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The Role of Computational Modeling and Simulation in the Total Product Life Cycle of Peripheral Vascular Devices

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Abstract

The total product life cycle (TPLC) of medical devices has been defined by four stages: discovery and ideation, regulatory decision, product launch, and postmarket monitoring. Manufacturers of medical devices intended for use in the peripheral vasculature, such as stents, inferior vena cava (IVC) filters, and stent-grafts, mainly use computational modeling and simulation (CM&S) to aid device development and design optimization, supplement bench testing for regulatory decisions, and assess postmarket changes or failures. For example, computational solid mechanics and fluid dynamics enable the investigation of design limitations in the ideation stage. To supplement bench data in regulatory submissions, manufactures can evaluate the effects of anatomical characteristics and expected in vivo loading environment on device performance. Manufacturers might also harness CM&S to aid root-cause analyses that are necessary when failures occur postmarket, when the device is exposed to broad clinical use. Once identified, CM&S tools can then be used for redesign to address the failure mode and re-establish the performance profile with the appropriate models. The Center for Devices and Radiological Health (CDRH) wants to advance the use of CM&S for medical devices and supports the development of virtual physiological patients, clinical trial simulations, and personalized medicine. Thus, the purpose of this paper is to describe specific

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examples of how CM&S is currently used to support regulatory submissions at different phases of the TPLC and to present some of the stakeholder-led initiatives for advancing CM&S for regulatory decision-making.

Introduction

The mission of the Center for Devices and Radiological Health (CDRH) is to protect and promote public health and to facilitate medical device innovation by advancing regulatory science [1]. The Office of Device Evaluation is responsible for the premarket evaluation of therapeutic medical devices, such as peripheral interventional and vascular surgery devices. These include, but are not limited to, stents, cardiac occluders, endovascular stent-grafts, inferior vena cava (IVC) filters, and vascular access devices. As depicted in Fig. 1, the pathway to successful device development is cyclical and iterative as ideas are generated, tested, improved, retested, optimized, and finalized [2]. This process has been referred to as the total product life cycle (TPLC).

Regulatory science can foster innovation and patient safety in all the aspects of the TPLC. In 2011, FDA published a report on priority areas to harness regulatory science; regulatory science is the science of developing new tools, models, standards, and approaches to assess the safety, effectiveness, quality, and performance of all the CDRH-regulated products [3]. In four of the nine priority areas, computational modeling and simulation (CM&S) was identified as one such tool.

Some of the proposed approaches include computer models of cells, organs, and systems to better predict product safety and efficacy, virtual physiologic patients for testing medical products, and clinical trial simulations that reveal interactions between therapeutic effects, patient characteristics, and disease variables. Comprehensive evaluation of a regulatory submission for peripheral interventional and vascular surgery devices is typically supported by a combination of scientific evidence from four types of models: animal, bench, computer, and human, i.e., a clinical trial. Each model has its strengths and limitations for predicting performance and clinical outcomes. We present a range of performance attributes (Fig. 2) and our assessment of the current capabilities of the different models for peripheral interventional and vascular surgery devices.

For example, the attributes “predict performance beyond the Instructions for Use (IFU)” in Fig. 2 mean that the model has the ability to demonstrate device performance under scenarios broader than those cleared/approved in the instructions for use (IFU) of the device. This is typically not possible for a clinical trial because the inclusion and exclusion criteria are established a priori. The attribute “represent disease states” indicates that the model has the ability to simulate the behavior of the disease; this is typically achieved best with clinical evaluation. However, as the investigation of a disease brings new knowledge about the underlying mechanisms, such knowledge would enable the iteration of a computer model to capture more features of the disease state. Moreover, because computational models are high in the attribute of “ability to vary the parameters,” it is also possible for the model to be more “adaptable for patient specificity.” In contrast, clinical trials are usually designed with a population-based outcome, e.g., safety endpoint is 90% freedom from aneurysm-related

mortality, and not designed for patient-specific outcomes; therefore, they are less adaptable. Finally, while cost and time are not performance attributes, they are important factors to consider when selecting a model to produce evidence for the evaluation of a medical device. While the upfront investment of computer models may be high, especially to perform adequate verification and validation (V&V), the cost remains much less as compared to clinical evaluation.

