MODELLING AND SIMULATION AS A TRANSFORMATIVE TOOL FOR MEDICAL DEVICES: THE TRANSATLANTIC REGULATORY LANDSCAPE
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I. Contributions

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II. Abstract

With the rising demand to demonstrate safety and efficacy to regulators worldwide, clinical trials have become larger, longer, and more complex; as a consequence, the cost of getting new medical products approved has drastically increased.

The integration of computer modelling and simulation (CM&S) in the regulatory process for medical products involves the merging of some of the most advanced in silico medicine technologies with traditional clinical testing practices.

Today, companies mostly operate in a global market and moving a product to a new market can involve significant time and cost as companies must meet the unique regulatory requirements for each new geography. The rapid and widespread adoption of in silico methods in the regulatory process could drastically reduce the cost of innovation, and ultimately the cost of healthcare, so long as the CM&S tools are supported by a clear and comprehensive policy framework within which to operate.

With CM&S technologies offering an understanding of complexity on a scale never before known in human history, the concept of the right treatment for the right patient at the right time no longer remains an aspiration – it has the potential to become standard practice.

This future can only be realised by enabling in silico medicine through effective regulation – a topic which this white paper addresses.

III. The Introduction of modelling and simulation in the regulatory process

In virtually every country in the world, the commercialization of medical products (medical device, medicine, or combination product) is regulated by a governmental authority. This means that before a new medical product can be sold, it has to undergo a systematic evaluation, hereinafter referred to as regulatory process. Since 1950 the number of new molecular entities (defined as total number of small molecule and biologic approvals by the FDA) per billion US dollar spent in R&D has been constantly decreasing, crossing the limit of one new drug approved per billion dollars spent in the late ’90s. More recent studies suggest that this negative trend continues unaltered, with the biggest costs attributed to the clinical trials conducted to produce the evidence required to obtain regulatory approval, which can vary country by country. Similar trends are also observed for medical devices; for example, while global device sales are expected to grow by 6% (CAGR), the global market for Contract Research Organizations (CRO) for clinical trials of medical devices is expected to grow in the same period by 12.5% (CAGR). It is now vital to find new and better ways to ensure the safety and efficacy of new medical products through faster and more cost-effective methods than those currently used.

The integration of computer modelling and simulation (CM&S; sometime referred generically as in silico methods) in the regulatory process for medical products involves the merging of some of the most advanced in silico medicine technologies born in the 1990s with clinical testing practices that are over 2000 years old. Today, large scale computer processing enables doctors and researchers to integrate vast quantities of data from previously separated disciplines of science and medicine, allowing for the first time, the investigation of the human body as a single complex system. Eventually this is expected to have a significant impact on the regulatory systems for all medical products. Because the regulatory pathways for medical devices and medicines are quite different, hereinafter we focus our attention on medical devices.

From a commercial standpoint, the most advanced computer model ever conceived might be deemed useless unless it is accepted by regulators as a validated means to demonstrate the suitability of a new medical device for commercialization (i.e., pre-marketing authorization). Therefore, a meaningful regulation of the use of in silico methods in the regulatory process is not only necessary to facilitate the assessment of the safety and effectiveness of a new medical device, but also to inspire innovators to pursue product improvement through the use of CM&S.

The EU Medical Device Regulation specifically provides for the possibility of submitting modelling and simulation data to Notified Bodies, with similar language now included in draft versions of the EU Health Technology Regulation. But many questions remain at the EU level and indeed internationally:

* A Medical device can be sold in a country when it has been certified to be safe, effective, and cost-effective. How this is assessed varies between countries. For example, the U.S. FDA is responsible for certifying both safety and effectiveness, whereas in Europe the CE Mark only ensures the safety of the medical device, while authorities in each member state assess effectiveness and cost-effectiveness.
IV. The need to innovate the regulatory process of medical devices

New medical devices are generally developed in response to a need expressed by a physician or an otherwise unmet clinical need. After the exploration, discovery and early development phase, the focus shifts towards the generation of evidence to support the regulatory submission. Depending on the risk classification, different levels of rigor are applied to demonstrate device safety and effectiveness. Low and moderate-risk products can be cleared for market introduction based on demonstration of equivalency to a predicate device (pre-market notification or 510(k)), whereas higher-risk devices require a premarket approval application (PMA). Evidence for a 510(k) submission can often be created through bench-top testing or CM&S. The PMA process, however, generally requires evidence from human clinical trials, which are seen as the gold standard for device evaluation. Through the application of advanced statistical methods, the predictive capabilities of clinical trials have become fairly reliable, but large numbers of patients often need to be enrolled to reach the desired significance. Depending on the question asked, such trials can take anywhere between days and years. With the rising demand to demonstrate safety and efficacy to regulators worldwide, the trials have become larger, longer, and more complex.

