

IN VIVO, IN VITRO, IN SILICO: Why computer modelling is the next evolution of the healthcare sector

International Avicenna Alliance Conference

4 September 2018, 15:00-17:00

European Parliament (PHS, 5B001), Brussels



Hosted by
MEP Lieve Wierinck

MEETING REPORT



#InSilico2018
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EXECUTIVE SUMMARY

MEP Lieve Wierinck, in collaboration with the Avicenna Alliance, organised this conference to strive towards a common international framework for the validation and acceptance of computer modelling and simulation (CM&S) and adding the topic on the agenda of regulators and policy makers. The event brought together experts speakers from the EU, the USA, and India, from the FDA, leading medical device, pharmaceutical and software companies, and elite academic researchers. They discussed why a regulatory framework is crucial, what are the benefits for patients, the various industry stakeholders and regulators in and outside of the European Union.

According to the participants, the legislation in place today for regulating healthcare products predates the existence of CM&S technologies also known as in silico medicine; it is no longer fit for purpose. To address the dilemma of reducing time and cost to bring new medical treatments to market without compromising patients safety and to deliver the promise of personalised medicine, we must embrace new digital solutions. The impact of modelling and simulation in providing regulatory evidence was illustrated by a variety of examples including tailored treatments that increase efficacy and safety as well as drastically reducing costs of clinical trials. One example demonstrated that adopting an in silico approach helped to release a product 2 years earlier than expected by reducing the clinical trials by 256 patients and the estimated cost by \$10 Million while allowing to treat 10,000 patients.

FDA will continue to raise awareness about in silico medicine, to engage with national and international stakeholders to pursue harmonisation efforts, and to advance regulatory decision-making by establishing Good Simulation Practices. Ms. Wierinck committed to ensuring that in silico medicine will receive funding as part of Horizon Europe.





Predictive medicine or “in silico medicine” as a broader term, is the use of computer modelling and simulation (CM&S) in the diagnosis, treatment, prevention of a disease and development of products.

In silico medicine has only been made possible in the last few decades with the vast roll out of high-throughput computing on an unprecedented scale. Processing huge quantities of complex data that can factor in all manner of variables and translating this into highly

valuable knowledge is something that would have been unthinkable just a decade ago.

With in silico methods 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 becomes an aspiration – it becomes standard practice. The use of CM&S has the potential to trigger a technology shift that can reconcile affordable medicine, fast medical innovation and patient safety.

That being the case, the legislation in place today for regulating in silico products actually predates the existence of these technologies. In order for the in silico market to grow and for research in this field to be encouraged, a policy framework for in silico medicine needs to be developed.

Why do we need a legal/regulatory framework? What are the benefits for medical device manufacturers, pharmaceutical companies, regulators and patients? How do regulators and policy makers approach in silico models outside the European Union?

The main objective of the International Avicenna Alliance Conference entitled “In vivo, in vitro, in silico: why computer modelling is the next evolution of the healthcare sector” that took place on 4 September 2018 was to provide answers to these critical questions. The key highlights of the discussions are included in this report.



AGENDA

- 15.00 – 15:10** **Introduction by Chair**
Lieve Wierinck, Member of the European Parliament (ALDE, Belgium)
- 15:10 – 15:40** **In silico medicine and the Avicenna Alliance: Making Medicine Modern**
Thierry Marchal, Secretary General of the Avicenna Alliance
Michael Hill, VP Science, Technology and Clinical Affairs, Medtronic
Geena Malhotra, Global Head of Integrated Product Development, Cipla
- 15:40 – 15:50** **V&V40 EU – Verification and Validation in CM&S of Medical Devices**
Tina M. Morrison, Deputy Director, Division of Applied Mechanics and Chair of Modelling and Simulation Working Group, FDA
- 15:50 – 16:15** **Feedback and questions from Participants**
Dr Adriano Henney, Chairman of the Board, Avicenna Alliance
- 16:15 – 16:25** **CM&S and medicinal products' lifecycle**
Dr Ingrid Klingmann, European Forum for Good Clinical Practice
- 16:25 – 16:50** **Feedback and questions from Participants**
- 16:50 – 17:00** **Closing remarks and next steps by Chair**
Lieve Wierinck, Member of the European Parliament (ALDE, Belgium)
- 17:00 – 18:00** **Networking reception and Q&A with speakers**

OPENING SPEECH

Lieve Wierinck is a Flemish politician from the liberal Open VLD party, who is also a Member of the European Parliament (MEP). She holds a Post-graduate degree of Pharmaceutical management from the University of Hasselt. From December 2011 until June 2014, she was a member of the Belgian Federal Parliament, where she was a member of the Committee for Public Health, Environment and Social Renewal, and of the Advisory Committee on Societal Emancipation.

