with time to market and improved probability of success that is associated with modeling/simulation. **Company Program Leader or Company Regulatory Leader Audience:** Open-source communication templates/timelines to assist with regulatory and clinical evidence planning. Scenarios should include amendments to existing plans and how to include simulation in various clinical analysis plans/protocols and amendment timelines. Examples of simulation plans and/or protocol and analysis templates could be developed. Educational resources to improve awareness of use the of modeling and applications of modeling delivered to development groups responsible for the oversight of the research. Education driven by the Institute of Electrical and Electronics Engineers (IEEE), FDA, others in partnership with organizations who lead clinical program directors, clinical trial operations, regulatory societies, (e.g., Regulatory Affairs Professionals (RAPS), Drug Information Association (DIA), Council of Medical Specialty Societies (CMSS), Transcelerate)

46 Center for Devices and Radiological Health. Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions. www.fda.gov. Published November 16, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions

DESCRIPTION OF MYTH AND/OR EXAMPLE OF MYTH	WHY THE MYTH IS FALSE	SUGGESTED APPROACH TO ADDRESS THE MYTH Includes approaches relevant to a specific audience
Myth: Institutional legacy inertia no resources or capabilities exist within the company/product sponsor to support the use of modeling**		
The capabilities or expertise within the organization do not exist to perform regulatory grade modeling and simulation.	Pharmacokinetics, and Pharmacoeconomics departments which are commonly positions that exist in house regularly perform modeling of drugs, diseases, and biomarkers. These groups possess the capabilities to perform modeling and simulation. Clinical biometrics/statistics groups that exist internally within companies regularly perform statistical modeling and have analytic plan templates which can be used to develop modeling and simulation plans that can be used for submission to regulatory authorities. External experts are readily available.	**Company Program Leader or Company Regulatory Leader Audience:** Educational presentations to specific societies (e.g., RAPS) around the existing capabilities within pharmaceutical and device companies which can be used to support drug development. **All Audiences:** A position paper on modeling could include educational competencies used for modeling and examples of which roles within various organizations are likely to possess these competencies; thus, demonstrating the internal capabilities often exist in companies which can support modeling and simulation activities. In the paper, special attention could be given to differences related to the size of companies and what smaller companies can do to support their more limited resources.
Myth: Modeling is only for select groups as the information they generate is siloed and not applicable to across stakeholder groups. Even different modelers do not use the same terms when they model something similar.		
Modeling groups often don't agree on the terms to be used to describe the model. —OR— Terms are siloed by disciplines (e.g., PK/PD use terms to describe a model as mechanistic, semi-mechanistic simulation model, quantitative systems pharmacology model) and are not broadly accessible/understood.	Many of the statistics and approaches employed are used across modeling groups and are applicable to multiple stakeholders. Language within the simulation and modeling community can be more broadly applicable if other common terms from different disciplines are also used to demonstrate the relationships of models and their results.	**All Audiences:** Individual industry groups can begin to use broader terms and incorporating how other disciplines might describe the model (e.g., use language such as dynamic transition model associating a drug and biomarker to predict events instead of describing as a quantitative systems pharmacology model used to predict exposure and long term responses) or describing a model as fitting in more accessible categories that are common to other disciplines such we developed a system dynamics model where the systems included a drug and a protein receptor. Instead of using terms such as simulation model describe the modeling with terms used by other groups such as clinical risk prediction or a dynamic model used for prediction of future clinical events when compared to the observed clinical events.

