WHY MODELING & SIMULATION MAKE SENSE IN THE MEDICAL DEVICE INDUSTRY

Written by:
Arieh S. Halpern, Dassault Sytemes
Darcy Sheerin, Dassault Systemes
Stuart Wright Ph.D., Dassault Systemes

STATE OF THE MEDICAL DEVICE INDUSTRY

MACRO FORCES MOVING THE MEDICAL DEVICE INDUSTRY

The medical device industry today faces rising pressure from healthcare communities, patients wanting more personalized care, consumers and policy makers to lower healthcare costs, reduce time and costs to market for new products, and comply with increasing onerous regulations.

How are medical device companies reacting?

They are focused on developing more innovative products that improve upon patient outcomes while reducing healthcare costs. Sounds simple enough, but what levers need to be pulled in order to achieve those objectives?

Reducing time and cost to market activities without sacrifice to quality and patient safety are critical to the financial stability and growth of the company in their ability to drive innovation. This has prompted companies to re-examine ways within which to streamline the total product lifecycle development process, by examining their development processes, pre-clinical verification and validation tests (V&V), clinical studies, regulatory compliance processes, manufacturing, sourcing, and other processes.

The design, and V&V processes are very dependent upon bench testing of physical prototype models, subsequent animal studies and human clinical trials. However, this escalating process has two very important limitations:

1. There are interactions and effects between device and patient that simply cannot be adequately tested nor observed at the bench

2. It is challenging to adequately quantify risk and test for safety with animal studies and human clinical trials

This results in post-product launch adverse events, and at times, patient deaths. Essentially, animals and humans became the final testing ground for determining safety and effectiveness of many medical devices over the past decades.

Knowing these limitations, the industry is evolving towards a model that leverages Computational Modeling & Simulation (CM&S) to lessen the burden of physical trials, build the products that will improve both the patient experience and patient outcomes, and better understand and qualify the risks.

ROLE OF COMPUTATIONAL MODELING & SIMULATION (CM&S)

ROLE OF CM&S IN PRODUCT DEVELOPMENT

A faster, better, AND less costly future

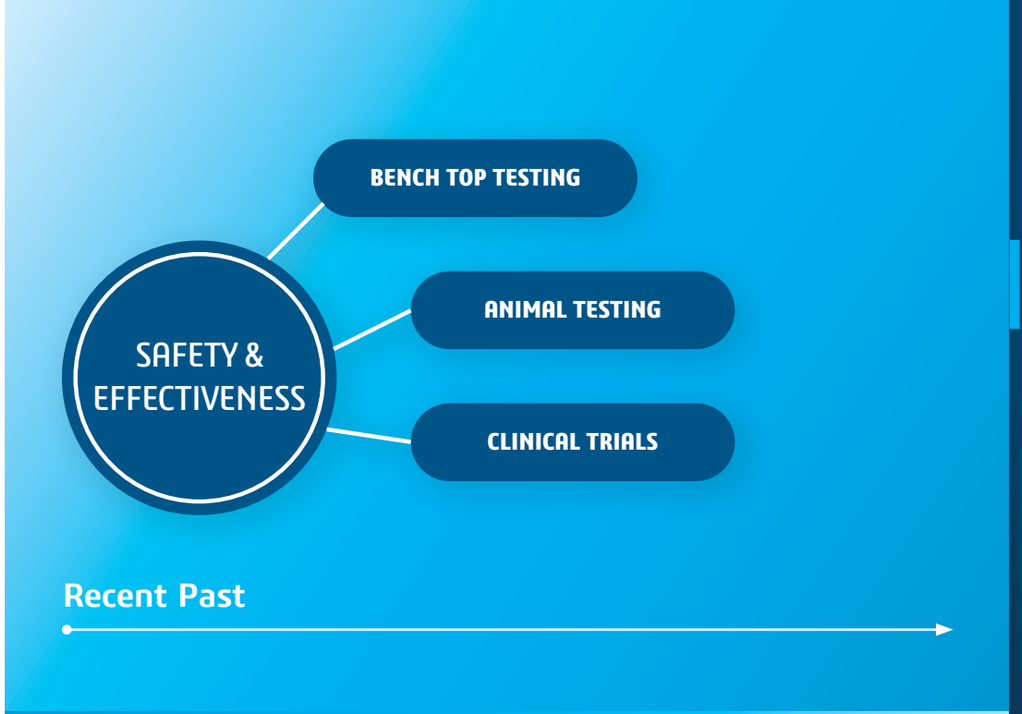
CM&S represents great opportunity for transforming the total medical device lifecycle development process and has the potential to revolutionize the devices themselves by:

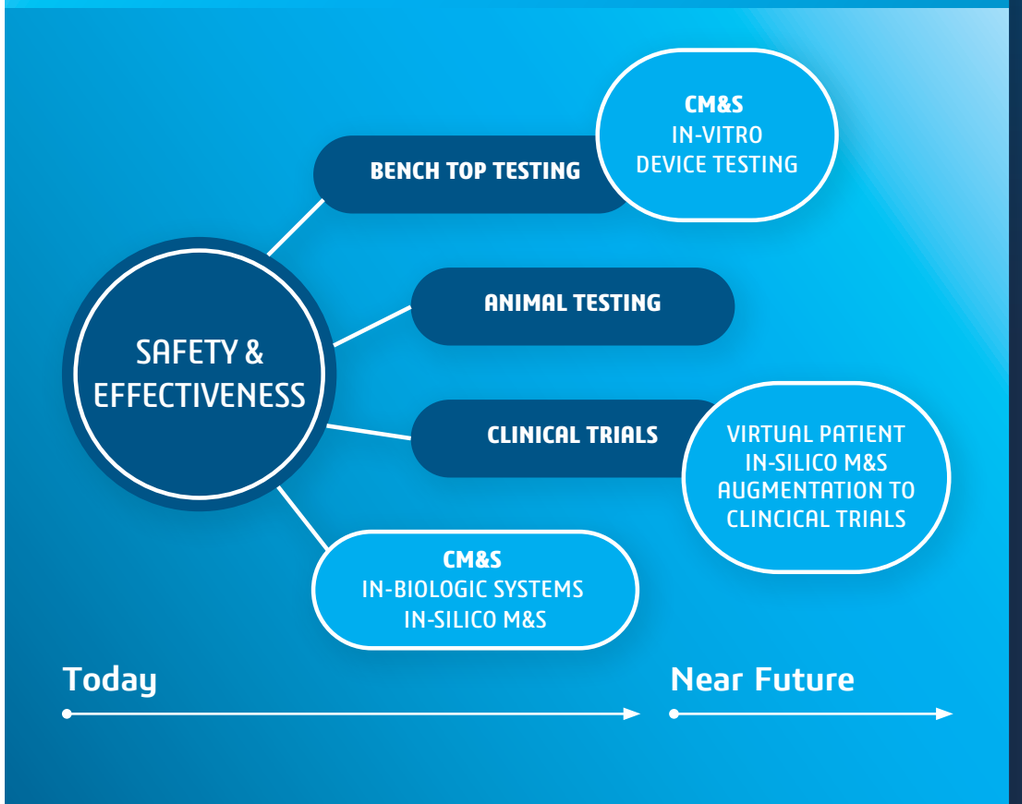
1. Accelerating innovation and providing more comprehensive evidence of short and long-term in-service device safety.