In May 2016, Lieve replaced Mr. Philippe De Backer as a Member of the European Parliament, where she is a full member of the Industry, Technology, Research and Energy Committee (ITRE) and a substitute Member of the Committee on Economic and Monetary affairs (ECON). Lieve also works on topics surrounding healthcare, as she strives for a progressive and affordable healthcare in Europe.

Dear ladies and gentlemen,

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Thank you all for being here today for this conference which looks to explore what we have called the next evolution of the healthcare sector.

In particular, I would like to welcome our speakers who have travelled from both east and west to be here and present their perspectives on how computer modelling and simulation could meet the test of this ambition.

It is always flattering when a constituent makes you aware of an issue and I am pleased that it was Professor Liesbet Geris from the University of Leuven who made me aware of the policy needs in this sector.

This topic may in fact be unique. It may very well be the first time that a stakeholder has come to a policymaker and asked for a sector or technology to be regulated. That is not something that you see every day.

That our current policy framework is no longer fit for purpose in this rapidly moving digital era however, is something that we are hearing more and more.

And, as with any rapidly advancing field of science, computer modelling and simulation in healthcare now brings that point into focus.

As policymakers, it is necessary for us to ensure that legal frameworks are up to date and that we develop policies that can continue to serve the needs of our citizens.

The digital era in which we find ourselves has been difficult. Today, previously completely separate areas of technological advancement are merging together. The policy implications that these advances present are complicated to say the least.



What I like about modelling and simulation, is it's potential to make sense of the complicated. If healthcare is to advance, there is no way back. There is no simplification, no niche examination that will help. While previous generations have been defined by making the complex simple, the digital era will be defined by our ability to make the complex work. And that is a crucial distinction.

For me this topic is a relatively new one and part of my role as MEP is to listen, learn and to assess what policy solutions can be put forward to tackle this challenge to society.

To do this, we will need the input from all researchers, industries, doctors, patients and indeed all stakeholders.

We have such representation here today that can get that conversation started.

We have put aside plenty of time for questions from the audience to make this an interactive session. We hope that the audience will take advantage of the expert panel here today and pose their questions and make their points.



Here to help us navigate between the overly technical and the oversimplified is Dr Adriano Henney who is a long time advocate in this field and will guide our discussions.

I am looking forward to hearing from colleagues what they have developed, what they feel computer modelling and simulation can offer in healthcare – why they feel this is not just a part of healthcare but something that can transform healthcare delivery itself and finally – what do we need to do to make that a reality.



IN SILICO MEDICINE & THE AVICENNA ALLIANCE

Thierry Marchal (Secretary General of the Avicenna Alliance and Global Industry Director Healthcare at Ansys) insisted on the fact that not only does computer modelling and simulation (CM&S) have the potential to help develop treatment faster, but also to reduce research costs, to tackle existing clinical trial-related issues (e.g. underrepresentation of certain population groups or ethical issues) and to improve patient safety. On average, up to 12 years and more than \$2.5 billion are necessary to develop a new drug. CM&S and in particular in silico trials offer the possibility of shortening and cost-reducing the time-to-market.

Against this background, Mr. Marchal suggested to use in silico testing to Complement, Anticipate and Reduce (CAR) clinical trials, which is what the Avicenna Alliance has been advocating for in the past years. Considering that the benefits of regulating in silico clinical trials would be tremendous and that the technology is already available, there is nothing preventing us from moving towards a regulated environment.

Michael Hill (Vice-President Science, Technology and Clinical Affairs at Medtronic) pointed out that although most people think that the pharmaceutical industry and the Medtech industry are equal, the latter is closer to the aerospace industry; both sectors being highly technical and regulated. On the one hand we need an airplane and a pilot, and on the other hand we need a medical device and a clinician. The procedure and the device go hand-in-hand to provide patient benefit.

