Slides will be on figshare

U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Advancing In Silico Medicine at FDA

Perspectives on Simulation in Medical Devices

Tina Morrison, Ph.D.
Deputy Director, Division of Applied Mechanics
Office of Science and Engineering Laboratories
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Tina.Morrison@fda.hhs.gov

28th Annual INCOSE international symposium
Washington, DC, USA
July 7 - 12, 2018

July 10, 2018

DISCLAIMER: The mention of commercial products, their sources, or their use in connection with material reported herein is not to be constructed as either an actual or implied endorsement of such products by the Department of Health and Human Services or the Food and Drug Administration.

What you'll hear about today?

To fully realize the power of ***simulation***, FDA has been

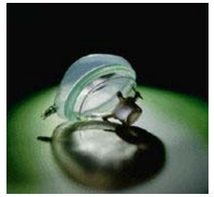
- advancing *in silico* medicine through ***partnerships***

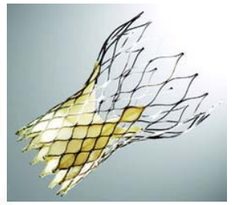
- establishing and implementing a statistical framework for incorporating data from ***virtual patients*** with real clinical data
  - 3 examples of ***digital evidence*** in place of ***clinical evidence***

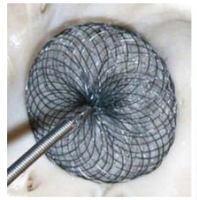
- developing mechanisms to determine the ***credibility*** needed for simulation in
  - research and development of medical products
  - regulatory decision-making
  - impacting the clinical care of patients

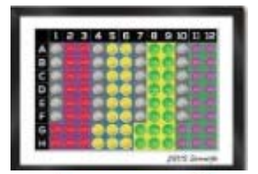
“We want patients have access to high quality, safe, effective medical devices, of public health importance, first in the world.”