2. Breaking the trend of cost escalation in support of device V&V.

CM&S accomplishes these goals by providing non-physical means to determine performance benchmarks, assess design parameter interdependencies, evaluate a variety of use conditions and visualize complex processes.

CM&S has broad applications across most medical devices, combination products and associated technologies. It is expected that this "In-Silico" approach to design and verification will become the primary approach. The ultimate evolution of this approach includes the individual virtual patient in the simulation – capable of replicating biology, chemistry, electro-chemistry and physics in one complete and accurate representation of the patient experience.





BENEFITS OF CM&S IN DEVICE DEVELOPMENT

CM&S IS UNLOCKING NEW VALUE IN THE PRODUCT DEVELOPMENT PROCESS

Reducing time and cost: Reducing time and cost: Traditionally the development time can take five years or more to bring to market a new medical device with animal studies, clinical trials and regulatory approval taking up a major portion of the schedule. Relying on the use of conventional physical prototyping which has been the mainstream within the medical device industry for over 25 years is a very time consuming and costly approach to driving innovation. The use of In-Silico programs has the potential to shrink, shorten, and even eliminate parts of the animal and human trials. It could cut years and many millions of dollars off the program.

Accelerating initial research: CM&S enables engineers to run an almost unlimited number of statistically driven in-silico tests to be run representing both likely and unlikely conditions which could not be otherwise tested for in-animal or human clinical trials. This allows researchers and engineers to better understand the functional behavior of the device within the intended use environment and under almost any set of conditions.

Reducing risk: Risk analysis is an important part in assessing product design concepts with regards to safety of the device. One of the problems in conventional product development and subsequent V&V testing, animal and clinical trials is that you are unable to perform certain types of animal studies and clinical trials. M&S is capable of much more rigorous evaluation of product risk and can less expensively direct the best course for minimized trials.

Improved patient-centric innovation: Modeling and Simulation (M&S) provides the ability to develop more patient specific devices (e.g. cardiovascular implants, orthopedic implants, exoskeleton devices, and artificial limbs), combination products, pharmaceutical drugs. It provides the ability to more closely simulate how the specific patient and specific medical device will interact with and respond to each other, and what therapies are most effective for an individual.

Better designs: M&S allows engineers to identify design deficiencies early on in the design process before proceeding to costly development / prototyping and V&V phases, thereby also reducing cost and time to market.

Safety: Unlike traditional physical models, computational models can be used to assess aspects of in-vivo performance without subjecting patients to potential harm or unnecessary risk. Human trials are inherently risky...unless conducted in the safety of the computer.

BEYOND TRADITIONAL BENCH-TOP TESTING

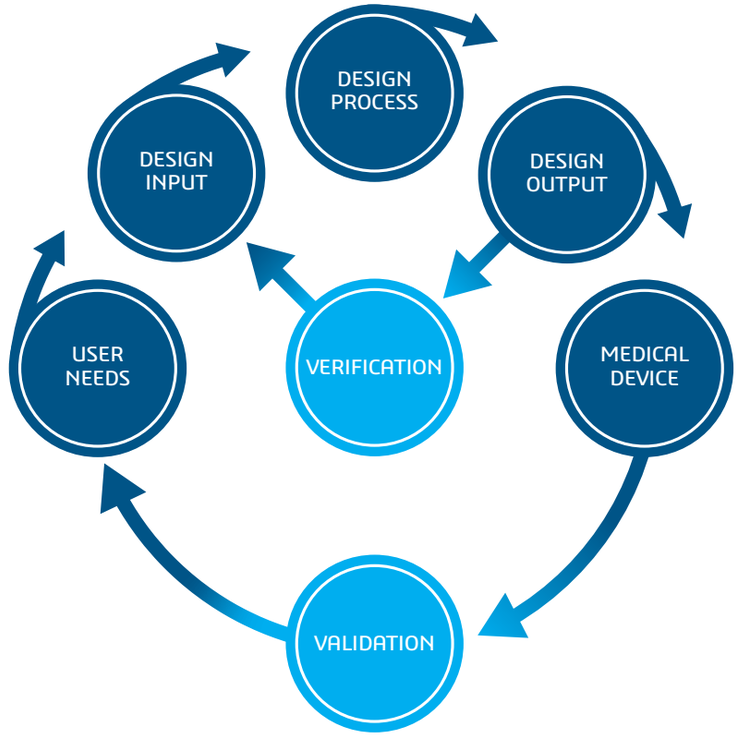
AUGMENTATION TO TRADITIONAL BENCH-TOP TESTING – WHERE VIRTUAL AND PHYSICAL COEXIST

Requirements decomposition, design, and then Validation and Verification are foundational principles in the engineering of anything engineered to fulfill a function. These four elements can be considered as firstly attending to the creation of the design, and then confirming that the design is 'correct'.

Notably in Aerospace, Defense, Transportation, and Industrial sectors CM&S is already a critical underpinning of these elements of system design/development/service. CM&S has direct application across entire multi-disciplinary design processes including electrical, electronic, mechanical, fluid, chemical and biological.

Medical device companies rely heavily on in-vitro and in-vivo testing for all four elements – clinical trials being the ultimate Validation test and the demonstration that unintended consequences are absent or manageable.

The U.S. FDA Center for Devices and Radiological Health (CDRH) and other regulatory agencies in collaboration with industry, academia and consortia (like the Medical Device Innovation Consortium (MDIC), Avicenna Alliance, ASME V&V 40, Office of Science & Engineering Laboratory (OSEL)) are now starting to embrace the use of CM&S testing as an augmentation to bench top V&V testing, animal studies and human clinical trials. This constitutes an effort to improve upon product quality & safety, accelerate the regulatory approval process, and reduce time and cost to market. The FDA has a vision of virtual physiological patients, virtual clinical studies, and personalized medicine, and for this to be realized stakeholders need to have ready-access to verified and validated CM&S capabilities.



