ANSYS

White Paper

Engineering Simulation: A Promising Tool for Securing Regulatory Approvals

Government regulators and policymakers are increasingly embracing the use of in silico medicine to demonstrate product compliance

Computational modeling and simulation (CM&S) is now widely used as a part of healthcare product and process development activities. By simulating the performance of healthcare devices and therapies in a low-risk, cost-effective virtual environment, the development process can be accomplished much faster and more cost-effectively. To date, CM&S technology has been largely ignored during the equally important and very costly regulatory approval process. Yet its acceptance for securing regulatory approvals is increasing, as more government agencies and other stakeholders are seeing its benefits. The United States Congress, the US Food & Drug Administration (FDA) and the European Parliament have all publicly recognized the value engineering simulation can add during the process of demonstrating product performance and gaining approvals. Today a number of healthcare companies and technology providers are joining forces within the Avicenna Alliance to accelerate the pace of adoption. With so many doors open, the failure to use engineering simulation as part of the regulatory approval process not only misses a major opportunity, but also wastes precious resources.

Engineering Simulation: Demonstrating Product Performance in a Risk-Free, Virtual Environment

The process of developing healthcare products, testing them and demonstrating their performance in patients is not only painstakingly slow, but also extremely expensive. For years, leading healthcare companies have leveraged the power of engineering simulation to accelerate the product development process and reduce costs – while still having complete confidence that their therapies and devices will perform as expected in the real world.

Cardiatis Multilayer Flow Modulator (MFM®)

By building 3-D geometric models of their products and the human body in a simulated, virtual design environment, hundreds of engineering teams worldwide have eliminated significant time and costs from the overall design cycle. Devices and therapies developed using engineering simulation are improving the quality of life for patients around the world, every day.

The next frontier is capitalizing on the power of engineering simulation to similarly impact the lengthy and costly clinical trials stage required by the regulatory approval process for medical devices and therapies. Just as simulation predicts real-world product performance during the development process, CM&S technology can be leveraged to help secure regulatory approvals by demonstrating physical and clinical product performance in a risk-free virtual space, an innovative approach known as "*in silico* clinical trials." Dramatic reductions in both the time and expenses associated with regulatory approvals can be achieved if regulatory authorities and policy makers accept that simulation can play a key role during this critical process.

Avicenna Alliance
Association for Predictive Medicine

The Avicenna Alliance: Joining Forces to Advance the Use of Simulation Technology

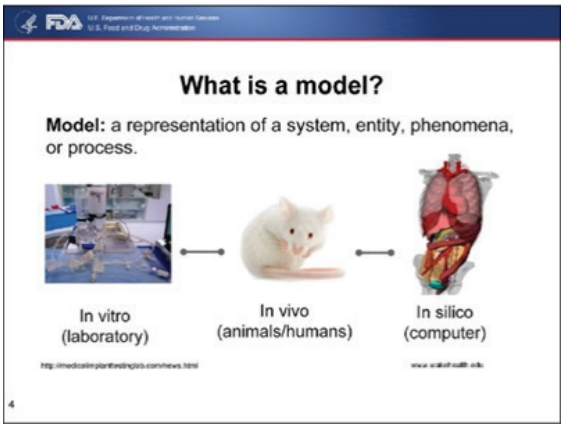
As a leading provider of engineering simulation software, ANSYS has seen its products used successfully to develop healthcare products for over 25 years — and today ANSYS is a pioneer of simulation for *in silico* clinical trials.

However, despite the fact that thousands of pharmaceutical and medical product development teams have leveraged ANSYS software, no single company can inform legislation and policy development regarding *in silico* medicine on its own. A strong community is needed to make global regulators and policymakers conscious of the need for change and educate them about the benefits of engineering simulation.

To create the foundation for such a community, the Avicenna Alliance was created in April 2016. Founding members include ANSYS, medical device manufacturer Medtronic and the Virtual Physiological Human (VPH) Institute, a European initiative that aims to enable collaborative investigation of the human body as a single complex system [1].

The Avicenna Alliance represents an essential interface that helps medical device, pharmaceutical, biotech and cosmetic companies interact with regulators and policymakers. This alliance ensures that there is rapid, thorough and careful progress toward the adoption of *in silico* medicine for securing regulatory approvals [2].