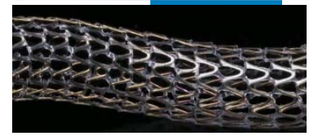
Jeff Shuren, Director, CDRH

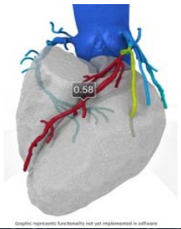






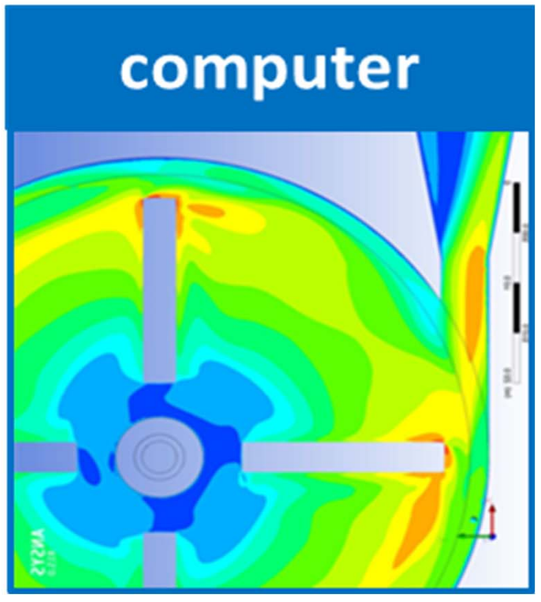






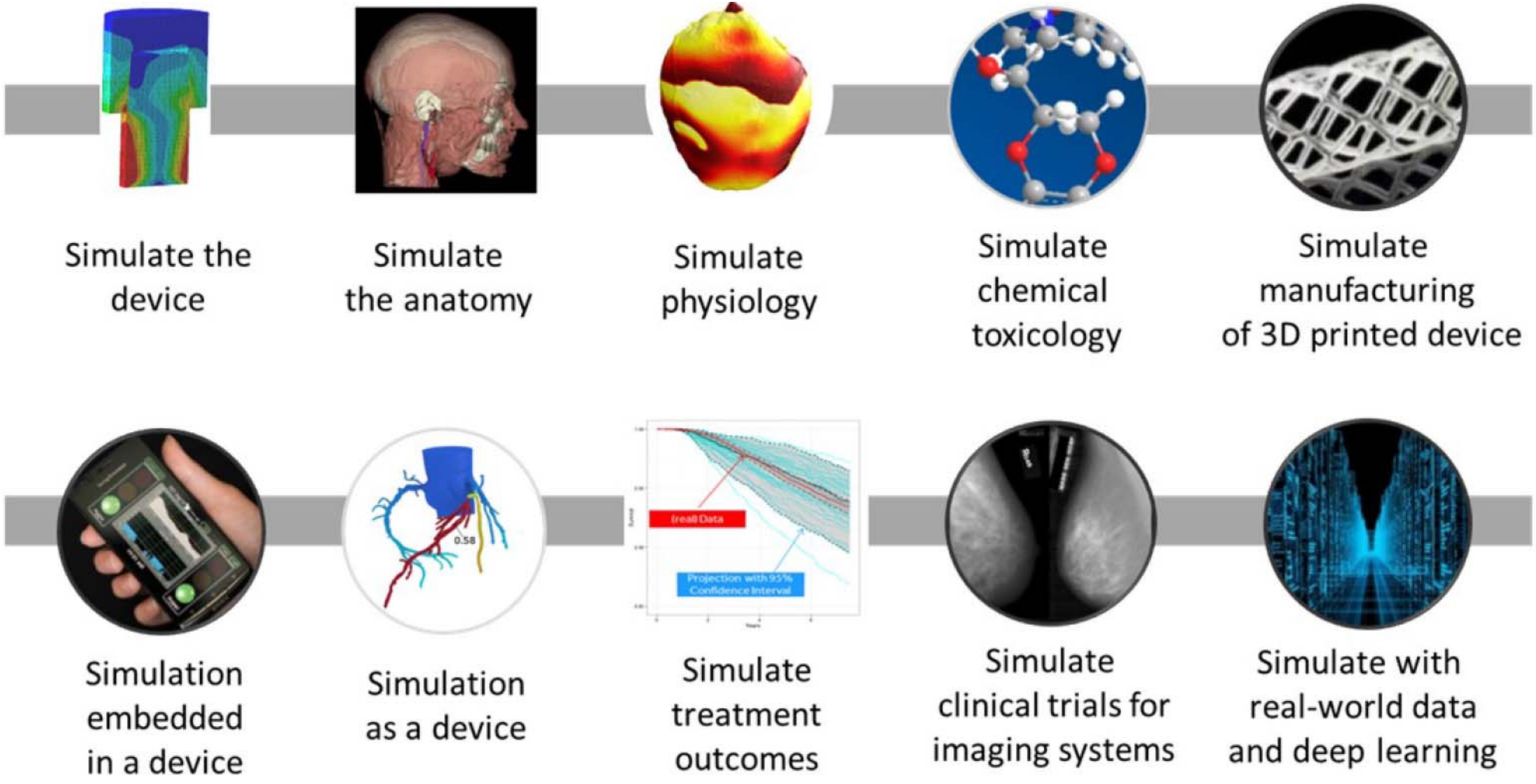
Images from Google

Medical Device Evaluation



Digital Evidence

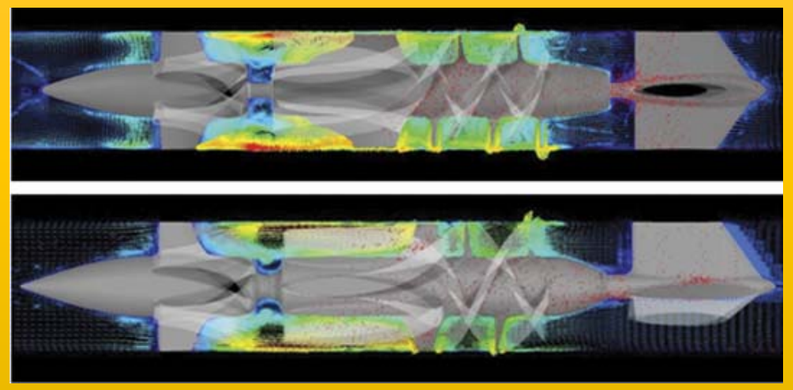
Simulation Opportunities for Medical Devices



Morrison et al., Advancing Regulatory Science with Computational Modeling for Medical Devices at the FDA's Office of Science and Engineering Laboratories, *accepted* Frontiers in Medicine, 2018

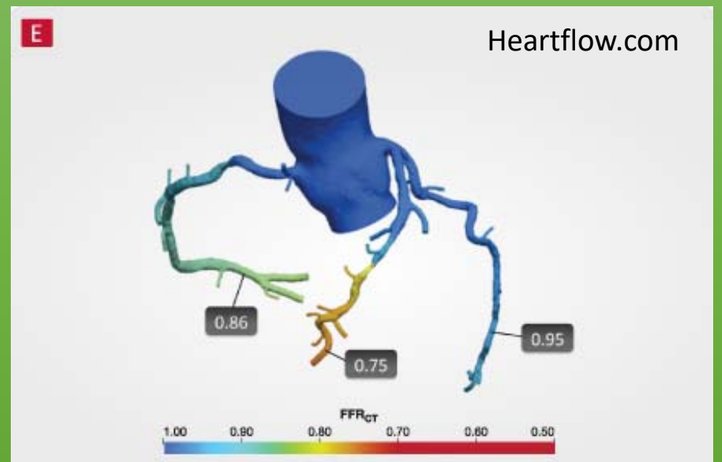
Digital Evidence in Medical Device Submissions

M&S as scientific evidence to support marketing application



Bluestein, PLOS - 2012

M&S as a medical device



- FDA-led Guidance on "**Software as a Medical Device**" can be found through IMDRF: International Medical Device Regulators Forum
  - http://www.imdrf.org/workitems/wi-samd.asp
- Many initiatives have focused on modeling and simulation as **scientific evidence**.
  - Article on "The Role of M&S in the TPLC of Medical Devices", Morrison *et al*, J Med Dev 2017 details more specifics

FDA's Approach for Advancing *In Silico* Medicine

- FDA's Simulation Research
- FDA Guidance
- Partnerships
- In silico Clinical Trials

The Office of Science and Engineering Laboratories

- CDRH's research arm support's the assessment of the enormous breadth of devices that the Center regulates
  - from MRI scanners and neural stimulation devices to pacemakers, cancer treatments and other lifesaving products.
- Score of highly experienced scientists in a broad range of fields and disciplines

OSEL has more than 3 dozen research projects involving computational modeling

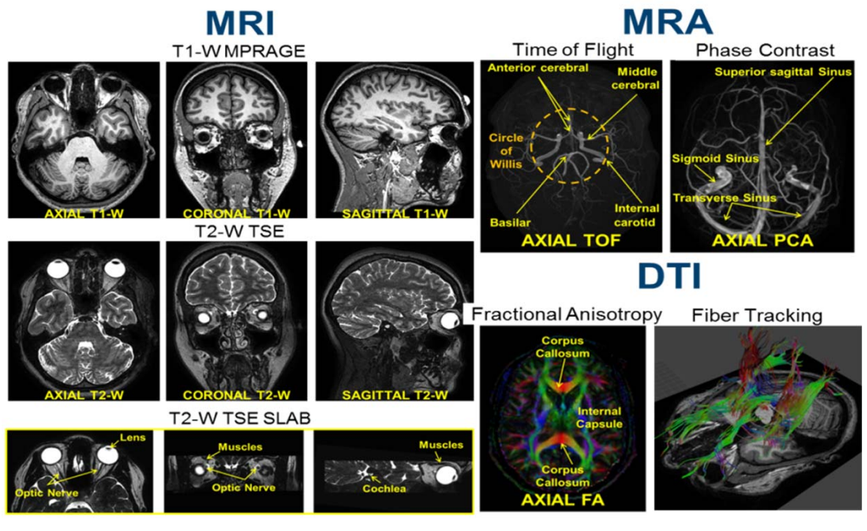
Multimodal Imaging Based Detailed Anatomical Model

FDA's Simulation Research

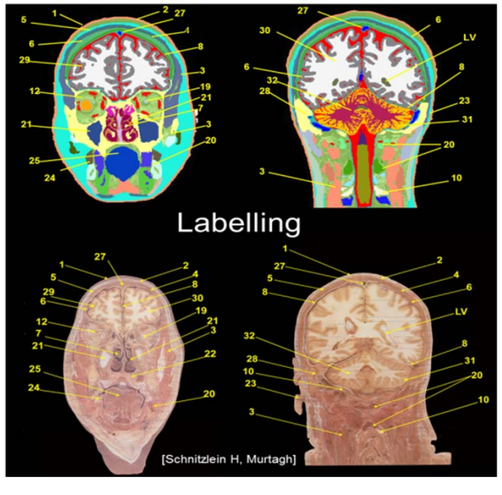
Open access model of the head and neck with 200+ structures

- FDA in collaboration with IT'IS Zurich, Medical University Vienna, Mass Gen & Harvard Medical
- 160 model downloads; 8500 views; 32 independent citations