Dr Hill pointed out that collaboration and technology are the foundation of innovation for developing medical device solutions to solve unmet healthcare problems. That is the reason why Medtronic partners with a wide range of stakeholders (e.g. regulators, reimbursors, clinicians, governments, engineers etc.) on design, as well as pre-clinical and clinical evidence generation. When it comes to regulatory approval, computational capability today is immense and even goes beyond what we can do with a clinical trial. Dr Hill illustrated the concrete impact of modelling and simulation on providing regulatory evidence by mentioning one of their product released 2 years earlier than expected reducing the clinical trials by 256 patients and the estimated cost by \$10 Million while allowing to treat 10,000 patients during these 2 years. 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. In addition, CM&S may enable predictive decision support tools for clinicians to provide patient specific optimized care and in the future coupled with surgical remote-control systems deliver autonomous and robotic care (full “autopilot” equivalent).

Geena Malhotra (Global Head of Integrated Product Development at Cipla) started her presentation by quoting Jeff Bezos (CEO of Amazon) “What’s dangerous is not to evolve”. Cipla’ inhalation device development process includes computer modelling, imaging, scintigraphy and computer simulations to visualize patient airways to predict and optimize drug delivery to the lungs. Ms. Malhotra is of the opinion that such in silico approach could be extended from adults to waive off clinical studies in paediatric population.

As for the development of generics, in particular of respiratory drugs, clinical trials for the demonstration of bioequivalence which forms the bulk of prescription guidance, generally require a much larger patient pool than the confirmatory Phase III clinical trials. Advanced analytics and computational modelling can however be used as an alternative approach to identify minor differences between products. Quicker approval of generics would therefore help promote access to healthcare in a world where affordable healthcare is the need of the hour.

Such in silico solutions and advanced analytics could bridge and harmonize multiple global regulatory authorities to share common clinical approaches.

KEY MESSAGES

- Modelling and simulation is a powerful tool for exploring new solutions and services while reducing patient exposure to unproven therapies and augmenting clinical trials;
- The benefits of regulating in silico clinical trials would be tremendous and nothing is preventing us from moving towards a regulated environment;
- The full value of CM&S can only be realized through international partnerships fostering the harmonization of regulatory evidence acceptance.





VERIFICATION & VALIDATION IN CM&S OF MEDICAL DEVICES

Tina Morrison (Chair, U.S. Food and Drug Administration (FDA) Modelling and Simulation Working Group at US Food and Drug Administration) provided the US Regulator's perspective on in silico methods. Computer modelling offers a different approach from bench testing which is one of the oldest models for regulatory approval. Over the past 10 years, part of Dr Morrison's mission has allowed FDA to move towards smarter evaluation. Today, most of FDA's decision making is still based on clinical trials with probably around 10% based on computer modelling and simulation (CM&S).

That being the case, these CM&S concepts translated into the 21st Century Cures Act (Cures Act) adopted in the U.S. in December 2016, which is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently. In order to support its activities and to continue developing its in silico programme, FDA will be getting money from the U.S. Congress in 2019.

The objective is for FDA scientists to use in silico data to fill the knowledge gaps of clinical trials. In silico clinical trials are therefore underway at FDA. As part of these trials, FDA scientists were able to implement a fully in silico clinical trial using only computational methods to arrive at the same regulatory conclusion as with evidence from the burdensome clinical trial.

FDA's next mission is to establish good simulation practice guidelines, based on two documents: (1) FDA, 'Reporting on Computational Modelling Studies in Medical Device Submissions' published in September 2016; (2) ASME, 'V&V40 Standard' to be published in September 2018 which focuses on the level of rigor and the amount of evidence needed for FDA evaluation. FDA is investing money in a project and working with the industry to use these two documents. A mock submission will be carried out.

KEY MESSAGES

- FDA is very serious about in silico medicine and harnessing the power of in silico methods to US public health;
- In silico methods impact regulatory decision-making at FDA and in silico clinical trials are underway at FDA;
- FDA will continue to raise awareness about in silico medicine, to engage with national and international stakeholders to pursue harmonisation efforts, and to advance regulatory decision-making by establishing Good Simulation Practices.