Manufacturers of peripheral interventional and vascular surgery devices mainly use three CM&S disciplines to support regulatory submissions: solid mechanics, fluid dynamics, and electromagnetics. These approaches have been historically used to aid in device development and design optimization, to establish bench testing configurations, and to make changes and/or assess failures of a device postmarket. The ability for computer models to easily vary design or model input parameters enables users to understand their impact on key outputs and in a timely manner [4]. While computer models have the potential to revolutionize the development and evaluation of medical products, many limitations prohibit broader adoption and utility, some of which we discuss in the last section, Advancing CM&S in Medical Device Regulatory Submissions. The goal of this manuscript is to present the current use of CM&S in three different aspects of the TPLC of peripheral interventional and vascular devices and to discuss possible future directions.

Device Development and Design Optimization

Early in the TPLC, computational solid mechanics, often implemented via finite element analysis (FEA), is a tool that facilitates optimization of a device design to the desired design inputs. For example, FEA can optimize features of a stent (e.g., strut width and thickness) to balance radial support with deliverability and to assess simulated-use conditions and fatigue performance. FEA supports the interplay between design inputs and outputs; it is useful because often times inherent tradeoffs exist for each design input. Successful implementation of this step, however, requires an adequate understanding of the expected in vivo loading conditions being simulated. Additionally, FEA is used to design clinically relevant simulated-use models in conjunction with patient-specific image-based methods. Likewise, if there are multiple designs available for a device family (e.g., different stent platforms, different strut designs, and different delivery system profiles), they can be simulated under the expected implantation and in vivo loading conditions to determine the optimal design performance envelopes and to better understand the design features that can be easily modified to directly impact performance attributes (e.g., flexibility). For example, FEA has been previously employed to evaluate migration of endovascular stent-grafts by comparing the active fixation mechanisms from one design to another. More commonly, FEA is used to design an implant for a specific location with anticipated simulated-use and loading conditions. However, peripheral vascular devices can be indicated for different vascular beds: carotid, iliac, superficial femoral, renal, and below the knee, and in both the arterial and venous sides of the circulation. Therefore, FEA makes it possible to better understand the mechanical performance of a device across different vascular bed(s) and to choose an appropriate implantation location based on mechanical performance. Finally, FEA may reveal that it is possible to have one stent platform that can be used for multiple vascular beds.

Computational fluid dynamics (CFD) facilitates the optimization of the design of blood-contacting devices to minimize wall shear stress and perhaps minimize the potential for thrombus formation or hemolysis. For endovascular stent-grafts, the distal ends of the device can disrupt flow and be a source for recirculation or stagnation. Thus, CFD can be used to understand inflow and outflow tracts and investigate the interruption in flow near the proximal and distal edges of the graft material. Furthermore, CFD may afford the assessment of the potential for IVC filters to capture blood clots of different sizes, allowing for design optimization to optimize clot capture efficiency.

Supplement Nonclinical Testing

After finalizing a device design, CM&S results are provided in regulatory submissions in the report of prior investigations for investigational device exemption (IDE) applications (i.e., request for clinical study) and for the nonclinical evaluations of 510(k) premarket notifications or premarket approval submissions to support regulatory decision-making. For example, FEA is often used to evaluate the entire product matrix under expected implantation and in vivo loading conditions to allow for a more complete understanding of the expected fatigue performance by calculating the fatigue safety factors (FSFs). Simulating the device under different expected in vivo loading conditions can provide insight into which loading modes (e.g., torsion, bending, and axial shortening) might most impact the device's mechanical performance. The predicted FSF for the entire product matrix and information on the most challenging loading modes drives the identification and selection of the worst-case device size, configuration, and potential loading mode (or combination thereof) to be used in bench top accelerated durability studies. Therefore, instead of physically testing every device size or oversizing condition in a product family (which can be costly and time-consuming), predictions from FEA minimize the testing burden and demonstrate reasonable assurance of structural integrity under single or multiple fatigue loading modes for the entire product matrix. Moreover, with adequate verification and validation, FEA could eliminate the need to conduct combined loading-mode bench testing. Finally, it is also possible in some cases to conduct a comparative analysis for a particular performance metric, such as a predicate comparison for 510(k) devices (e.g., IVC filters and embolization coils).

For vascular surgical devices, the flow predictions from CFD supplement nonclinical testing of endovascular stent-grafts. For example, to determine if an endovascular stent-graft will migrate under blood flow, the drag force from blood flow can be computed with CFD and the device can then be physically tested under those predicted loads to determine the migration resistance. Also, CFD may allow the investigator to determine the potential for thrombus formation via wall shear stress calculations in the limbs of endovascular stent-grafts. Finally, IVC filter clot trapping efficiency can be computed for a range of clot sizes and shapes and complement the data from the physical evaluation of blood clots capture efficiency from the bench test.