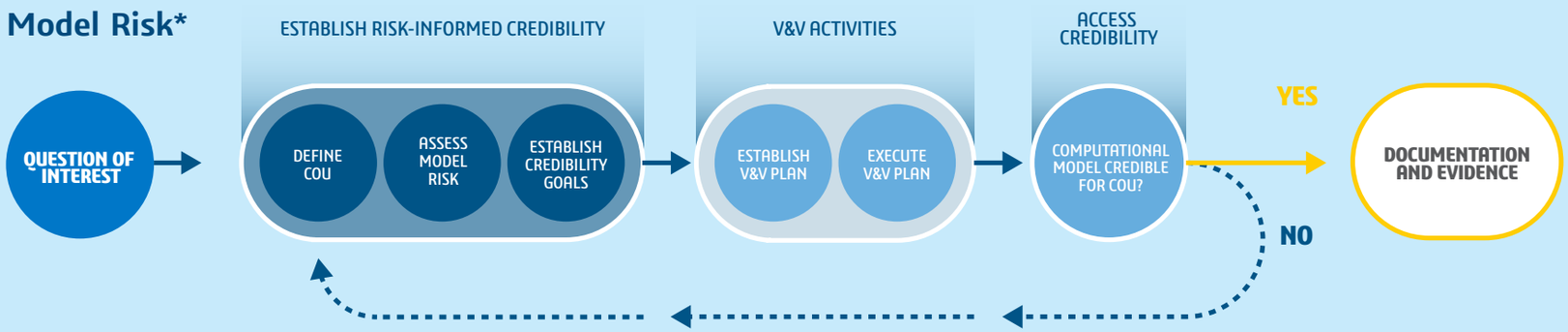
REQUIREMENTS DECOMPOSITION: The Splitting up of one function into smaller ones and the allocation to sub-ordinate system elements.

DESIGN: The configuration of form fit and function of systems elements by formalized methodology to assure that all requirements are met at all levels.

VERIFICATION: The process of checking at each stage whether the output conforms to requirements. Are we designing and building the device right? Demonstrating that the device is being created to perform as specified by requirements.

VALIDATION: Are we designing and building the right device? Demonstrating that the device as specified fulfills the needs.

CM&S GUIDELINES AND STANDARDS



REQUIREMENTS OF THE NEW CM&S MODEL

Enforced standards for using CM&S

As with many methodologies, if the models are not properly validated, it will call into question the validity of all the test data derived from the process. CM&S is no different. Guidelines and standards for the validation of "models" and collecting appropriate data for in-silico studies is an important element in developing standards for CM&S during the device testing lifecycle from benchtop V&V to animal studies to human clinical trials.

Without complete validation and complete control the results from simulation become indefensible and therefore inadmissible as evidence in regulatory submissions. The requirements themselves define the simulation management support discipline that imposes no less rigor than that required by any form of physical test evidence. This is done transparently to the user to avoid burdening them with the onerous book-keeping tasks associated with records and defense of audits.

*Ref: Tina Morrison, Ph.D. Modeling and Simulation Approaches: Enhancing Certainty, Reducing In Vivo Studies, Speeding Development

Managed Risk:

Today the risk in relying upon CM&S-based decisions is managed via a restriction of its use. CM&S is generally used as an aid to device design – augmenting (and duplicating) bench and animal testing rather than replacing it. New CM&S is risk-informed. An evaluation of risk is made which allows the reliance upon simulation to be objectively evaluated prior to the planning of In-Silico, in-vitro, and in-vivo activities. To this end:

FDA CDRH, in cooperation with the American Society of Mechanical Engineers (ASME) Verification and Validation Committee formed Computational Modeling of Medical Devices subcommittee (V&V 40) providing procedures to standardize V&V for computational modeling of medical devices (2010-11).

Model risk framework was developed to guide the analyst through the risk-informed credibility assessment, which helps determine how much V&V is necessary to support using a computational model for a context of use (COU).

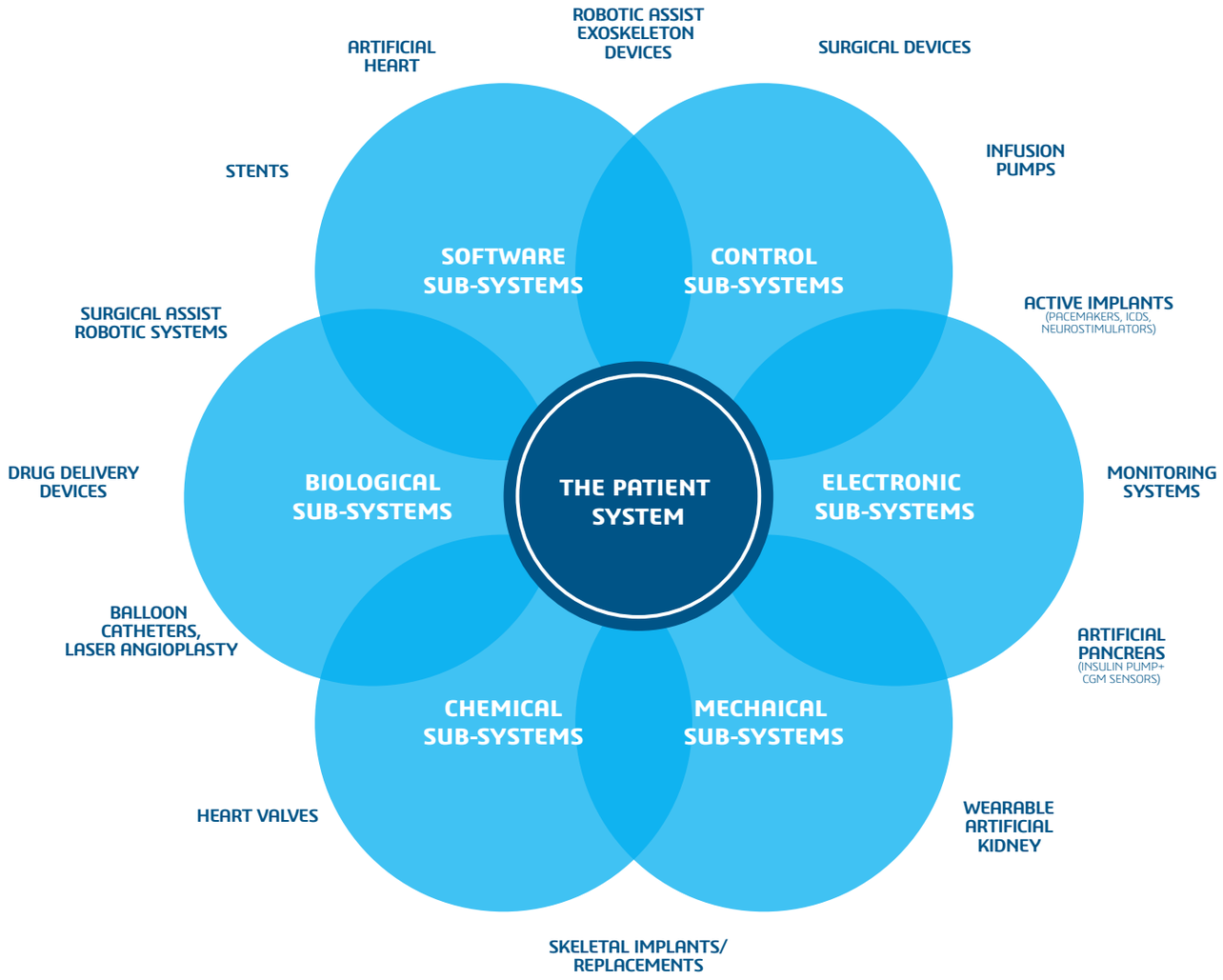
The V&V 40 Committee covers subgroups for Endovascular, Fluid Dynamics, General Methodology, Heart Valves, Orthopedics, Solid Mechanics, and Stents.