CM&S AND MEDICINAL PRODUCTS' LIFECYCLE

Ingrid Klingmann (European Forum for Good Clinical Practice) stressed that CM&S offers great opportunities for the development of medicinal products:

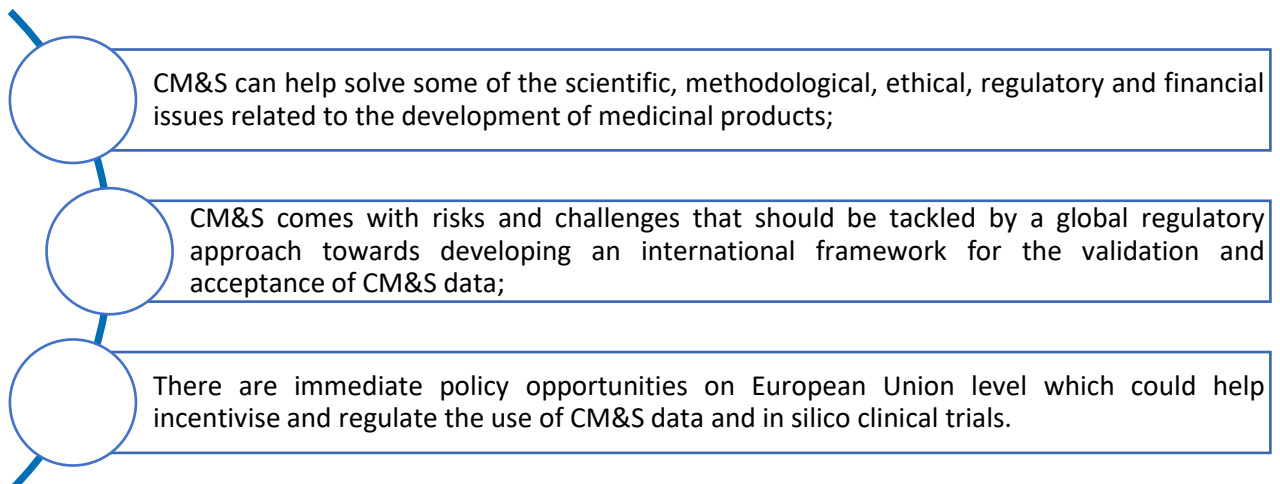
- Reduced number of patients involved in clinical trials;
- Reduced number of clinical trials required;
- Lower risks and burden for patients involved in clinical trials;
- Efficient option to test new medicines in different population groups and health conditions;
- Faster and cheaper medicine development, which results in improved access for patients, in particular, children elderly, and rare disease patients.

How to make the best use of these opportunities? Dr Klingmann advocated for regulating the sector if we were to use a combination of methodologies to complete clinical trials. A common international framework for the validation and acceptance of CM&S data should become a priority for regulators. The challenge facing regulators today is to take on their share of the global responsibility to avoid a risky approach and risky uses through a harmonization of the rules.

There are currently a few regulatory initiatives on European level which provide excellent opportunities to include the possibilities of CM&S:

- The upcoming revision of the EU Orphan Medicinal Product Regulation should properly recognize, incentivise and clarify the requirements for the inclusion of CM&S and in silico clinical trials;
- The preparation of the EU Health Technology Assessment (HTA) Regulation should take particular note of the need for HTA bodies to accept and share CM&S data to avoid duplication of work and to ensure that all Member States are in a position to make the best possible judgments on the value of a medicinal product.

KEY MESSAGES



CLOSING REMARKS & NEXT STEPS

Answering a question from the audience on the level of funding allocated to in silico medicine in the current Framework Programme for Research and Innovation (Horizon 2020), **Lieve Wierinck** recalled that she was Rapporteur for the work that the European Parliament's Committee on Industry, Research and Energy has been doing on the Framework Programme for the period 2021-2027 (Horizon Europe). As Rapporteur, she committed to ensuring that in silico medicine will receive funding as part of Horizon Europe.

Concluding the debate, she stated:

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In this Parliament we often hear of challenges without solutions – so I am particularly pleased that in these white papers and from your presentations we have some concrete ideas on how to progress.

From these discussions, I feel we move one step closer to bringing old practices in line with technologies of the new millennia.



Lieve Wierinck, Thierry Marchal, James Kennedy, Lies Geris, Tina Morrison

SPEAKERS



Lieve Wierinck, Member of the European Parliament
European Parliament

Lieve Wierinck is a Flemish politician for the liberal Open VLD party. Mrs. Wierinck holds a pharmaceutical degree from the VUB (Vrije Universiteit Brussel). In addition, she obtained a post-graduate degree of Pharmaceutical management in 2006 at the University of Hasselt. In line with her academic background, she owned and managed a pharmacy for nearly 30 years.