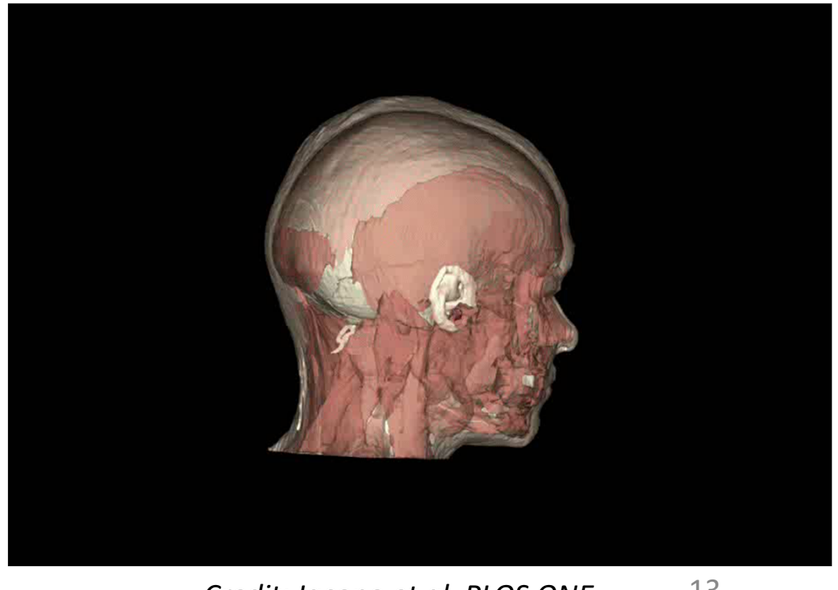
1. Multimodal Data Acquisition



2. Segmentation



3. Mesh Generation & Simulations



https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm444659.htm

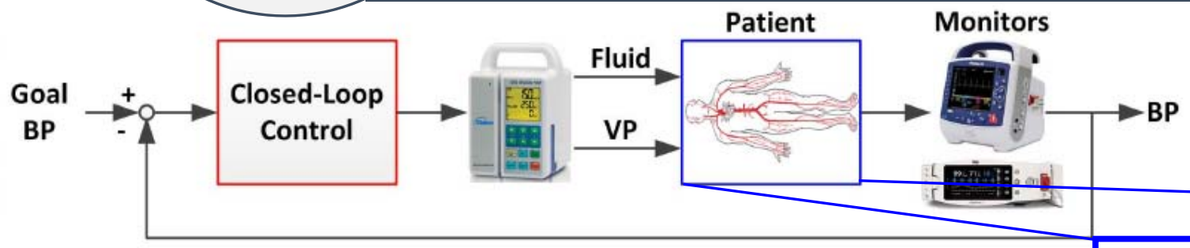
Credit: Iacono et al. PLOS ONE

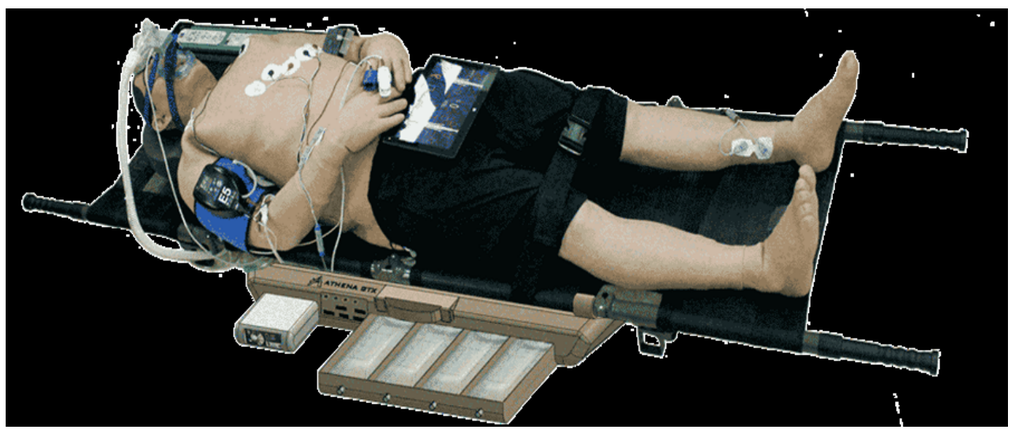
Physiological Closed-loop Control (PCLC) Medical Devices

FDA's Simulation Research

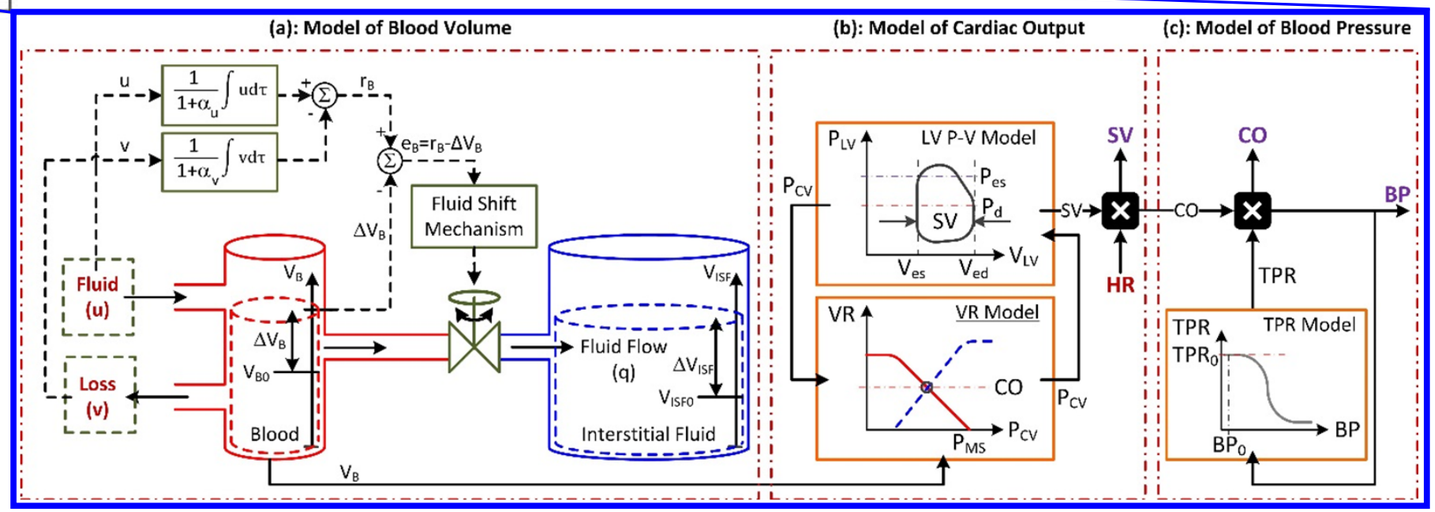
Development & Validation of a Computational Patient Model

- To leverage computational modeling for the design and evaluation of PCLC devices, a validated patient model for a specific context of use is needed.
- Harness model-based engineering for complete *in silico* evaluation