VALUE TO COMPLEX MEDICAL DEVICE DEVELOPMENT

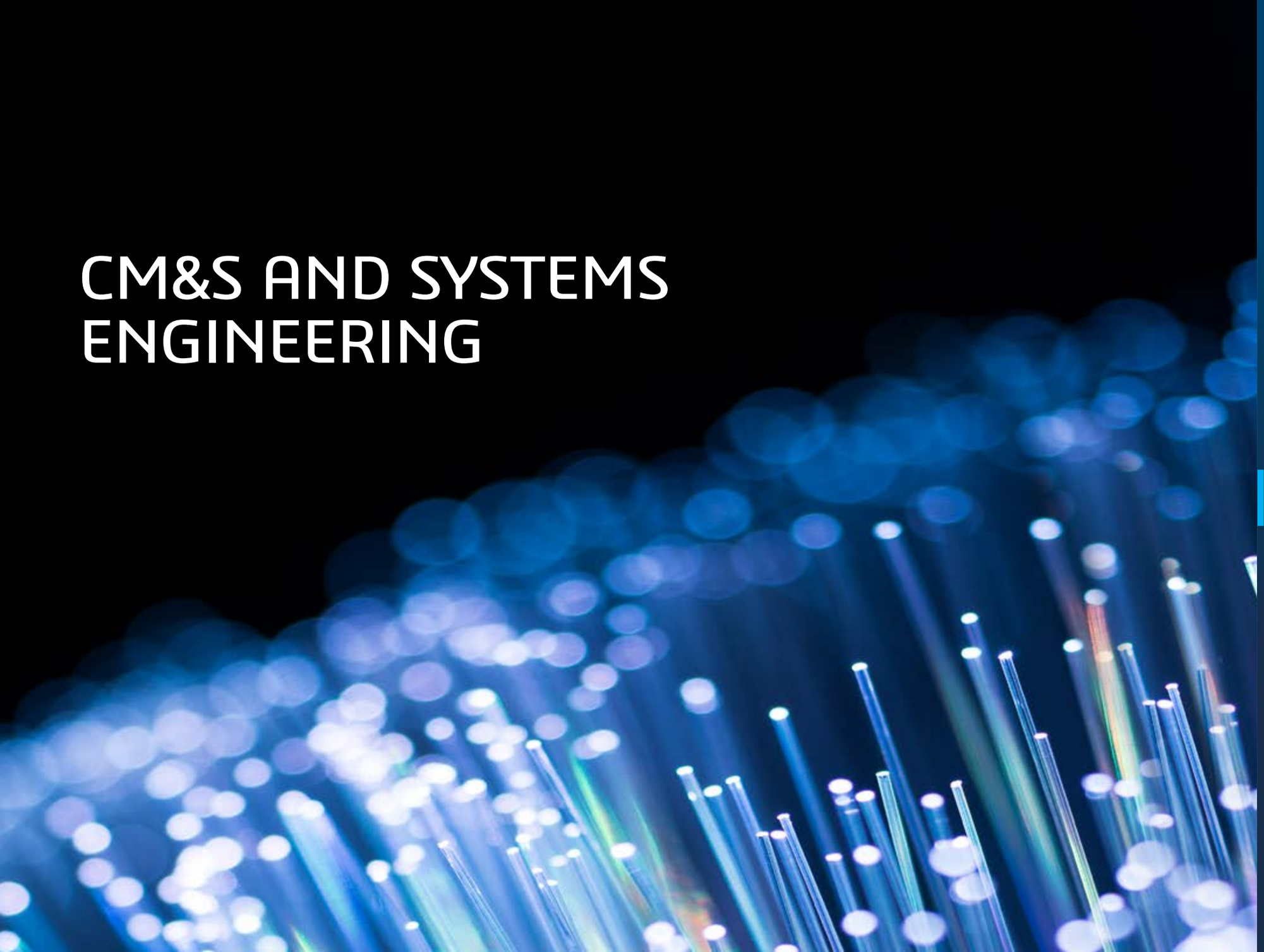
CM&S AND COMPLEX MEDICAL DEVICES

What are Complex Medical Devices?

The complexity of medical device systems perpetually increases given external pressures to deliver innovative products that improve upon patient outcomes and quality of life at lower cost without sacrifice to quality ensuring upon patient safety. Complexity is linked to the number of competing requirements the device is designed to satisfy. Extensive demands result in complex systems often comprising a number of inter-related sub-systems including mechanical, chemical, biological, electrical, electronic, software, fluid and others. Each sub-system may itself comprise heterogeneous assemblies or parts, and the whole operates within the human biological environment – itself a heterogeneous system. To meet this technology evolution, companies are shifting from a traditional product development process to a systems engineering process.