DESCRIPTION OF MYTH AND/OR EXAMPLE OF MYTH	WHY THE MYTH IS FALSE	SUGGESTED APPROACH TO ADDRESS THE MYTH Includes approaches relevant to a specific audience
Myth: Modeling and simulation cannot tell us about the unknown; thus, it cannot tell us anything we don't already know.		
Modeling uses only known information and thus is not very useful when parameters or outcomes are not known.	Modeling and simulation can use known information to make predictions of unknown events. Much like statistical techniques which may estimate event rates, modeling and simulation employs some of the most sophisticated mathematical approaches to provide predictions and new datapoints that can be used for decision making.	**CEO/Investment Audience:** White paper or business article of How modeling and simulation reduces investment uncertainty by generating new predictions to improve the probability of investment success. **All Audiences:** Industry workgroups (e.g., IEEE) could compile more case studies and/or a compendium of published research to highlight what unknowns a model or simulation exercise was able to solve for and/or what new evidence was generated.
Myth: Modeling and simulation are a black box or models are unreliable and can't be used as the basis for important decisions		
Models are overly technical and do not show all the assumptions which makes them opaque if not impossible to understand. —OR— Models maybe used for some decisions, but they are not reliable enough for important decisions.	Several transparency and best practice initiatives have been published by international workgroups and professional societies to drive consensus on how to develop and show assumptions to create more transparent models. Models are used for a variety of highly important decisions such as clinical trials operations for size of a study, go/no go clinical trials, long term results of clinical or device trials, extrapolation to populations of interest (e.g., pediatrics).	**All Audiences:** Industry workgroups (e.g., IEEE) can make modeling templates, reporting, and quality checklists available. Industry professionals developing models can use evidence-based checklists as part of their submission practice to regulators and/or scientific publications to drive the uptake of consistent reporting methodologies of assumptions used for modeling. Compendia of modeling results that demonstrated predicted versus actual results. If a model predicted certain rates, was it later noted by another study type that the model was accurate or not? A systematic approach to revisiting predictions of models and documenting the results would also greatly enhance their acceptance by more stakeholders.

* *ROI is usually financial and includes considerations of cost to development, time to market, and anticipated sales*

** *Inertia is usually intimately coupled with the **perceived** benefits of known costs and previous success, which generally translate to increased regulatory and hence business predictability*

ANDA = abbreviated new drug application, BLA = Biologic License Application, CEO = Chief Executive Officer, DIA = Drug Information Association, EMA = European Medicines Agency, FDA = Food and Drug Administration, ICPE = International Society for Pharmacoepidemiology, IEEE = Institute of Electrical and Electronics Engineers, ISPOR = professional society for health economics and outcomes research MIDD = Model Informed Drug Development, NDA = New Drug Application, PK/PD = Pharmacokinetic/Pharmacodynamic, R&D = Research and Development, RAPS = Regulatory Affairs Professional Society, ROI = Return on Investment, SMDM = Society of Medical Decision Making

APPENDIX C: RESOURCES

Guidance Documents/Governmental Policy

Regulators (e.g., FDA, EMA, UK, Australia) have provided resources on the importance of modeling and simulations for use in applications. Modeled evidence is often part of a standard submission package for drugs when a 505b2 application is used. Simulation of modeled evidence (e.g. investigational drug on a biomarker) can be part of a standard drug or device application (e.g., NDA, ANDA, BLA) and can be accepted by regulators as part submission to FDA/EMA. For drug applications, modeling or simulations can be submitted in the NDA/ANDA in Module 5.3.3.5. as part of the Pharmacometric analysis.

Australia

- Clinical Evidence Guidelines: Guidelines on the clinical evidence requirements for medical devices, including In Vitro Diagnostic medical devices (IVDs), under Australian legislation. https://www.tga.gov.au/resources/resource/guidance/clinical-evidence-guidelines

China

- https://chinameddevice.com/medical-device-regulations-in-china/

Europe

- EU MDR: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745
- EMA: https://www.ema.europa.eu/en/about-us/what-we-do/legal-framework

Japan

- https://www.pmda.go.jp/english/

United Kingdom

- Regulatory Horizons Council: The role of regulation in supporting scaling-up
- https://www.gov.uk/government/publications/regulatory-horizons-council-the-role-of-regulation-in-supporting-scaling-up
- MHRA Redrup, E., Mitchell, C., Myles, P., Branson, R., & Frangi, A. F. (2023). Cross-Regulator Workshop: Journeys, experiences and best practices on computer modelled and simulated regulatory evidence—Workshop Report (Version v1). InSilicoUK Pro-Innovation Regulations Network. doi: 10.5281/zenodo.10121103
- UK Pro-Innovation Regulations Review https://www.gov.uk/government/collections/pro-innovation-regulation-of-technologies-review including the Regulator's Growth Duty FDA Guidance "Reporting of Computational Modeling Studies in Medical Device Submissions"

United States

- FDA Guidance "Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions" https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/credibility-computational-models-program-research-computational-models-and-simulation-associated

Other Resources

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Educational Partnerships

- The Association of Clinical Research Professionals: https://acrpnet.org/
- Council of Medical Specialty Societies (CMSS): https://cmss.org/
- Drug Information Association: https://www.diaglobal.org/
- Regulatory Affairs Professionals Society: https://www.raps.org/
- TransCelerate: https://www.transceleratebiopharmainc.com/

APPENDIX D: ACKNOWLEDGEMENTS

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