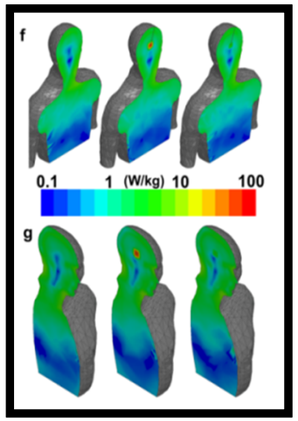
doi: 10.1115/1.40338330



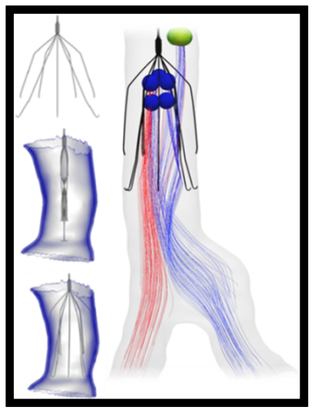
 Credit: Parvinian et al

BV – blood volume, HR – Heart rate, CO – Cardiac output, LV – Left ventricle, SV – Stroke volume, BP – blood pressure

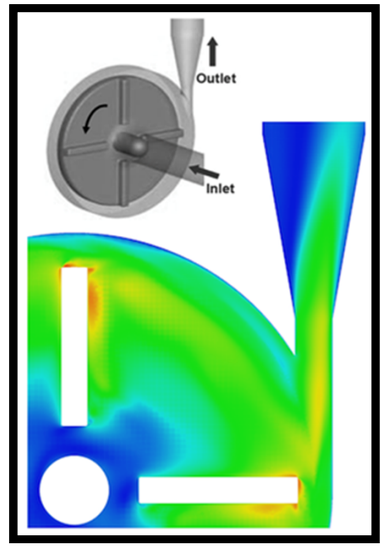
Dozens of Research Efforts at CDRH with Simulation



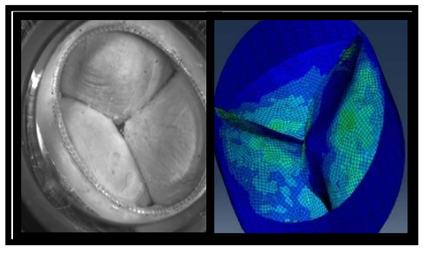
Serano et al.


Craven et al

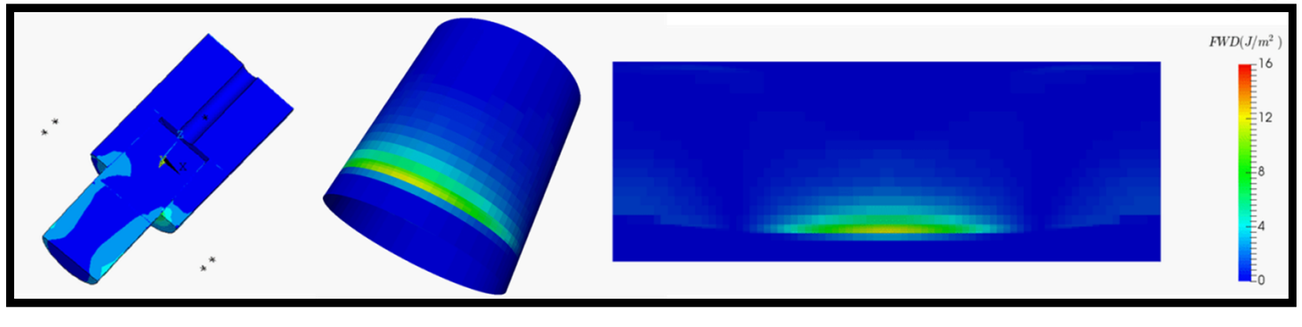
Benchmarks for Computational Fluid Dynamics	Computational Risk Assessment
Computational Patient Models for Closed-Loop Medical Devices	Assessing the Trustworthiness of Models via frameworks, metrics, standards
Virtual Clinical Trials for Imaging Systems	Dynamics of Cardiac Fibrillation
Simulations of Electrocardiogram	Biomarkers for Allergic Risks
Deformation of Bioprosthetic Aortic Valves	In silico Breast Phantoms
Patient-specific Modeling of IVC Filters	Lesion Insertion into Clinical Images
RF Coils for MRI Machines	Ultrasound Enhanced Drug Delivery
Constitutive Model for Absorbable Materials	Aerosol Leakage of Respirators
Multimodal Imaging-Based Model of the Whole Body Models and Human Head and Neck	Ganglion Cell Model for Epiretinal Electrode Stimulation
HIFU Simulator	Electromagnetic Exposure Maps
Fretting of Total Hip Arthroplasty	Spinal Implants for Pediatric Population



Malinauskas et al

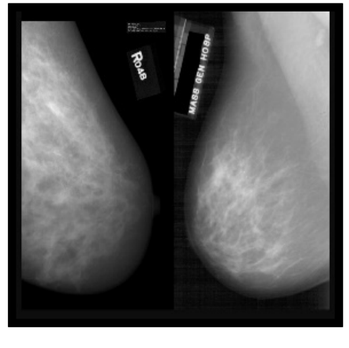

Duraiswamy et al

Baumann et al

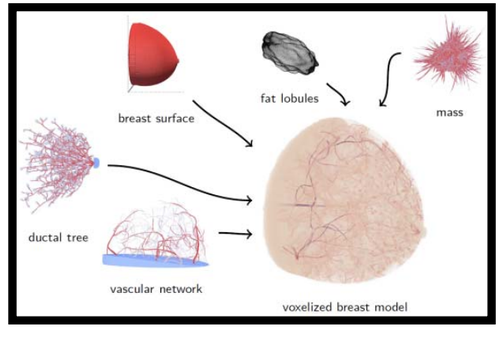


Iacono et al

Badano et al



Graff et al



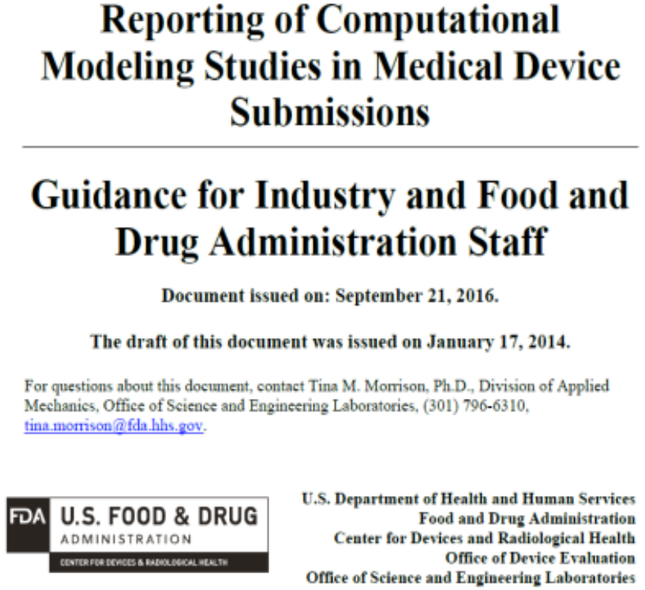
FDA Final Guidance

FDA Guidance

Reporting on Computational Modeling Studies in Medical Device Submissions – September 21, 2016