Despite the sophistication of today’s technology, we need to consider that even clinical trials are only one model of reality. The existence of a performance gap between clinical trials, registries, and clinical practice is well known. Double-blind randomized trials are frequently not possible for medical devices, as the patient and/or physician is generally aware of the procedure or the device. Safety related trials are often impossible or impractical for ethical reasons and could introduce unacceptable risk to the patient. It is also known that paediatric patients, patients with rare diseases, women, and ethnic minorities are underrepresented in clinical trials, and the extrapolation of expected clinical outcomes from the general population is not straightforward. Large clinical trials can expose many patients to unproven therapies. Despite our best efforts, it cannot be guaranteed that the new therapy is comparable or superior to the standard of care during the trial. We also need to recognize that the continuously increasing cost of generating regulatory evidence through clinical trials can stifle innovation.

Much can be learned by simulating the interaction of a medical device with the patient’s anatomy and physiology. In general, it can be said that simulation has the advantage that a causal relation between model input and output can be established, whereas animal testing and human clinical trials can only provide a statistical correlation. Through the creation of virtual patient populations that account for the inter-subject variability in anatomy and physiology, or in the use condition and/or product performance, virtual equivalents of in vivo clinical trials can be constructed. The use of such individualized computer simulations in the development or regulatory evaluation of a medicinal product, device, or intervention is called an in silico clinical trial (ISCT). While completely simulated clinical trials assessing all necessary endpoints are not feasible with the current understanding of biology, ISCTs have successfully been used to reduce the complexity, size and duration of in vivo clinical trials. For example, ISCTs have been used to demonstrate that it is safe for a patient implanted with a pacemaker system to undergo magnetic resonance imaging (MRI). In another application,
real world data has been used to generate a large number of virtual patients with Type 1 Diabetes Mellitus, and subsequently a mathematical model was used to study the interdependence of insulin sensitivity, pharmacokinetics, and meal absorption rate13. Such a model can potentially be used to evaluate the long-term therapeutic benefits of hybrid closed-loop insulin therapy, also known as artificial pancreas. A third application is the replacement of one specific endpoint of a human clinical trial with an ISCT, which may reduce trial size or duration. To improve the predictive capabilities of the ISCT, a Bayesian statistical approach can be used to augment computer predictions with in vivo clinical trial data or real-world observations. As confidence and maturity in the computer predictions increase, the weight of the simulation in the ISCT can be increased14. Despite all sophistication and technical rigor, CM&S can only simulate mechanisms that are included in the model. Thus, a model cannot predict unforeseen outcomes; in the best case, it can demonstrate that certain mechanisms are important.

In the long-term, ISCTs will not only play an important role in the development and regulatory evaluation of a new therapy, but might also impact the effectiveness of clinical practice and highlight socio-economic benefits as compared to other alternatives. As we transition from a fee-for-service to an outcomes-based healthcare system, computer models and ISCTs will become increasingly more important.

V. FDA strategic priorities

The Food and Drug Administration’s (FDA) primary mission is to protect the health of the American public which is the core of the Agency’s fundamental consumer protection role. The mechanisms in place that enable FDA to achieve its mission are:

- pre-market review, (an assessment of product safety and effectiveness before products are available for public use);
- post-market monitoring of the performance and safety of products once they are in the public domain;
- enforcement to ensure compliance to design control, manufacturing process control and other quality system requirements.