Before joining the European Parliament, Lieve was leader of the party fraction in Zaventem, followed by her twelve-year presidency of the OCMW (Public Centre for Social Welfare), where she managed a staff of 150 people. She combined this with her obligations as a fulltime member of the City Council of Zaventem. From December 2011 until June 2014, she was a member of the Belgian Federal Parliament, where she was a member of the Committee for Public Health, Environment and Social Renewal, and of the Advisory Committee on Societal Emancipation.

In May 2016, Lieve replaced Mr. Philippe De Backer as a Member of the European Parliament, where she is a full member of the Industry, Technology, Research and Energy Committee (ITRE) and a substitute Member of the Committee on Economic and Monetary affairs (ECON). Lieve also works on topics surrounding healthcare, as she strives for a progressive and affordable healthcare in Europe.



Ingrid Klingmann, MD, PhD, FFPM, FBCPM
European Forum for Good Clinical Practice, PHARMAPLEX bvba

Physician, specialized in General Medicine, Clinical Pharmacology and Pharmaceutical Medicine with over 30 years of experience in different senior medical, operational and managerial functions in pharmaceutical industry, Contract Research Organisations and clinical trial sites with focus on clinical trial design and management, ethical and regulatory aspects.

Since January 2003 she has her own pharmaceutical development and site management support consulting company.

Dr Klingmann is Chairman of the Board of the European Forum for Good Clinical Practice (EFGCP). On behalf of EFGCP she was and is involved in different FP7- and IMI-funded projects (ICREL, PatientPartner, PharmaTrain, EUPATI, Combacte-Magnet) and with her company in the FP7-funded paediatric LENA project and the IMI-project SPRINTT. Her broad professional background as physician with experience in patient care, clinical development, site management and patient engagement

enables Dr Klingmann to bridge the gaps between the interests and skills of all different stakeholders in medicines development with the aim to develop new patient-relevant treatments more efficiently.

Dr Klingmann is also President of PharmaTrain Federation and teaches different medicine development topics in diploma and master courses at the University of Bonn, Germany, University of Basel, Switzerland, and the Université Libre de Bruxelles, Belgium.



Adriano Henney, PhD

Chairman of the Board of the Avicenna Alliance

Dr Henney has a PhD in Medicine with research interest in cardiovascular diseases at the pathological, cellular, molecular and genetic level. After an academic career in laboratories in London, Cambridge and Oxford, he moved into industry, spending 13 years with AstraZeneca.

Ultimately, leading global programmes exploring strategic improvements aimed at reducing drug failure in development, he created and headed a new department that focused on pathway mapping and modelling, which evolved to establish the practice of Systems Biology, supporting projects in discovery and development. Dr Henney has extensive experience in directing and managing large, complex cross-disciplinary teams, cultural and geographic boundaries, latterly in the area of Systems Biology and Systems Medicine. His experience in this area led to an invitation to direct the major €50M German national flagship programme, The Virtual Liver Network (VLN), at the time the largest Systems Biology programme in Europe, involving the management of over 200 contributing scientists from a range of disciplines, including clinicians, in 36 independent institutions, and industry, located across Germany.

Following the end of the VLN Programme, Dr Henney was elected to be part-time Executive Director of the Virtual Physiological Human Institute, a not-for-profit organisation promoting the use of computational modelling and simulation to interpret quantitative biological information and understand the dynamics of biological and physiological function. As part of that role, he was responsible for establishing a new partnership with industry, and the Avicenna Alliance for Predictive Medicine.



Michael R.S. Hill, PhD, MBA

Vice President Corporate Science, Technology and Clinical Affairs, Medtronic

Michael Hill joined Medtronic in July 1992 as a Scientist in the Cardiac Rhythm Management division of Medtronic in Minneapolis, Minnesota, U.S.A. He has served in research, clinical, program, international and management roles over his tenure at Medtronic. He is a Technical Fellow (1998) and Bakken Fellow (2001). He was awarded a CRDM Star of Excellence award in 2011. In 2012, he was inducted as Fellow of the American Institute of Medical and Biological Engineering. In 2013, he was awarded the Distinguished Engineering Alumni award from Duke University. He was awarded the Medtronic Patent of Distinction Award in 2014. He currently leads the global Corporate Science, Technology and Clinical Affairs organisation. He holds over 60 patents, has authored several manuscripts and abstracts, and often is an invited lecturer at international cardiac-related conferences and university events.