- FDA training slides on guidance and ASME V&V40 Standard:

https://doi.org/10.6084/m9.figshare.5018783.v1



Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

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

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

FDA U.S. FOOD & DRUG ADMINISTRATION CENTER FOR DEVICES & RADIOLOGICAL HEALTH

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

Table of Contents

- Introduction
- Scope
- Outline of Computational Modeling Report
  - 15 components
- Glossary
- Five subject matter appendices
  - Fluid Dynamics and Mass Transport
  - Solid Mechanics
  - Electromagnetics and Optics
  - Ultrasound
  - Heat Transfer

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM381813.pdf

Partnerships

BMES.org

Medical Device Special Interest Group (SIG)

- Yearly conference in Washington DC Area focused on advancing simulation of medical devices.

Abstracts: https://link.springer.com/article/10.1007/s10439-016-1710-7/fulltext.html

2019 Conference: The Role of *Digital Evidence* to Support Personalized Patient Healthcare.

Goals of Medical Devices SIG

- Provide opportunities for rich, meaningful collaborations between partners working in academia, government, industry, and the clinic.
- Build a strong community of students and professionals interested in creating safe and effective medical devices.
- Serve as a mechanism for best practice sharing and professional development in the areas of design, manufacturing, quality, and regulatory.

Save-the-Date: March 19-21, 2019

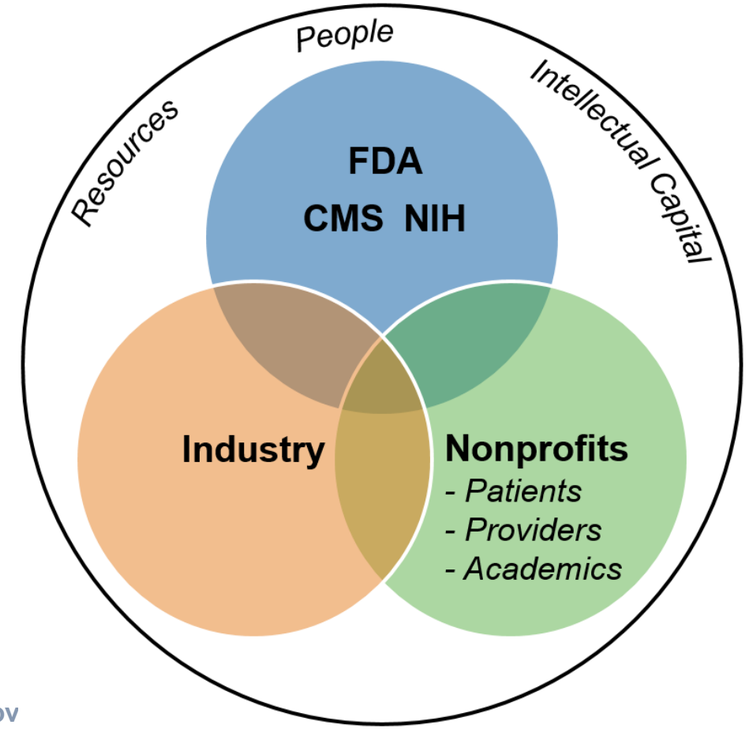
Washington DC Area

Partnerships

MDIC.org

Medical Device Innovation Consortium, a 501(c)3 - Public-Private Partnership collaborating on Regulatory Science

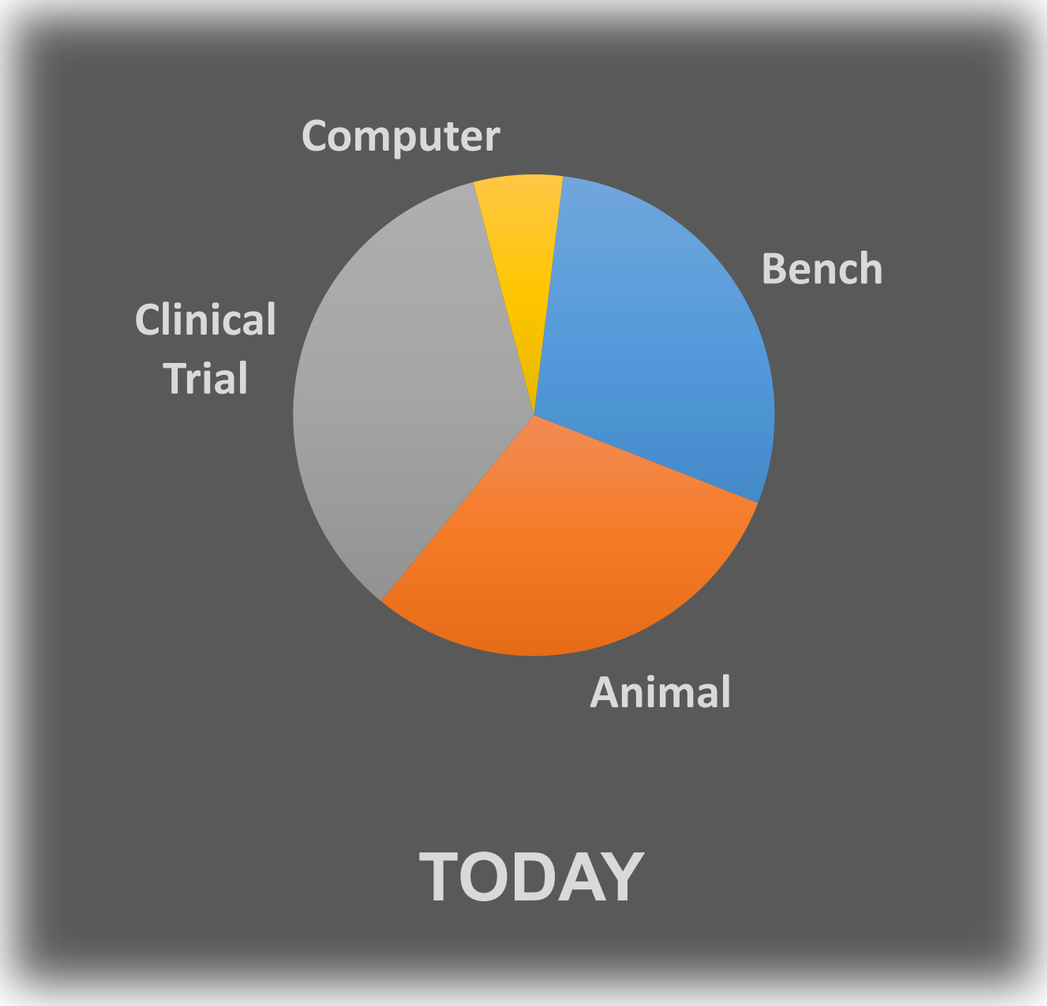
- to make patient access to new medical device technologies faster, safer, and more cost-efficient