Members of the Alliance regularly meet with policymakers and legislators, as well as research groups. One of the group's key goals is to foster international collaboration and create a global dialogue about engineering simulation and its role in advancing innovation by facilitating the approvals process.



Regulatory Authorities Increasingly Champion Engineering Simulation

The relentless work of pioneering healthcare companies through the Avicenna Alliance is building on some encouraging moves from global regulatory bodies and policymakers regarding the use of engineering simulation (see sidebar, "Recent Developments in the Adoption of Simulation."). Since 2011, the U.S. FDA has been active in assessing the role that computational modeling and simulation could play in accelerating the pace of medical device and pharmaceutical innovation, including the approval of new therapies. Tina Morrison, the FDA's deputy director in charge of computational modeling and simulation, has been tirelessly pushing companies to demonstrate the value and accuracy of this *in silico* technology, but also communicating the essential role that engineering simulation will be playing in the future [3,4].

Recent Developments in the Adoption of Simulation

Recently, ANSYS has attended a number of executive meetings with policymakers and other events that signal a growing interest in engineering simulation as a regulatory approvals tool.

- In May 2017, Senator Thad Cochran, as chair of the U.S. Senate Appropriations Committee and a supporter of in silico medicine, invited leaders of the medical device, pharmaceutical and software industries – including ANSYS – together with representatives of regulatory agencies for a discussion on the benefits and hurdles of *in silico* medicine, as well as to brainstorm the next steps for facilitating global collaboration regarding CM&S technology [5].

- On October 11, 2016, based on an Avicenna Alliance initiative, the European Parliament hosted a roundtable meeting to review and discuss the role of in silico medicine to accelerate medical innovation in Europe. ANSYS presented the software solution used for *in silico* clinical trials.

- On April 5, 2017, the European Parliament approved text stressing that any simulation results submitted within the frame of a regulatory approval process must be considered. While this does not imply that any submission must include simulation results, it acknowledges the importance of any available modeling data – and states that such data cannot be ignored.

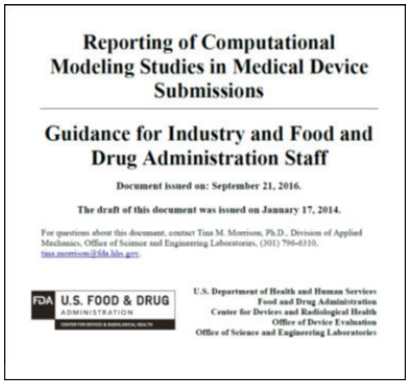
- In a July 2017 press release, Commissioner Scott Gotlieb, FDA, suggested that "the new focus on *in silico* clinical trials could soon be a Congressional requirement." [6]

In various presentations, FDA leaders have stressed that computational models are now seen as the fourth pillar in the approval process — along with animal, human and experimental testing — needed to validate a given therapy. The FDA is therefore suggesting that the developers of any medical device or pharmaceutical therapy should consider leveraging this *in silico* technology for regulatory approval. The FDA is also advising companies that intend to use computer modeling in their submission report to approach the agency first. This will ensure that simulations are being conducted in a manner consistent with the FDA's established guidelines.
In addition, the European Medicines Agency has also identified modeling and simulation as an important technology for the future — and has created a new working group devoted to this topic. The Agency is maintaining a close relationship with the FDA to pave the way toward a harmonization of global regulatory policies, using an *in silico* approach as a common language.

This transatlantic collaboration is not unique. Other important regulatory authorities in Japan, China and Brazil, to mention a few countries, are also investigating this approach. In many regions, it is now acceptable to submit simulation results to support the local regulatory approval submission report.

Submitting Simulation Results to the FDA

As both regulatory authorities and policymakers are opening the door to engineering simulation, it is crucial to define how healthcare companies can concretely use *in silico* medicine and properly report their simulation results to streamline the regulatory approval today. On September 21, 2016, the FDA published a document titled "Reporting of Computational Modeling Studies in Medical Device Submissions, Guidance for Industry and Food and Drug Administration Staff" [7], describing in detail the structure format that companies should follow to submit their simulation results as part of the approval process.


Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

The draft of this document was issued on January 17, 2014.