Computational electromagnetics modeling has also been used to assess the safety of patients with implanted peripheral interventional and vascular surgery devices undergoing magnetic resonance imaging (MRI). Radiofrequency (RF)-induced heating of tissue during an MRI exam is affected by several parameters. As such, it is challenging to assess RF-induced

heating using only animal, bench, or computer models of the human anatomy. CM&S is employed to determine the temperature distribution around a medical device, with variable configuration and orientation, estimating locations of high temperature. CM&S also drives the estimation of RF-induced heating with respect to variable patient population and scan conditions for which the device is indicated. It would be cumbersome or at times ethically impossible to evaluate such effects using animal or in humans, because of the high variability of the RF-induced heating with respect to patient characteristics. CM&S enables the simulation of such variations, because the device is virtually implanted in a representative virtual patient [5] and then simulated in an MRI machine to determine the temperature change of the implant due to the RF of the coil. These values then support the MRI safety of the implants.

Postmarket Design Changes and Failure Assessment

Once a device is marketed, CM&S plays an important role in supporting design changes based on real-world clinical experiences as well as identifying the root cause of failures that may occur under broad clinical use. Device manufacturers use this information to develop and test the next generation design. Those design changes will require some evaluation which can, in part, be determined by CM&S. For example, if the change to the design is a smaller stent strut thickness, larger wire diameter, or a change in material, FEA could determine if the change warrants additional accelerated durability testing. Moreover, CM&S results later support changes to manufacturing or processing steps, such as changes in material supplier, heat treatment times, or wire forming. Manufacturing process changes evaluated through CM&S can be used in conjunction with appropriate material characterization to demonstrate that the mechanical performance remains unchanged without the need for additional significant bench testing.

Furthermore, depending on the specific indications for use and available data, it may be possible to reduce the testing burden for adding a new device size to a product matrix by comparing the mechanical performance of the new size to the currently approved sizes. Likewise, it is possible to support adding a new implant size (e.g., larger or smaller diameter or length) to demonstrate that the new size does not introduce a new worst-case for mechanical performance. CM&S could demonstrate that additional bench testing might not be necessary. For such a change, if the mechanical performance is determined to not be affected by the change, it is possible that the clinical performance could be affected. Therefore, additional data might be needed to demonstrate satisfactory clinical performance.

When failures occur postmarket after approval in broader clinical use, knowledge gained from these failures is useful for re-evaluating the design inputs and thus improving device performance and supporting design changes. For example, the original CM&S can be augmented with the new data to mimic the nature of the failure mode, and the outcomes from this analysis can be used to redesign the implant. Then, the mechanical performance of the redesign is analyzed and compared to the current device to demonstrate that the identified failure mode has been addressed, e.g., location and severity of stent fractures. Additionally, CM&S further aids in complaint investigation of returned devices to identify the root cause of failure. Since there are often many unknowns in this situation, the ability of

CM&S to handle large variations in parameters in a short time frame can speed the investigation and corrective action.

Advancing CM&S in Medical Device Regulatory Submissions

CM&S supports medical device development and evaluation in several phases of the TPLC of medical devices and has demonstrated utility in aiding in the establishment of reasonable assurance of safety and effectiveness when provided to CDRH in regulatory submissions for peripheral intervention and vascular surgery devices. To date, CM&S has largely served as a qualitative tool for comparing outcomes from one design to another, demonstrating relative performance. Therefore, while CM&S studies in regulatory submissions are often supplemental and complement data acquired using animal, bench, and human testing, they can significantly reduce the physical testing burden for new and modified peripheral intervention and vascular surgery devices. However, rarely, if ever, CM&S is used as an absolute predictor of a quantitative value that determines success or failure. Some reasons for this are the lack of relevant data to drive model development, reference and engineered solutions for verification, acceptance criterion for validation, and detailed guidance to quantify and assess the computational and experimental uncertainties. The current use of CM&S to support peripheral intervention and vascular surgery device submissions also reflects its use in other medical device areas. In order to advance CM&S as tool to support regulatory decision-making, CDRH has committed resources to develop solutions in the areas described above and has recognized CM&S as a regulatory science priority for 2017 [6].