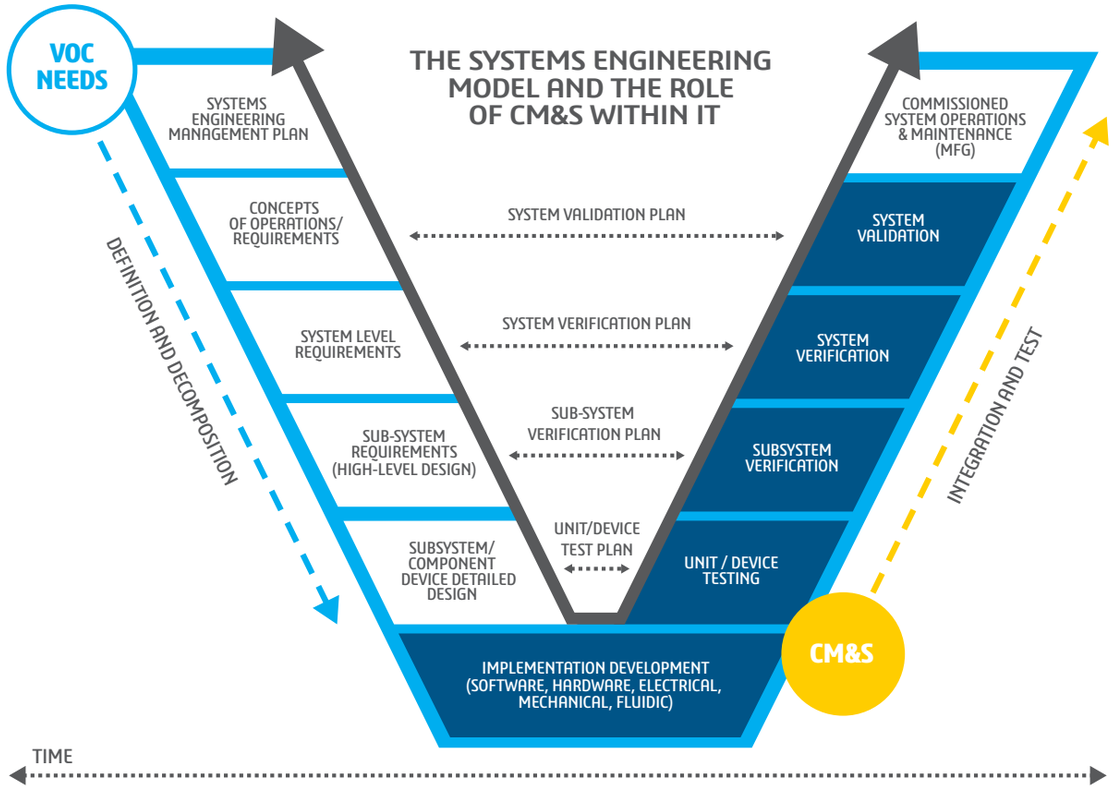


CM&S AND SYSTEMS ENGINEERING



THE SYSTEMS ENGINEERING MODEL

The systems engineering 'V' is a familiar representation that expresses the principles of requirements driven system design, verification, and validation. All verification must be traceable to requirements, and validation traceable to needs.



CM&S AND SYSTEMS ENGINEERING

The Need for Connections

The objective that almost all companies are pursuing is an instantiation of systems engineering that is model-based (MBSE) rather than diagram- and document-centric. The value of MBSE lies in the potential of full digitalization to further eliminate error and effort from the engineering process and assure quality and managed risk. Characteristics of an MBSE capability can be summarized as: One current and complete set of requirements sequentially decomposed from needs to design targets, limits and allowables; One current and complete system model, with all sub-systems, assemblies and components modeled in the master system context, associated to the hierarchy of requirements; The ability for all engineering participants to access the single model as a source of truth for all aspects of the design; Disambiguated representations of content, data, requirements, sub-models, etc.; Provides the ability to view, explore and utilize the model for different purposes and perspectives; Can act as a virtual prototype of the system.

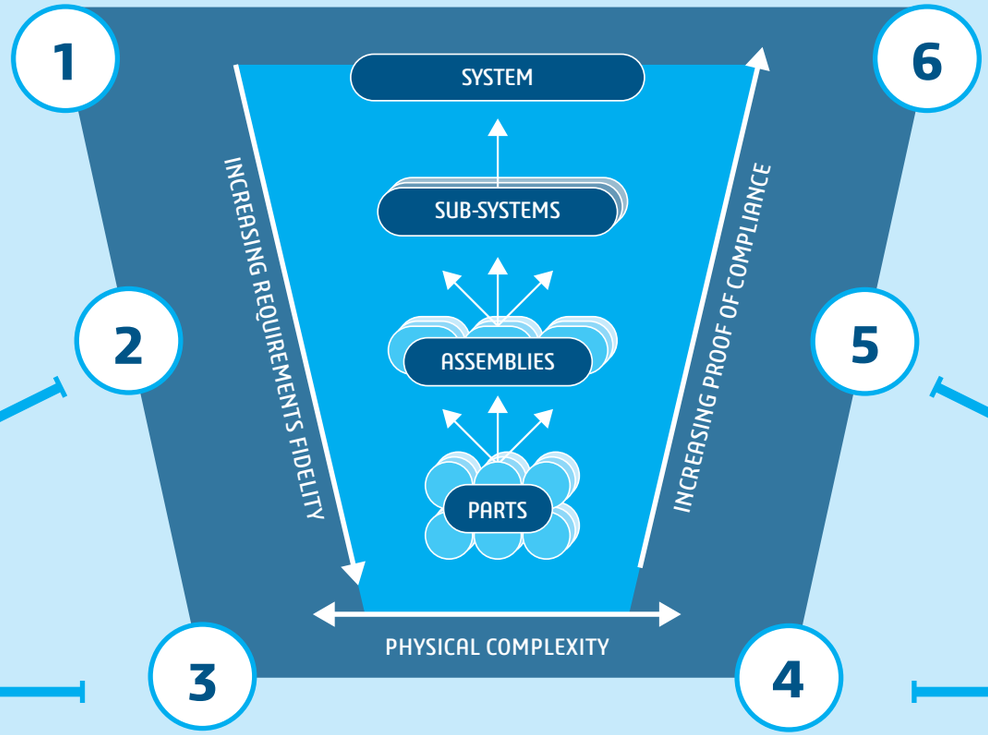
THE EXPANDING ROLE OF CM&S IN MEDICAL DEVICE MBSE

There are very few closed form numerical solutions available to the medical device design engineer to help her develop the device functionality to meet requirements in the optimal way. This is why physical testing has always, and continues to dominate this industry. However, the need and the ability to comprehensively integrate CM&S into the MBSE paradigm are together changing the game of medical device development.