FDA is uniquely positioned to remove barriers and facilitate innovation and must continue to do so in an era of rapid technological advancements. The 21st Century Cures Act15 gave FDA many new authorities and resources to accomplish this mission. “Cures” provides FDA with legislative mandates aimed at modernizing its regulatory programs. Adoption and implementation of digital tools and technologies is critical for all stakeholders, and thus, FDA is actively strengthening its regulatory toolbox. One of the key tools identified by the Agency is modelling and simulation. Dr. Gottlieb, FDA’s Commissioner, has been vocal in advocating for modernization of the regulatory processes and the importance of regulatory science, including the important role that modelling and simulation can play in the regulatory review process. Congress has also been a driver to ensure FDA’s regulatory considerations include in silico clinical trials for medical products. Through FDA’s Scientific Computing Board and the Modelling and Simulation Working Group, scientists in the Agency are engaging, collaborating and sharing resources to advance CM&S.

Moreover, as part of a new digital health initiative, the Agency is creating new pathways for software and application providers through the pre-certification program16 that will focus on the appraisal of the company and less so on the individual products themselves. Revisions and updates to software and applications (such as mobile wellness apps and clinical decision support tools) occur on a time scale much faster than that which the Agency currently regulates products. FDA recognizes the need for transforming its regulatory pathways in order to expedite product approvals, while at the same time ensure high-quality, safe and effective products. The Case for Quality program17 incentivizes manufacturers to embrace new tools and promotes practices that support consistent quality manufacturing, and align FDA’s regulatory, compliance and enforcement approaches with those practices. It has also been recognized that by adopting digital tools and software platforms across the product life cycle, the industry can more easily harness real-world data. The National Evaluation System of Health Technologies (NEST)18 promotes the generation of evidences across the life cycle and their communication to all stakeholders through a system that links and synthesizes data. This opens new possibilities to improve the entire product development and production lifecycle and makes way for digital technologies to transform medical product design and evaluation. Real-world data can then be employed for further validation and refinement of models and simulation.
We have presented the vision that lies ahead for adopting CM&S for medical products; and with great opportunity comes great responsibility. Therefore, the important question remains, how do we trust the predictive capability of CM&S, whether it is for development, evaluation, or augmenting clinical studies? The consensus standards organization ASME20 formed a Committee focused on the development of approaches and methods to assess the accuracy and credibility of computational models. The ASME20 Committee on Verification and Validation (V&V) in Computational Modelling and Simulation has six subcommittees, one of which is focused on the credibility of computational modelling for medical devices. The subcommittee’s new standard on risk-informed credibility assessment will be published soon19. FDA has been part of the leadership of that subcommittee since 2011 and will adopt the approach for credibility assessment for medical devices. In summary, FDA is committed to strengthening its regulatory toolbox with reliable and credible methodologies, frameworks, approaches, and software tools that will transform the Agency’s ability to more effectively accomplish its mission in the 21st century.

VI. The need for harmonization and the current challenges

While we can recognize the positive changes by the FDA, there is a need for harmonized global change as companies mostly operate in a global market. It is not unusual, even for small and medium enterprises, to operate beyond their domestic market; this is particularly true for medical device companies. And while the Asian market is growing at impressive rates, the global market for medical devices is currently dominated by North America and the European Union. Therefore, most medical device companies aim to sell their products in these two markets, regardless of their country of incorporation. Bringing a medical product to a new market requires that the product meet the unique regulatory requirements for that country. The regulatory approval process must be repeated for each new geography. This can involve significant time and cost as companies strive to meet unique documentation, testing and evidence generation requirements.

To counteract this barrier to the global marketplace, a number of harmonization initiatives are underway, aimed at evolving different regulatory systems toward a consensus approach. These harmonization activities are led by a variety of organizations, including:

- Asia-Pacific Economic Cooperation Life Sciences Innovation Forum Regulatory Harmonization Steering Committee;
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH);
- International Pharmaceutical Regulators Forum;
- Pan American Network for Drug Regulatory Harmonization;
- International Medical Device Regulators Forum (IMDRF).

For medical devices, a number of important harmonization initiatives are being undertaken by IMDRF.

Until recently, CM&S was not accepted by regulators as primary evidence to support market authorization. Moreover, the lack of standardized approaches to assess the credibility of in silico methods was also hindering broader adoption. With respect to the EU, the regulators at the Notified Bodies may lack the necessary expertise to fully exploit this new opportunity.

