InSilicoTrials

WHITE PAPER

In Silico Standard Testing

insilicotrials.com
info@insilicotrials.com

Introduction

With the very rapid evolution of science and technology, medical devices are becoming increasingly sophisticated and innovative.

The safety and quality assessment is one of the most crucial procedures in the medical device development lifecycle, according to the Regulatory Affairs Professionals Society. Inadequate preclinical testing is one of the most common difficulties that leads to delays or rejection of regulatory approvals.

In silico approaches offer a great chance to improve safety, efficacy, timeliness, and cost effectiveness of medical device standard testing. The term in silico refers to computational modeling, in which a computer simulation is used to study fatigue, fracture, and other aspects of a system, and offers the opportunity to shorten the time needed to design, build, and test medical devices [1]. In most cases, in silico approaches can be used to provide efficiency and reduce the physical testing to be conducted

This article has the aim of shedding light on the concept of **In Silico Standard Testing** for medical devices and highlighting its benefits, with an emphasis on the orthopedic and cardiovascular sectors.

The need for In Silico Standard Testing

Medical device manufacturers strive to improve patients' quality of life by restoring function and relieving pain. This sector is highly regulated since implants must demonstrate quality while posing minimum risk to patients. Hence, every producer is required to provide data confirming their products' long-term safety, performance, and clinical advantages. In particular, regulatory bodies impose stringent pre-market controls to certify the safety, efficacy and compatibility of medical devices before regulatory submission and approval. Medical devices must be tested for biological and chemical safety as well as mechanical properties, functionality, and durability to ensure patient safety.

Harmonized compliance with the regulations, a key element of timely market introduction of advanced technology, is facilitated by the appropriate use of relevant medical device standards. Standards developed by organizations like ISO (International Organization for Standardization) and ASTM (American Society for Testing and Materials) represent a consensus on testing procedures that foster innovation while protecting public health and outline the essential principles of safety and performance of medical devices.
However, international standard testing may be expensive (up to $100k), time-consuming (up to-12 weeks) and challenging because of many possible sizes and configurations.

Computational modeling offers the opportunity to shorten the time needed to design, build, and test medical devices. Regarding the testing procedure, **In Silico Standard Testing** represents a digital reproduction of physical standard testing.

Potential weaknesses in design variables and their effect on design performance can be recognized in advance and addressed sooner in the design process before prototyping, leveraging computer-aided design and numerical simulations, while potentially successful products can be verified more quickly than with traditional testing. For example, **In Silico Standard Testing** can be used for worst-case assessment within a series of different sizes of the same implant design to reduce the physical test burden.

In the Regulatory Science in the Center for Devices and Radiological Health overview, Tina Morrison, Director of Office of Regulatory Science and Innovation at the FDA mentions that *computational modeling, which uses computer-based mathematical techniques, could revolutionize the field of medical devices by predicting how a device will perform before a single prototype is produced. By providing these new computer model to device designers, we're helping ensure that cutting-edge devices are safe and effective, and that they can reach physicians and patients as quickly as possible* [2].

Benefits and challenges ahead

In silico solutions enable scientists and engineers to simulate the performance of medical devices and therapies in a low-risk, cost-effective virtual environment. Analyzing hypothesis, validating ideas and testing against standards can now happen in a faster and safer way.

Among the main expected benefits of In Silico Standard Testing we list:

- Minimizing the need for physical pre-clinical testing, following a Reduce, Refine and Replace approach [3].
- Lowering development costs and time-to-market, leading to reduced costs and wider access availability of device-based treatments.
- Enhancing the quality of medical devices released into the market resulting in increased treatment efficacy and patient safety through reduction in device failure.

Additional major benefits of **In Silico Standard Testing** are also expected for 3D-printed devices. In the case of patient-specific devices, it is not feasible to apply experimental standard testing which was designed and developed to be used for generic devices. The advantages of personalized additive manufacturing would be nullified by the cost and time of traditional physical testing. Moreover, since the custom-made devices are intended for individuals' specific needs, the patient-specific conditions at which the device will be exposed would be not represented by the traditional standard testing, and "worst case" considerations would not be applicable.