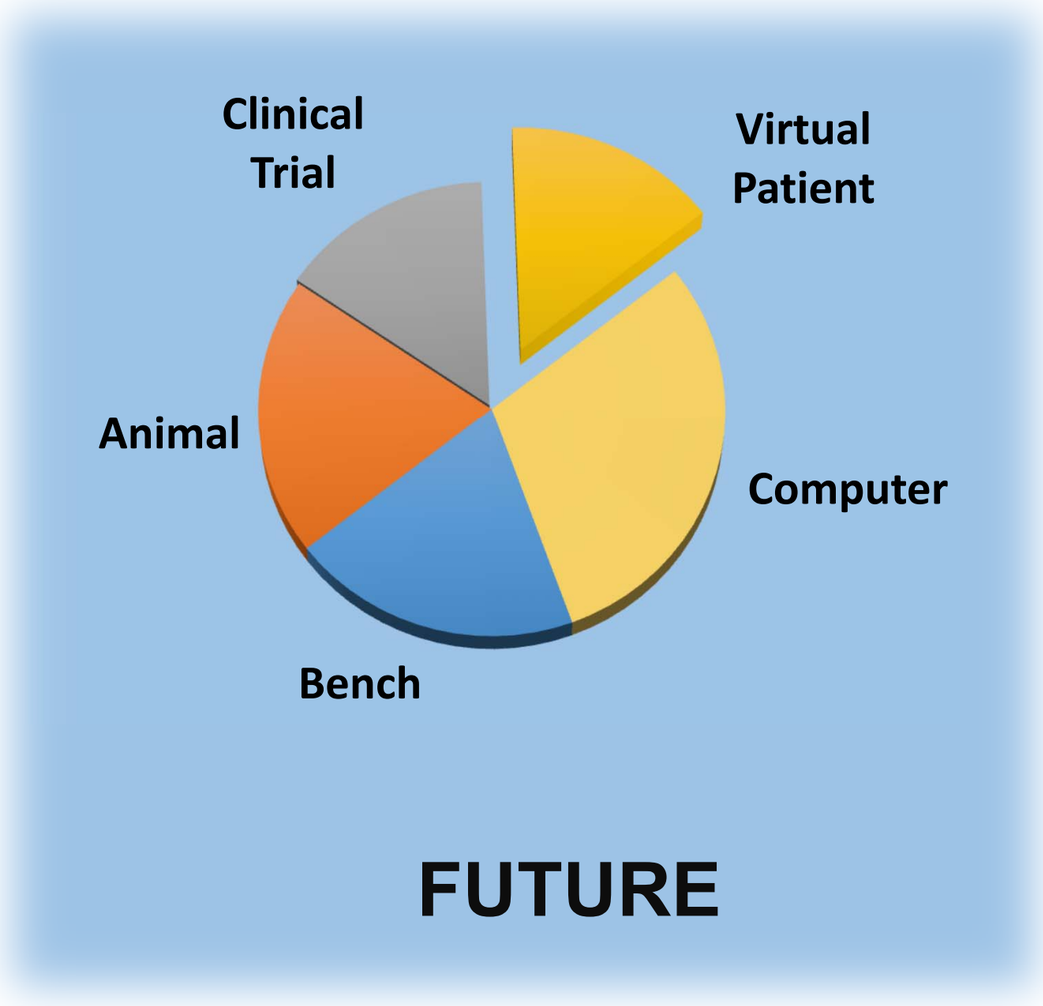


Access to safe and effective medical device technology through Regulatory Grade computer models & simulations

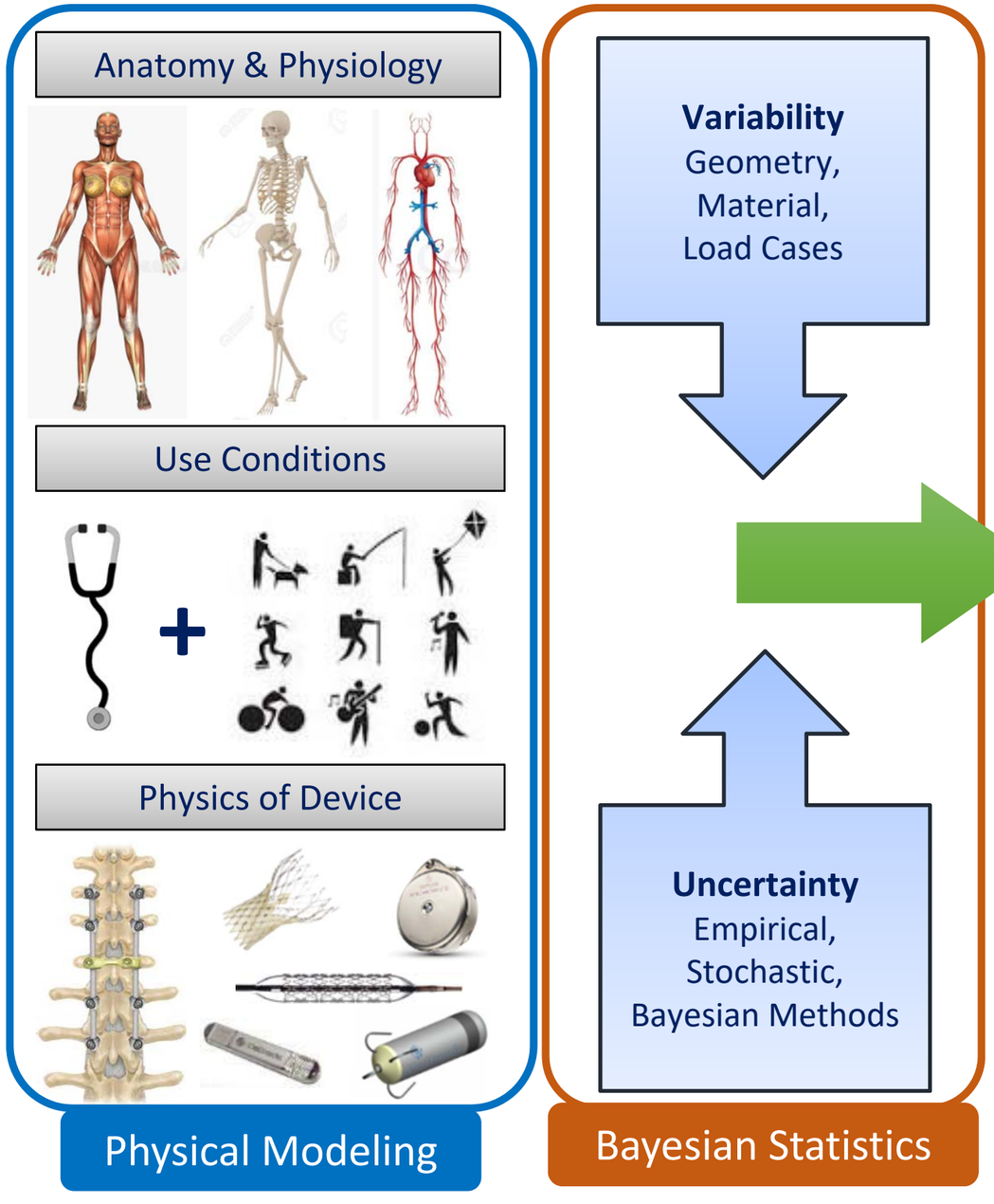
MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM

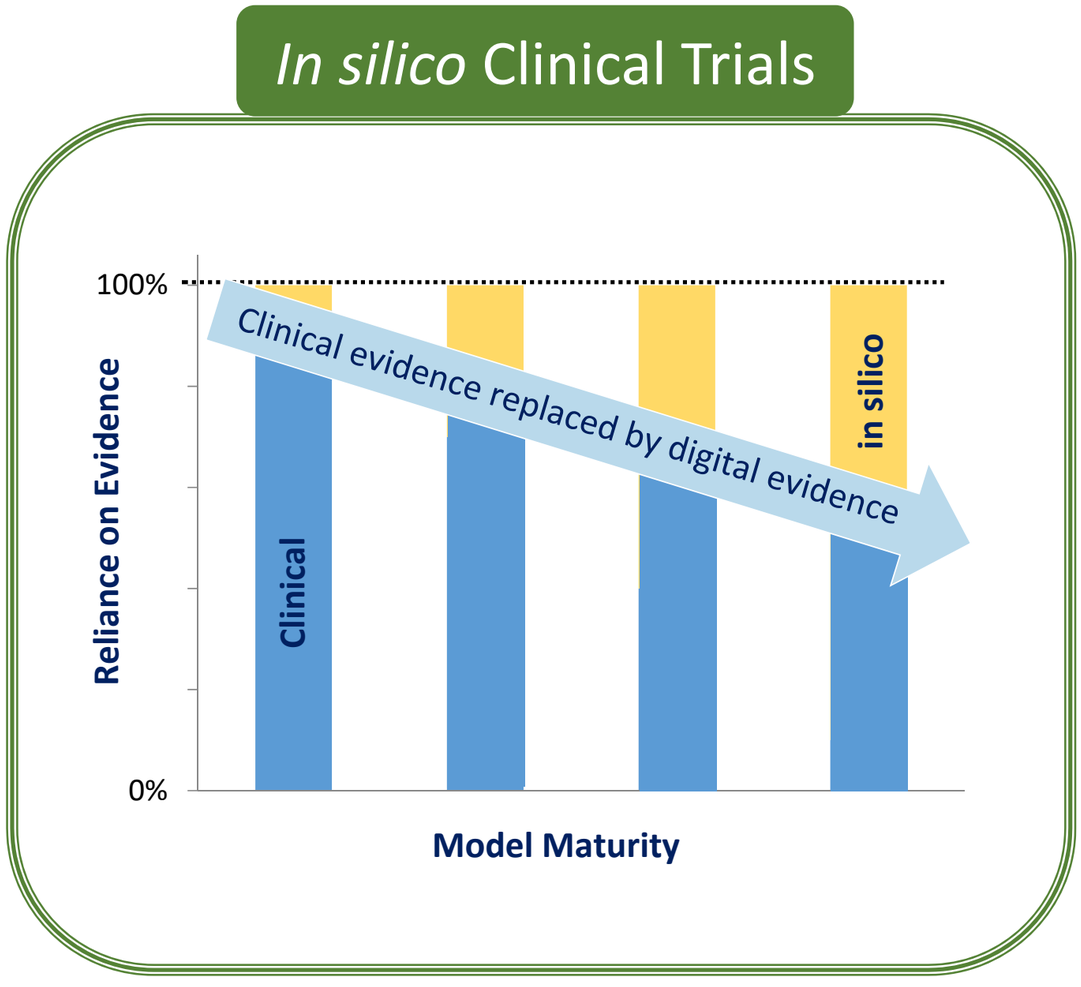
State of *Digital Evidence* in Medical Devices





Concept of "*In Silico* Clinical Trials"



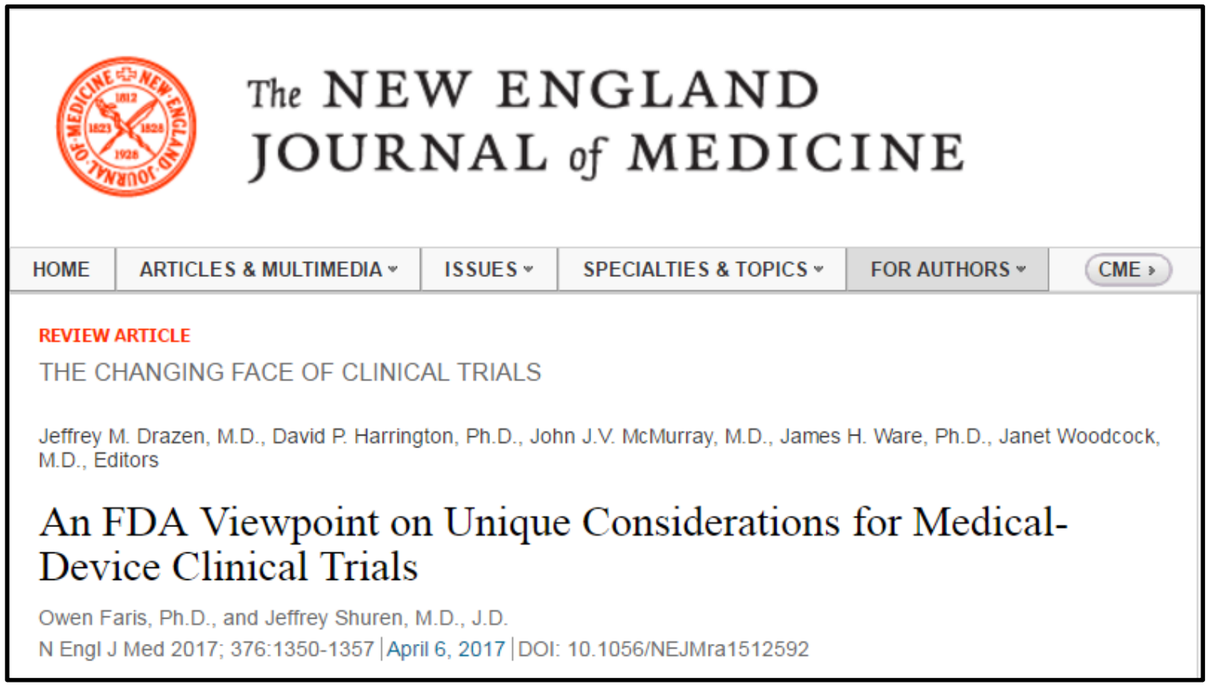


Haddad, et.al., *Reliability Engineering and System Safety*, 123 (2014)

Modified: Original by Mark Palmer, Medtronic, Inc.