1. Where system concepts and preliminary designs were validated using bench top testing we can now drive development from a single system model capable of predicting behaviors and validating alternatives prior to determining the best system concept.

2. CM&S can be used to assist in the decomposition of requirements into design objectives and targets, and then again.

3. In the process of the design of parts, assemblies and sub-systems against those decomposed requirements.



6. CM&S can be used to conduct a virtual clinical trial – utilizing an expansive virtual patient group that can direct the physical trial towards those patient characteristics representing outliers or the limits of design space.

5. Serves to guide the design of a rationalized plan, and replace/augment the execution of in-vitro and vivo verification.

4. CM&S steps in for the process of verification of performance against requirements.

PUTTING IT ALL TOGETHER

OUT WITH THE OLD, IN WITH THE NEW

ELIMINATING THE PAINS OF WORKING IN A SILOED ENVIRONMENT

In a typical siloed work environment, there can be poor collaboration amongst functional departments or groups. This is usually due to data being stored in multiple locations and multiple systems. It's human nature that people tend to be protective of the systems they are used to, event, at times, to the detriment of collaboration.

CM&S is often more siloed than most – there existing numerous specialized sub-disciplines within the whole. Effective MBSE demands that work-groups are closely digitally connected so that continuity exists across all functions of a project. New CM&S operations are capable of associating all simulation work conducted to the hierarchy of requirements and to the managed configuration of the design or virtual test. The process of conducting simulation is no longer the territory only of the analysts, but instead is an integral aspect of requirements decomposition, design, verification and validation.

TYPICAL PAINS WORKING IN DATA SILOS

- Increased development cost & time
- Manual data exchange between teams and functions
- Scattered processes and product data
- Late error discovery during integration
- High total cost of ownership
- Multiple change control systems
- Lack of common product data model
- Difficulties fulfilling regulatory, risk and quality standards

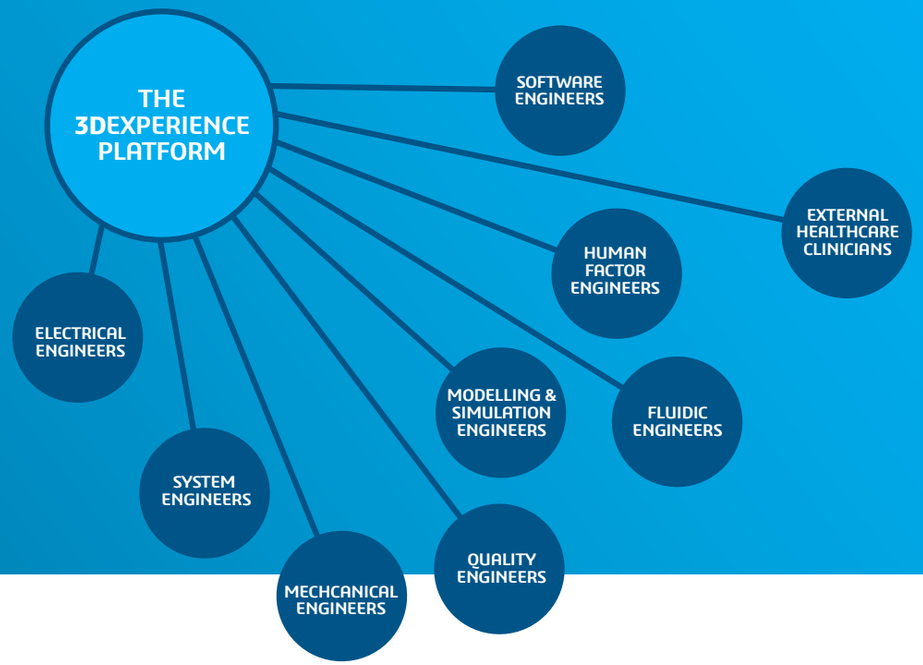
"How does a collaborative systems engineering environment work?"

CRITICAL FUNCTIONS ARE CONNECTED IN A PLATFORM ENVIRONMENT

Collaborative Systems Engineering in-silico Modelling & Simulation Environment

- Requirements Definition
- Specifications & Parameters
- Standards
- Trade-Off Studies
- Legical models
- Physical Models
- System Designs
- Electrical Design
- CAD Mechanical Designs
- Embedded Software Design
- Human Factor Designs
- Engineering Notebook
- Data Analysis
- V&V Test Designs/Reports
- Modeling & Simulation Test Designs: Finite Element Analysis (FEA), Computational Fluid Dynamics (CFD), Electromagnetic (EM)
- Simulation Model V&V (V&V 40 Framework)
- Simulation Reports
- Certification Documents
- Reports

Product Innovation Platform:



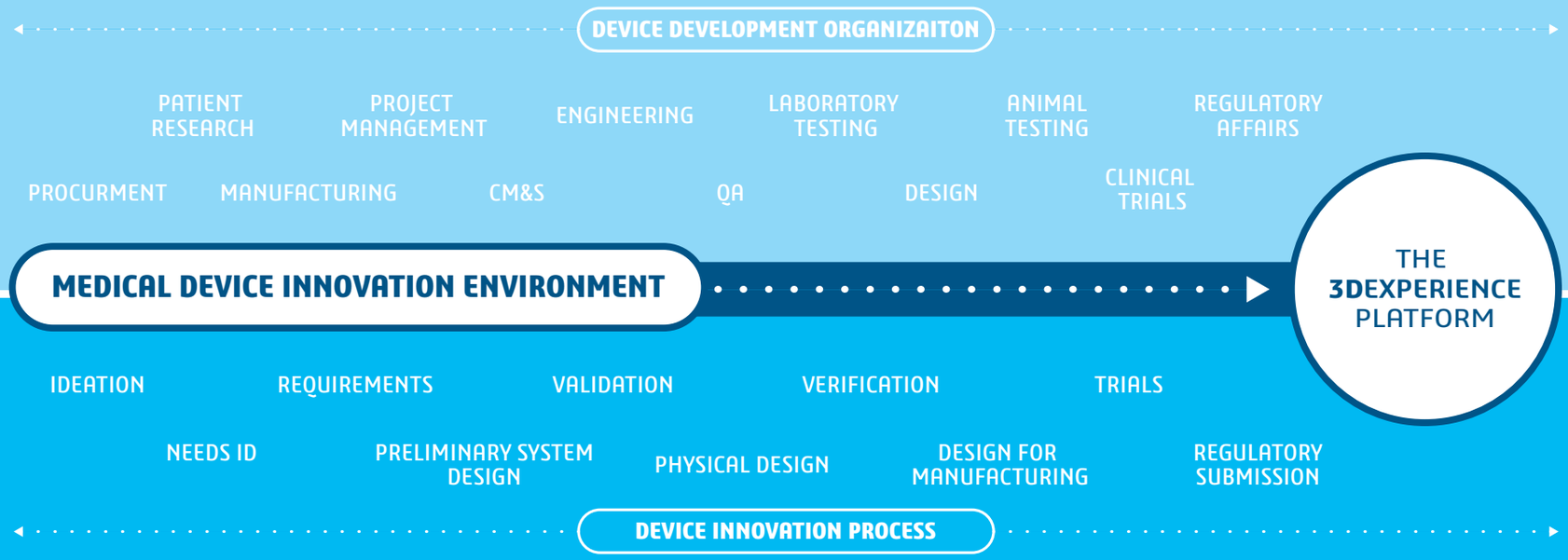
Key Benefits:

- Reduced Time & Cost to Market
- Short Time from Concept to Final Design
- Common Single Unified Change Management System
- Cross-Discipline Collaboration
- Access to the most Up-to-Date information from any location
- Establish Single Source of Truth (Data)
- Integrate Engineering Process with Downstream Functions
- Establish Standard Platform for External Coordination
- Digitally Connected Processes
- Common Development Design & Simulation Tools
- Reduction in Manual Rework
- Improved Productivity
- Improved Process Efficiency
- Eliminated time spent searching for existing product design data
- Improved Communication and Decision-Making Process

NEW CM&S AND IN-SILICO REQUIREMENTS CAN BE MET VIA A PLATFORM APPROACH

An enabling platform for effective In-Silico capabilities is required wherein integrated CM&S provides for device requirements decomposition, design, Verification, and Validation activities. The platform must connect people and business processes in a data-driven paradigm that is both local to product development workgroups, and across other business functions.

The platform must provide the environment for methods development, distribution, control, execution, and record. It must also be configurable to manage, conduct and report CM&S according to specific standards, such as V&V40, thus taking the heavy administrative burden off the development personnel. Ideally the platform should be the channel to and from regulatory bodies, such as the FDA, potentially digitizing, streamlining, and quality assuring submissions audits, and iterations.



3DEXPERIENCE COLLABORATIVE PRODUCT PLATFORM ACCELERATES INNOVATION

3DEXPERIENCE is the platform that can provide for all of the requirements dictated by both the medical device innovator and the regulatory bodies. It can deliver capabilities across all of the disciplines of program/project definition, management and execution; across all of the requirements regarding collaboration between people and business processes; across all of the requirements associated with planning, Lean execution, and management of CM&S capabilities; and the integration of all data associated with new product development, animal studies, human clinical trials and down the road in-silico studies and regulatory submissions. 3DEXPERIENCE represents the opportunity for business transformation.

CM&S capabilities are enabled by a large technical portfolio

An impactful In-Silico paradigm requires a broad and deep numerical technology portfolio. This portfolio is the foundation of effectiveness, and each method and tool must be extensively validated and sufficiently accurate in the context of use of the In-Silico study. Quality standards such as V&V40 dictate the requirements for supporting evidence that proves these aspects of In-Silico methods, but it does not prescribe the tools.

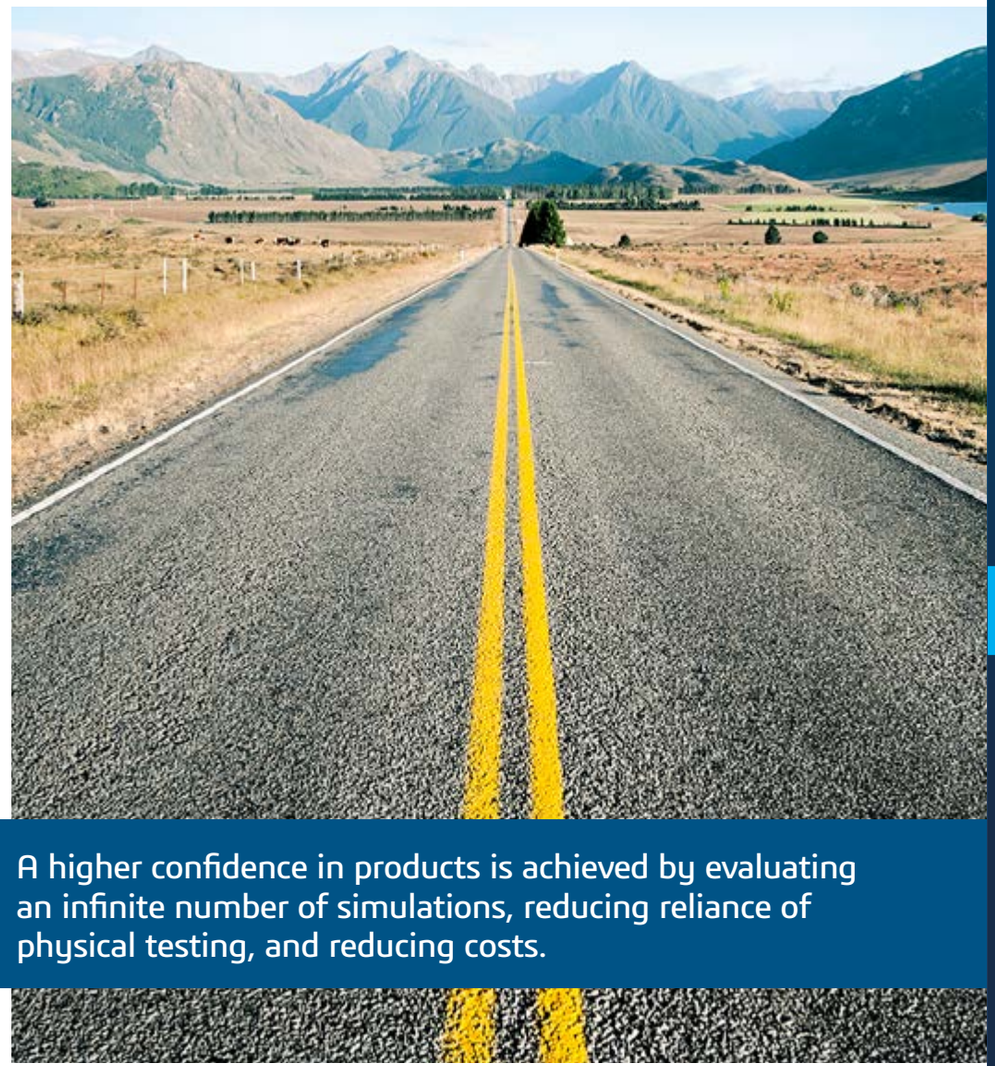
SPEED, CONFIDENCE AND SAVINGS WITH IN-SILICO TESTING

In the medical device product development cycle, the path is cyclical and iterative in nature. New ideas are created, designed, built, tested, improved, re-designed, and re-tested, all before proceeding to animal studies and eventually human clinical trials. Human clinical trials can result in approvals or findings that may require an interactive re-design and re-testing process before being optimized, finalized and released.