Establishing credibility represents an important challenge for **In Silico Standard Testing**. Moving in this direction, industry, medical and research groups, regulators, and academia have collaborated on the development and release of ASME V&V 40 standard [1], providing a framework to establish the credibility of a computational model used for medical devices. Additionally, the US Food and Drug Administration (FDA) have recently released a draft guidance document on Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions [4]. These documents are intended to promote consistency and facilitate efficient review of medical device submissions containing **In Silico Standard Testing.**

Another challenge is related to Cybersecurity, which must be taken into account and ensured for regulatory, ethical and financial reasons. The FDA has issued a draft guidance on software assurance for computer and data processing systems associated with medical device production. [5]

InSilicoTrials.com cloud platform for In Silico Standard testing

InSilicoTrials engineered an integrated cloud platform to perform in silico testing for implants, assessing for example mechanical safety and electromagnetic compatibility in a virtual environment, in line with recognized standards and regulatory guidelines.

The integrated Modeling and Simulation (M&S) workflows on InSilicoTrials cloud platform allow the user to upload the 3D geometry and the material properties of the medical device to be tested, automatically set up the standard testing scenarios, run simulations, and process outcome, with the option to summarize the numerical results in accordance with current FDA guidance on M&S reporting [6].

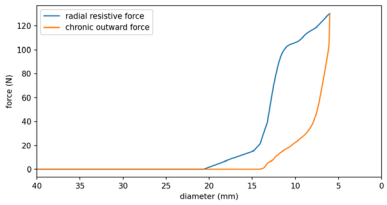
The easy-to-use interfaces run through commercial web browsers, requiring no specific computational expertise and no additional on-premises software and hardware resources, since all simulations are run remotely on cloud infrastructure.

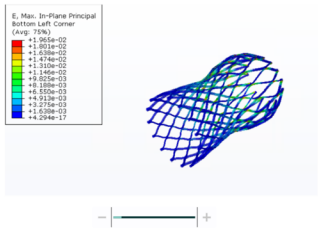
The integrated cloud platform can be used to evaluate design alternatives, test multi-configuration devices, perform multi-objective design optimization, and identify worst-case scenarios within a family of implant sizes, thus reducing the amount of physical testing to be conducted.
The tools can be used to test different prototype designs before manufacturing, or to test the final device design for regulatory submission, as a report following FDA guidelines is provided to the user.

Cardiovascular

Self-Expandable Valve Radial Force Test is based on a computational finite element model which describes the compression and expansion of a self-expandible heart valve prosthesis, following ISO 5840-3 standard.
The test aims to characterize Radial Resistive Force and Chronic Outward Force in self-expandible heart valves. The product also provides maps of mechanical strain within the valve geometry.

Standard test suite for balloon expandable devices. We are currently developing this suite comprehensive of various in silico reproduction of standard tests to assess the performance of balloon-expandable stents or heart valve substitutes. Standard test suite for balloon expandable devices is based on finite element models replicating the mechanical systems used to assess device mechanical behavior and performance, as well as durability under pulsatile conditions.





- Resistive Force and Chronic Outward Force
- Colored maps of device strain

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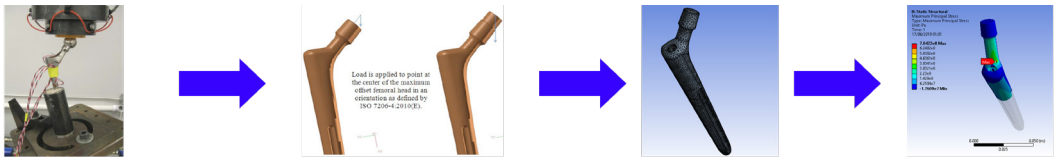
Developed by: InSilicoTrials Technologies and Politecnico di Torino