In this scenario, it is absolutely vital that the American and European regulators invest in efforts to harmonize the emerging regulations for the qualification/certification of in silico methods for regulatory purposes; any substantial difference would further delay their adoption as companies invest in significant staff training on the use of in silico methods under one regulatory system and would have to retrain if another regulatory system has very different requirements and practices. The same principle applies to the regulatory agencies: by co-developing the credibility framework for in silico methods, regulators can more rapidly stand up to the challenge that this innovation involves.
However, there is a structural barrier to the proposed harmonization process. In the U.S., the FDA has full responsibility for all medical products, including medical devices. In the European Union however, the European Medicine Agency (EMA) jurisdiction is limited to medicinal products. Medical device regulation is instead under the responsibility of 33 National Competent Authorities, which operate through 58 different Notified Bodies, all acting under the same European legislation (the EU Regulation on Medical Devices 2017/745). Many of these authorities have limited technical infrastructures, potentially limiting their ability to actively contribute to the harmonization process and ensure its robust adoption and implementation.

The best evidence of this challenge is the comparison of the current situation between the U.S. and the EU. For medicinal products, the EMA and the FDA Center for Drug Evaluation and Research have taken similar approaches in the adoption process for in silico methods. However, for medical devices, while the FDA Center for Devices and Radiological Health supports a regulatory framework for the incorporation of CM&S in the premarket review process, the same is not true for the EU, and it remains unclear how the 58 Notified Bodies will approach a submission that includes in silico evidence.

VII. The impact of delayed adoption on healthcare provision in Europe

The Organisation for Economic Co-operation and Development (OECD) Health Statistics 2018 data was released on June 28, 2018. This data shows that health spending in 2016 has grown by its fastest rate in seven years with an increase of 3.4%, and that it is expected to further increase in 2017. An aging global population coupled with the ever-increasing costs of research help to account for this.

The integration of CM&S in the workflow of clinical trials has been suggested for some time as an effective approach to increase efficiency and to decrease the costs of research & development (R&D) processes. While efforts are underway to harmonize in vivo clinical trial requirements across countries, similar harmonization efforts have yet to be initiated for in silico clinical trials. A best practices guidance on CM&S is necessary to support R&D and regulatory processes, and to stimulate the creation of new kinds of digital healthcare products. Among these new kinds of digital healthcare products, decision support systems (DSS) are finding their first applications in areas like automatic imaging analysis for diagnostic and prognostic purposes, individualized dosing, patient specific or disease specific therapeutic strategy and management, to mention a few.

In medical practice, for instance, doctors are eager to adopt modern approach to further refine diagnoses and prescribe the corresponding optimal treatment. They are struggling however with the complexity of highly specialized therapies combined with an increasing number of patients’ laboratory tests, clinical and genetic data. In this case, the development of specific evolved DSS designed for data integration and analysis could enable the generation of quick, comprehensive and in-depth solutions, while reducing patient risk. Moreover, specific and sensitive diagnostic tests can be too invasive, and doctors might have to rely on simplified and less accurate procedures. In these cases, the use of CM&S could help to overcome these difficulties by supporting and providing patient-specific and non-invasive diagnostic predictions.

In areas like cardiovascular and orthopaedics, where increasing healthcare demand is linked to the ageing EU population, CM&S can provide significant added value by supporting physicians, surgeons and other stakeholders in the standard of care workflow. For example, companies are working to develop digital companion tools to complement traditional products; to facilitate their application and to enhance health outcomes, especially for non-expert users. To ensure quality, verification and validation processes are recommended as necessary steps for the development, implementation and utilization of these devices. These processes should not stand alone but should be integral part of a good simulation practice guideline indicating the recommended procedures for the development and utilization of these new tools and/or devices.

In accordance with the philosophy behind the good clinical practice guidelines, it is of paramount importance to plant the correct seeds, which will grow into the most favourable ecosystem for CM&S development. A good simulation practice guideline endorsed by regulators and other official bodies is urgently needed to complement the proposed uses for modelling & simulation contemplated by the MDR and to support regulated procedures like HTAs. The possibilities with CM&S are vast and need adequate nurturing and direction to reach full potential.
VIII. The impact of delayed harmonization on the European industrial sector

Because Europe is participating in a global healthcare system, delaying the harmonization of CM&S utilization for regulatory approval in this region could have a dramatic impact as other parts of the world are entering the in silico era. This scenario would leave both European patients and industries in an unfavourable situation. Today, the excellent balance between the need for patient safety and that for simpler regulatory processes offered by the European system ensures that European citizens have first access to many innovative medical devices; any delay in adopting a fully harmonized approach to the use of in silico methods in the regulatory process could penalize European citizens, in terms of both healthcare innovation and economic growth; and the lack of clear guidelines for in silico methods may make it much less attractive for companies to initiate their marketing approval from Europe.