One important initiative to aid in advancing CM&S in regulatory review is the Medical Device Innovation Consortium (MDIC), a public–private partnership that CDRH helped to establish in 2012. The MDIC was formed to create a collaborative environment where industry, government, and nonprofit groups can share expertise and resources to advance precompetitive medical device research, benefiting patients by speeding the rate at which important technologies reach the market. MDIC members, including CDRH, share a vision of using CM&S to accelerate medical device innovation and regulatory decision-making. MDIC has formed teams which include broad functional expertise that includes biostatisticians, physical chemists, engineers, and physicians, all representing different stakeholders in the community, with a goal to tackle challenges that affect everyone and that can be addressed together. One of the six program areas established by MDIC is computational modeling and simulation. MDIC “created the computer modeling and simulation project to achieve the delivery of medical product solutions in a responsible, patient-sparing way that balances the desire for certainty in the device performance while limiting the delay in patient access associated with increased certainty through the use of computer modeling and simulation as valid scientific evidence [7].” MDIC is working toward a future that will include more reliance on CM&S, and less on other data sources, to support the regulatory evaluation of medical devices.

Other collaborations with stakeholders occur through the development of consensus standards. CDRH is coleading a large international standards group through the American Society of Mechanical Engineers (ASME) called the V&V40 Subcommittee, the verification

and validation (V&V) of computational modeling for medical devices. CDRH recognizes that adequate V&V, including uncertainty quantification, are necessary to achieve wider adoption of CM&S in medical device evaluation. The standards group has developed a framework called the risk-informed credibility assessment method [8]. The framework can be used to help determine the level of V&V necessary to support using CM&S within a specific context of use. This approach will be particularly useful to medical device stakeholders, including CDRH and industry, to help determine the appropriate level of evidence when CM&S supports regulatory decision-making. CDRH hosted a public meeting in June 2013 with relevant stakeholders to openly discuss these ongoing efforts [9]. FDA has also published draft guidance on how to report on the CM&S studies used in regulatory submission [10]. This document was issued as final in September 2016. Additionally, FDA led an effort with the Institute of Electrical and Electronics Engineering (IEEE). That collaboration led to the completion of an FDA-recognized standard called the Standard for Validation of Computational Electromagnetics Computer Modeling and Simulations [11].

The power of CM&S to simulate multiple design parameters and in vivo use conditions, to predict relevant outcomes, and to visualize complex processes can revolutionize the way medical devices are investigated and patient data are utilized. As a community, we have been successful at using CM&S at different phases of the TPLC. However, for CM&S to have a greater role in regulatory decision-making, for it to serve as a significant source of valid evidence, to predict successes and failures, and for FDA's vision of virtual physiological patients, virtual clinical studies, and personalized medicine to be fully realized, stakeholders need to have ready-access to verified and validated CM&S tools. The success of the stakeholder-driven initiatives will take us one step closer to that future.

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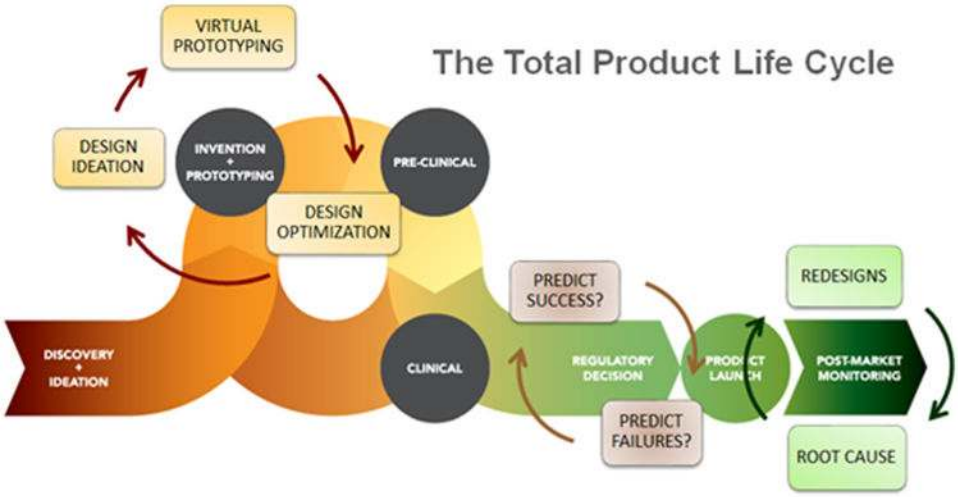

Fig. 1.

Total product life cycle of medical devices. Note that the phase "preclinical" refers to evaluations conducted before the clinical evaluation. This could include in vivo animal studies, in vitro bench testing, and in silico models.

Fig. 2.

Four different models (top row) can be used for regulatory evaluation of peripheral intervention and vascular surgery devices. The shading represents our interpretation of how well the models can be used for different aspects of performance, as listed in the left column. Note that while cost and time are not attributes of performance, they are important factors to consider when selecting a model for use as scientific evidence.