For questions about this document, contact Tina M. Morrison, Ph.D., Division of Applied Mechanics, Office of Science and Engineering Laboratories, (301) 796-6310, tina.morrison@fda.hhs.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of Science and Engineering Laboratories

Any companies wishing to submit simulation results to the FDA are strongly encouraged to follow this format. They should also approach their regulatory contact during the early stages of the process to signal their intention to use simulation results in the submission document, as well as seek specific guidance that would maximize the probability that their results will be accepted.

The Importance of Model Validation

As patient safety is the primary preoccupation of regulators, an in silico approach is not acceptable if the models it relies on are not properly verified and validated. While some physical or clinical validations may be somewhat straightforward, others – such as the increase in the temperature of soft tissues due to the interaction between high-frequency waves and implanted metal prostheses – are much more complex and challenging.

Under the guidance of the FDA, a working group of experts led by ANSYS, Medtronic and device manufacturer Zimmer Biomet has developed a common industry standard to help ensure that computational models are robust enough to support the regulatory approval process.

The V&V40 (Verification and Validation for medical device) process is designed to assess and minimize the uncertainties related to any data and modeling simplification. By carefully complying with the V&V40 standard, device manufacturers can simplify and accelerate the process of submitting their simulation results to the FDA and other healthcare regulators

An important tool has recently been developed by simulation industry leaders to help companies ensure their models are properly verified and validated to meet the strict guidelines of the FDA. By following this standard, called V&V40, companies can streamline the submission process and submit the strongest possible simulation results (see sidebar, "The Importance of Model Validation.").

Leveraging the Power of Engineering Simulation: Get Started Now

Most healthcare companies — with perhaps the exception of startups and small to medium sized enterprises (SMEs) — are already exploiting simulation as part of their product development process today. Many have created large, well-defined engineering teams dedicated to simulation.

Companies that are not using engineering simulation — or not leveraging it for regulatory approvals — should contact a simulation technology leader such as ANSYS to get up to speed as quickly as possible. With the current push to incorporate simulation results into regulatory approval submission reports, healthcare companies of all sizes and types need to embrace the power and potential of computational modeling and simulation.

How can companies get started? The following is a step-by-step approach:

1. The first step for any regulatory group interested in using simulation to accelerate the approval process would be to Iidentify the company's simulation leaders and experts to gain more knowledge about the modeling work currently done in the company and gauge the existing expertise level.
2. Understand that Simulations that support regulatory approvals are quite different from the routine modeling activities that support product development. The key differences are:

a. To be used within the regulatory process, the simulation process must be formally validated experimentally —and possibly clinically. If the requirements for validation are considered from the beginning of the modeling activity, preliminary regulatory assessment and possibly *in silico* clinical trials could be performed from the very early stages of product development.

b. Regulatory agencies will require that the same simulation be repeated on a large representative sample of the target population. Therefore, it is important to access a proprietary or public library of patient-specific data representing the target population, including pathologies to address. Then the team can design an automated process that allows the simulation to quickly run for the virtual population sample and synthesize the results of this *in silico* clinical trial.

c. The detailed results of the simulation should be reported in a format that is acceptable to the involved regulatory authorities.

These three differences (2a, 2b and 2c) between development-driven simulations and regulatory-focused modeling must be acknowledged from the outset to avoid costly delays. It is therefore critical to initiate a communication process that creates a convergence between real-world regulatory needs and the existing experience and expertise of the simulation team.

3. It is important to communicate early and regularly with the regulatory authority in charge of the approval. The authorities need to know the intention of using simulation results during the approval submission so that they can express their specific requirements and expectations. This approach will streamline the consideration of simulation results in the approval process.

In Conclusion

To paraphrase Professor Stefan Thomke from the Harvard Business School, who investigated best practices in the automotive industry in the late 1990s, adopting simulation for product design is not a competitive advantage anymore; NOT using computational modeling and simulation is a competitive DISadvantage. The global healthcare industry has clearly reached the same level of maturity regarding computer modeling and simulation today.

However, adopting engineering simulation pervasively — including during the regulatory approval process — remains a strong competitive advantage. Supporting the approval process with engineering simulation enables companies to capitalize on their existing resources and leverage them to accelerate and amplify the pace of medical and pharmaceutical innovation. Companies wishing to seize this opportunity should consult with their internal simulation team, software provider and regulatory experts to begin realizing the full potential of engineering simulation.

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