A native of Jackson, Tennessee, Dr Hill received his BSE [Biomedical and Electrical Engineering] and BS [Mathematics] Degrees from Duke University, MS and PhD [Biomedical Engineering] Degrees from Case Western Reserve University, and MBA [Management] Degree from the University of St. Thomas.



Geena Malhotra

Global Head of Integrated Product Development, Cipla

Geena Malhotra is the Global President of Integrated Research & Development and also is a part of Management Council of Cipla Ltd the leading pharmaceutical company in India, with an annual turnover of over \$2 billion in sales. Cipla is the third largest company in India, with anti-HIV and respiratory as its main forte. Cipla has over 70 % market share in respiratory space in India.

Geena Malhotra completed her bachelor's degree in pharmacy in 1985 in Mumbai and an pursued Executive MBA from Washington University, St. Louis in 2017.

Geena has been the pillar of research and development for Cipla for over 3 decades, a company that started as an Active Pharmaceutical Ingredients (API) manufacturer and diversified to over 40 dosage forms, enabled singularly by Geena's leadership over the last three decades, touching almost every product and device that Cipla has in the market today. She has changed the trajectory of the company by introducing and delivering complex generics based on technology of nanoparticles, liposomes and the world's first-in-class range of respiratory products and drug device combinations, all in the environment of Quality by Design. Geena is a technologist at heart, and her passion has led her to develop not just pharmaceuticals but even the machines behind it. She has been instrumental in bringing the science of efficient drug delivery systems such as drug device combinations for respiratory therapeutics, targeted drug delivery using simulation tools etc. at Cipla. She has to her credit 300 patents filed in the areas of formulation development and technology in solid oral dosage forms, topical delivery systems and inhalation medical devices. She is responsible for providing technical leadership to multi-disciplinary R&D teams as well as operate within a cross functional environment to build and deliver a high throughput R&D with technology being the core focus. To her credit she has been constantly reinventing and repurposing to keep the momentum of research of her teams to adopt computational sciences and simulations to improve the quality and speed of development, keeping the needs of patients above all and fulfil the purpose of "caring for Life".



Thierry Marchal

Secretary General of the Avicenna Alliance, ANSYS Global Industry Director

As the ANSYS Global Industry Director since 2006, Thierry Marchal leads the medical devices, pharmaceutical and biotech strategy of ANSYS through the in silico and personalized medicine evolution by closely interacting with industrial innovators and small and medium sized enterprises (SMEs), academic leaders and governmental and regulatory authorities such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency. In his 25+ years of professional experience, Thierry has worked as the Global Materials Market Segment Manager with Fluent and Product Manager for Polyflow. Thierry holds a degree in Mechanical Engineering from UCL.



Tina Morrison, PhD

Deputy Director, Division of Applied Mechanics and Chair of U.S. Food and Drug Administration's (FDA) Modelling and Simulation Working Group

Dr Morrison is the Chair of the new FDA-wide working group on Modelling and Simulation, sponsored by the Office of the Chief Scientist, which launched in the Fall of 2016. She has been serving as the Regulatory Advisor of Computational Modelling for the Office of Device Evaluation since 2011. In that capacity, she leads the Regulatory Review of Computational Modelling working group at the Center for Devices and Radiological Health, which has developed guidance documents on the use of modelling and simulation in the regulatory evaluation of medical devices. She dedicates much of her energy towards advancing regulatory science through modelling and simulation because she believes the future of medical product design and evaluation, and thus enhanced patient care, lies with computation and enhanced visualization.

She serves as Chair of the American Society of Mechanical Engineers Committee on Verification and Validation of Computational Modelling, as well as the subcommittee (V&V40) on Computational Modelling of Medical Devices, where she is leading the development of a strategy to assess the credibility of computational models. She is working with a team at CDRH to implement this strategy into the review of premarket submissions that leverage computational modelling. For seven years, she was a scientific reviewer on a variety of medical device premarket submissions in Cardiovascular Devices.

Dr Morrison is a mechanical engineer who studied Cardiovascular Biomechanics as a post-doctoral fellow at Stanford University. During that time, she investigated the in vivo biomechanics of the aorta using gated computer tomography imaging; those data are now used as boundary condition inputs for computational modelling and bench-testing of endovascular devices in premarket submissions. She received her PhD in Theoretical and Applied Mechanics from Cornell University in 2006.