So how does CM&S change the game?

Modeling and simulation enables the performance of investigations where experimentation does not exist, or is costly or unethical.

With CM&S, Engineers are able to evaluate almost all aspects of product performance without the extra time or expense of bench testing. CM&S allows design engineers to perform modeling simulation tests on their designs prior to costly time consuming physical prototype builds and iterative re-design, re-test, re-build cycles. This dramatically reduces the number of animal studies and human clinical trials that need to be performed in order to establish safety, efficacy and effectiveness of the product.



A higher confidence in products is achieved by evaluating an infinite number of simulations, reducing reliance of physical testing, and reducing costs.

THE FDA AND CM&S

FDA SUPPORTIVE OF CM&S

In 2012, FDA published a report on Advancing Regulatory Science and noted that CM&S can play a role in 4 of its 8 strategic priorities. One in particular:

"Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes, would involve the development of Computational models of cells, organs, and systems, such as virtual physiologic patients, to better predict product safety and efficacy and performance of medical products."

7 PRIORITY AREAS OF ACTIVE RESEARCH

- Simulation of the heart and vasculature
- Orthopedics
- Blood damage, hemolysis and thrombosis
- Neurostimulation
- Magnetic resonance-induced heating
- Libraries for publicly sharing models, inputs, and validation data
- Combining simulations and experiments to inform clinical trials

The FDA envisions Quick and predictable access of innovative technologies to patients enabled by M&S

EXAMPLES OF CM&S BENEFITS IN ORTHOPEDIC IMPLANTS

ORTHOPEDIC IMPLANT DESIGN & PHYSICAL PROTOTYPE TESTING — WITH AND WITHOUT CM&S

Side by side, CM&S saves thousands of dollars and hundreds of labor hours.

	CONTACT MECHANICS	IMPLANT CONSTRAINT
PROCEDURE	Evaluate tibiofemoral contact mechanics at static positions throughout flexion	Measure laxity between femoral and tibial components in the absence of soft tissue structures
PHYSICAL TESTING	Cost per test: **$14,000** Time: **4 Weeks**	Cost per test: **$7,500** Time: **4 Weeks**
CM&S WITH ABAQUS KNEE SIMULATOR	Import & Setup: **10 Minutes** Analysis: **5 mins –2 hrs**	Import & Setup: **5 Minutes** Analysis: **10 mins –2 hrs**

SAFETY AND EFFECTIVENESS

A FUTURE OF SAFETY & EFFECTIVENESS

Finding the balance between the amount of testing and the number of test patients needed

New life changing/life saving products are being developed by companies across the globe, and in order for FDA to achieve its mission of bringing innovative therapies to patients first in the world, we need to find a balance between the amount and type of testing and the number patients necessary to evaluate the experimental therapies, and rely on other scientific data sources, such as computational models. Recently, some medical device submissions for therapeutic devices have contained data from four types of evaluation models–bench, computational modeling, animal, and human–to demonstrate a reasonable assurance of safety and effectiveness

Today, In-Silico (Computer based) methods allow multidisciplinary design teams to perform an almost infinite number of simulations to test variant designs under various conditions prior to costly and time-consuming physical prototype builds that would otherwise not be possible with animal studies and human clinical trials. It can:

- **REDUCE** reliance on animal modes and human clinical trial data
- **ACCELERATE** innovation
- **IMPROVE** quality design and patient safety
- **FASTER** time to market
- **LOWER** development and clinical trial costs

It seems very likely that it is only a matter of time before these alternative methods and models eventually eliminate the needs for testing on animals and humans.

Inceptra

Inceptra supports engineering and manufacturing organizations with best-in-class solutions to digitally design, simulate, produce, and manage their products and processes, enabling enhanced innovation and productivity.

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North America Headquarters
1900 N. Commerce Parkway, Weston, Florida, 33326 USA Phone (954) 442-5400

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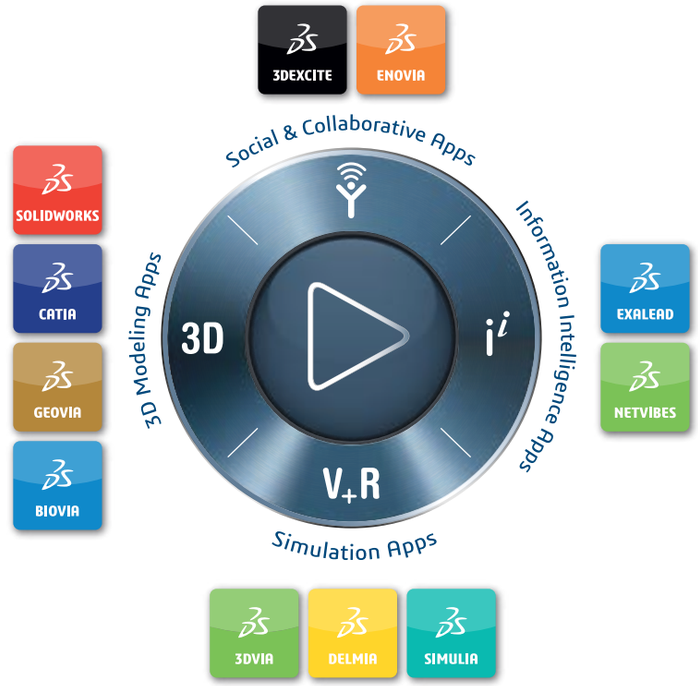

Europe/Middle East/Africa
Dassault Systèmes
10, rue Marcel Dassault
CS 40501
78946 Vélizy-Villacoublay Cedex
France

Asia-Pacific
Dassault Systèmes K.K.
ThinkPark Tower
2-1-1 Osaki, Shinagawa-ku,
Tokyo 141-6020
Japan

Americas
Dassault Systèmes
175 Wyman Street
Waltham, Massachusetts
02451-1223
USA