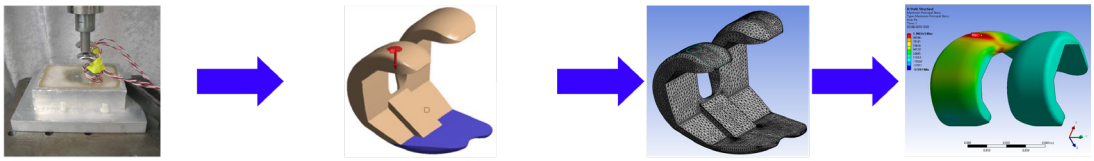
Orthopedic

ASTM Standard Test for Finite Element Analysis. A suite under development for which we have implemented automatic simulation workflows, following recommended guidelines, requirements, and considerations for the evaluation of static implant stresses and strains of metallic orthopedic device designs (hip femoral stems, total knee femoral components under closing conditions, and total knee tibial components).

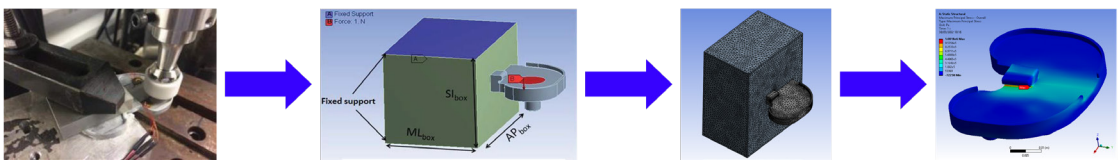
ASTM F2996-20
Standard Practice for FEA of Non-Modular Metallic Orthopaedic Hip Femoral Stems



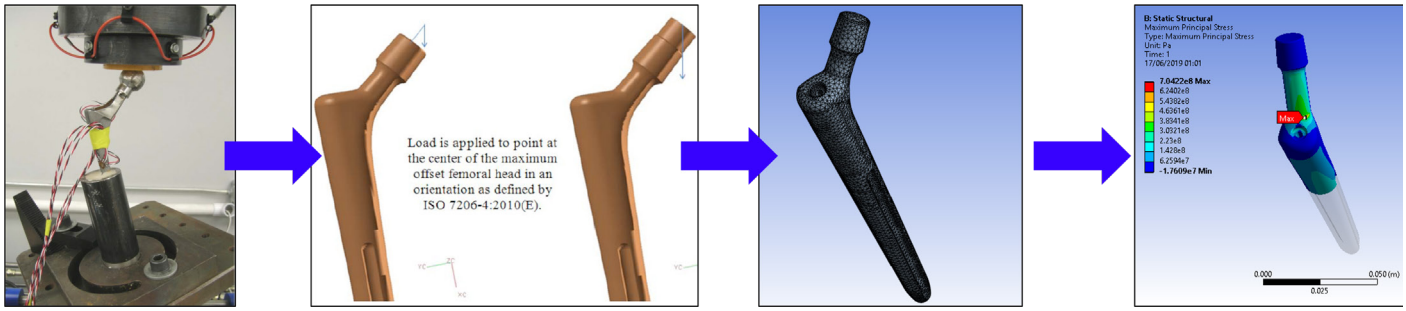
ASTM F3161-16
Standard Test Method for FEA of Metallic Orthopaedic Total Knee Femoral Components under Closing Conditions



ASTM F3334-19
Standard Practice for FEA of Metallic Orthopaedic Total Knee Tibial Components