Five key impacts could be felt quickly by European organizations:

1. The cost of releasing a product in Europe would be significantly higher because of the additional investment required by a traditional clinical trial. This additional cost might be primarily supported by the European market if this is the only one still requiring extensive human clinical trials. Healthcare companies would also be more hesitant to release new products in Europe first, despite the size of its market.

2. The release of new products will be delayed compared to other regions. The delay will be due, on the one hand, to the time necessary to complete the clinical trial and get the product formally approved and the reluctance of companies to release new products in Europe as a priority, on the other hand. The results for European patients could be more expensive medical solutions that take longer to release.

3. Loss of European medical and pharmaceutical innovation. Companies are likely to release their products in regions where the regulatory approval process is more streamlined because of a large-scale adoption of the in silico clinical trial approach. It is likely, that part of the R&D necessary to finalize and customize new products would be relocated close to the regions of initial release. Some research and development will still be carried out in Europe, to benefit from EU funding, but there is a serious risk that part of the R&D, and related employment, may take place in regions where the products will be first released. Associated 2nd-tier businesses such as contract research organizations, animal testing laboratories, clinical trial management organizations, and others may also relocate to these new R&D centers.

IX. Conclusions

4. Status quo would slow down the emergence of start-ups and SMEs. The cost and time to get a new medical device or pharmaceutical drug approved is a huge burden to start-ups and small and medium enterprises (SME). Delaying the adoption of technologies that could compress time and cost would prevent the flourishing of new healthcare start-ups in Europe and endanger smaller companies that struggle to support the long investment and late return on investment of traditional clinical trials.

5. Delaying the adoption of CM&S may slow down the harmonization of Notified Bodies. Considering the number of Notified Bodies regulating medical devices in Europe, some groups may follow innovative regulatory agencies and recommend the local adoption of CM&S in the absence of clear guidelines from the European Authorities. This approach would not favour the harmonization of the regulatory approval process throughout Europe.

As a first choice for the review and release of medical devices, European citizens enjoy first-in-the-world access for many of today’s most innovative medical devices. But the rising costs of introducing new devices into a global marketplace is stifling innovation. Computational modelling and simulation can significantly accelerate the introduction of new devices to market at a lower cost. It is evident however, that there is a need for a rapid and effective harmonization between the U.S. and Europe for a Good Simulation Practice guideline on the use of CM&S in the regulatory approval process for new medical devices. The rapid and widespread adoption of in silico methods in the regulatory process could drastically reduce the cost of innovation, and ultimately the cost of healthcare for European citizens, so long as the CM&S tools are supported by the appropriate level of credibility.
X. Key Messages from Avicenna

1. The ever-increasing cost of research and product development in the healthcare industry requires that we find new and better ways to ensure the safety and efficacy of new medical products through faster and more cost-effective methods;

2. Computer modelling and simulation (CM&S) can make use of vast quantities of raw data and turn them into actionable information that can be used by industries and regulators to understand safety, efficacy and value on a scale never possible before the dawn of the digital era.

3. CM&S has the potential to drastically reduce the cost of research, increase patient safety and raise the standards for expected efficacy, but only with a policy framework to enable it;

4. The creation of “Good Simulation Practice” guidelines as well as incorporation of CM&S into medical devices marketing authorization and reimbursement processes is essential to meeting the many challenges facing our healthcare systems;

5. American and European Regulators must invest in efforts to harmonize the emerging regulations for the qualification/certification of CM&S approaches and welcome any other region willing to join this global harmonization process.
The Avicenna Alliance is an association of industry and research organisations who have a commercial or research interest in the development of in silico medicine. The Association, established in 2015, has its origins in the Virtual Physiological Human Initiative, a European Commission funded project focused on research into computer modelling and simulation. Tasked by the European Commission with developing a "Roadmap for in silico medicine", the Association now seeks to put this roadmap into policy and ensure the development of a regulated in silico market.

This Association bridges the gap between the scientific community, industry and policy makers by advocating for policy changes that take into account scientific and market developments.

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