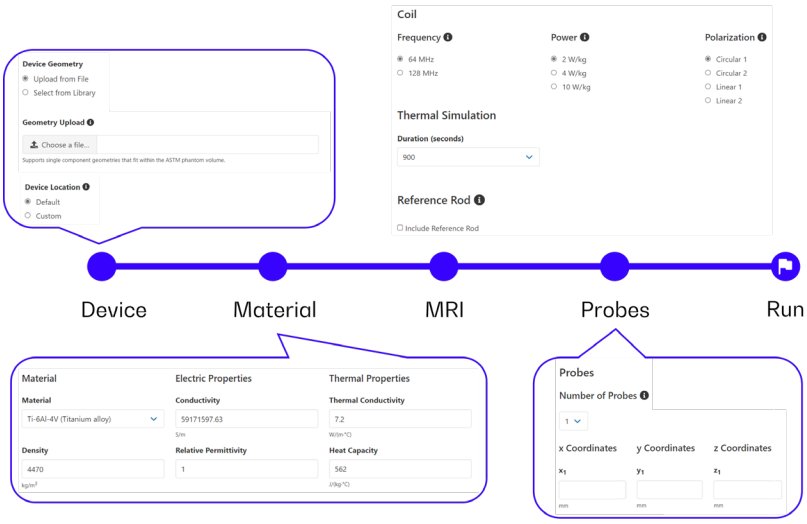
ASTM F2996-20 - Standard Practice for FEA of Non-Modular Metallic Orthopaedic Hip Femoral Stems

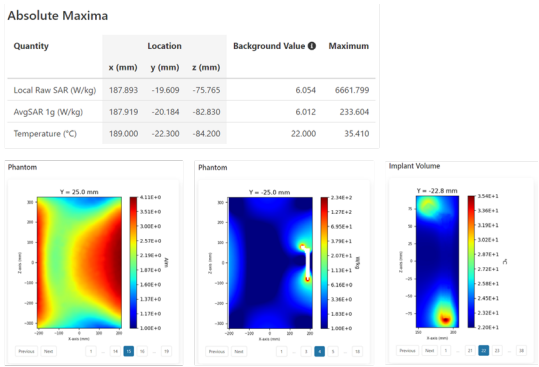


Experimental Test Setup | ***Requirements and considerations for numerical simulation*** | ***3D Mesh*** | ***FEA Results***

MRI Safety

NuMRis (numris.insilicomri.com) - a tool created during a research collaboration with the FDA - uses ANSYS HFSS and ANSYS Mechanical to compute radio-frequency energy absorption and induced heating during MRI using 1.5T and 3T coils, replicating the ASTM F2182-19e2 Standard Test Method [7]. Simulation results were validated against in vitro measurements.





- Maximum values of **SAR** and **Temperature**
- Color maps of **E field**, **H field**, **SAR** and **Temperature** over **ASTM Phantom** and **Implant Volume**

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Concluding remarks

Known obstacles in gathering accurate and reliable data across the breadth of sizes and configurations that characterize modern medical devices may be overcome by supplementing pre-clinical data with computational evidence. Patients, healthcare systems, manufacturers, and regulators may benefit from safety and performance evaluations that are potentially less expensive, faster, and more efficient.

In silico methodologies for medical device testing and validation and the use of virtual cohorts of animal and human patients represent a clear opportunity for increasing devices' efficacy and safety, meanwhile reducing costs and time-to-market, and minimizing the need for live testing on animal and human subjects.

InSilicoTrials.com is the first cloud platform offering a collection of M&S tools to perform **In Silico Standard Testing** for medical devices. The proposed tools allow manufacturers and points-of-care to easily assess mechanical safety and electromagnetic compatibility of generic and custom devices before prototyping, preventing risks and criticalities for the patient, and helping to accelerate time and reduce costs of device development.

The proposed platform promotes the broader adoption of digital evidence in preclinical trials, supporting the device submission process and pre-market regulatory evaluation, and helping accelerate regulatory approval.

In order to achieve these objectives, **InSilicoTrials** has always considered it fundamental to create cooperation with regulatory bodies. The **NuMRis** tool is the outcome of a five-year Research Corporation Agreement signed with the FDA's Center for Devices and Radiological Health (CDRH) on " Investigation on the use of web-based computational frameworks for MRI radiofrequency safety assessment." Furthermore, InSilicoTrials' CEO Luca Emili co-chairs the Good Simulation Practice Task Force within the Avicenna Alliance's Policy Development Working Group, with the goal of driving a consensus approach toward standardization for reliable development and use of in silico solutions.

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