CDRH Support for "Virtual Patients"

"If it can be shown that these virtual patients are similar, in a precisely defined way, to real patients, future trials may be able to rely partially on virtual-patient information, thus lessening the burden of enrolling additional real patients."



The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., Janet Woodcock, M.D., Editors

An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials

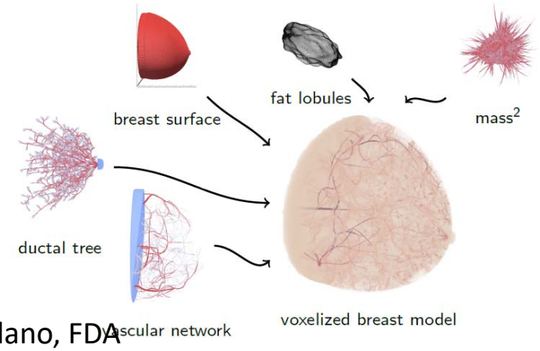
Owen Faris, Ph.D., and Jeffrey Shuren, M.D., J.D.

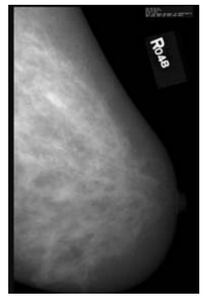
N Engl J Med 2017; 376:1350-1357 | April 6, 2017 | DOI: 10.1056/NEJMra1512592

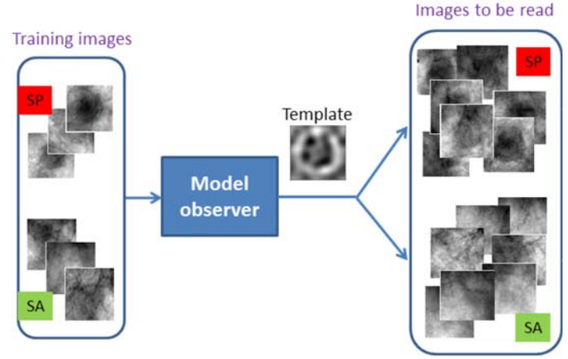
"In the future, computer-based modeling may change the way we think about device validation in other ways, allowing for much smaller clinical trials, or may change the way we think about running trials, in that some "clinical" information may be derived from simulations."

3 Examples of *in silico* medicine approaches

1

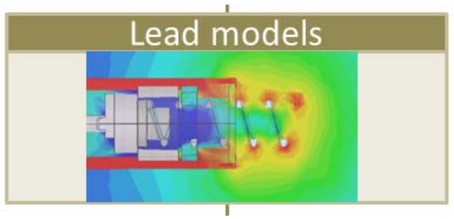


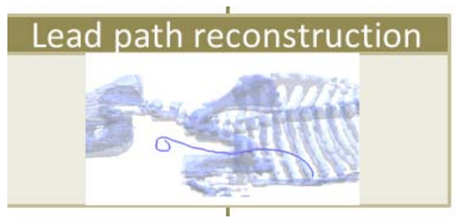


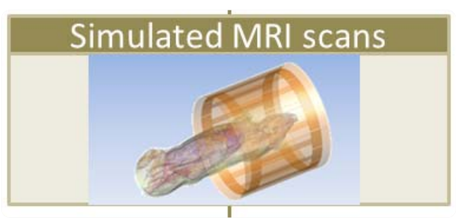


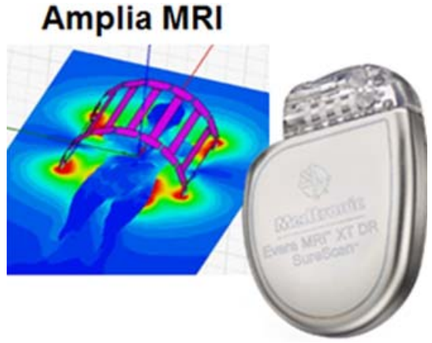
Courtesy Badano, FDA

2



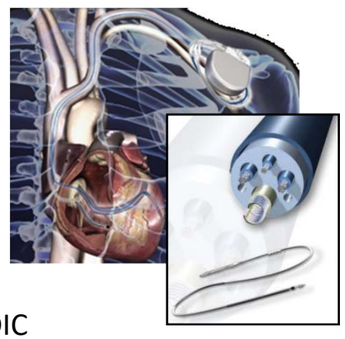


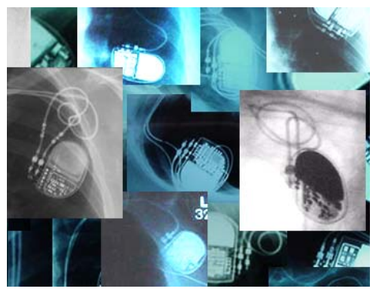


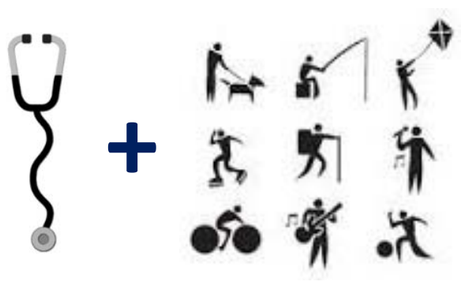


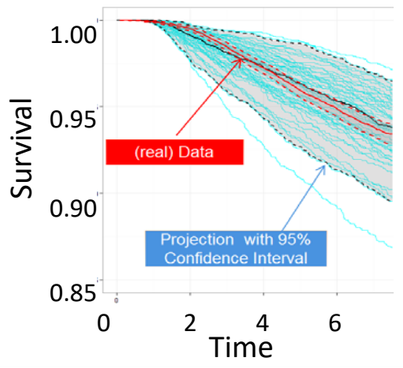
Courtesy Medtronic, Inc.

3





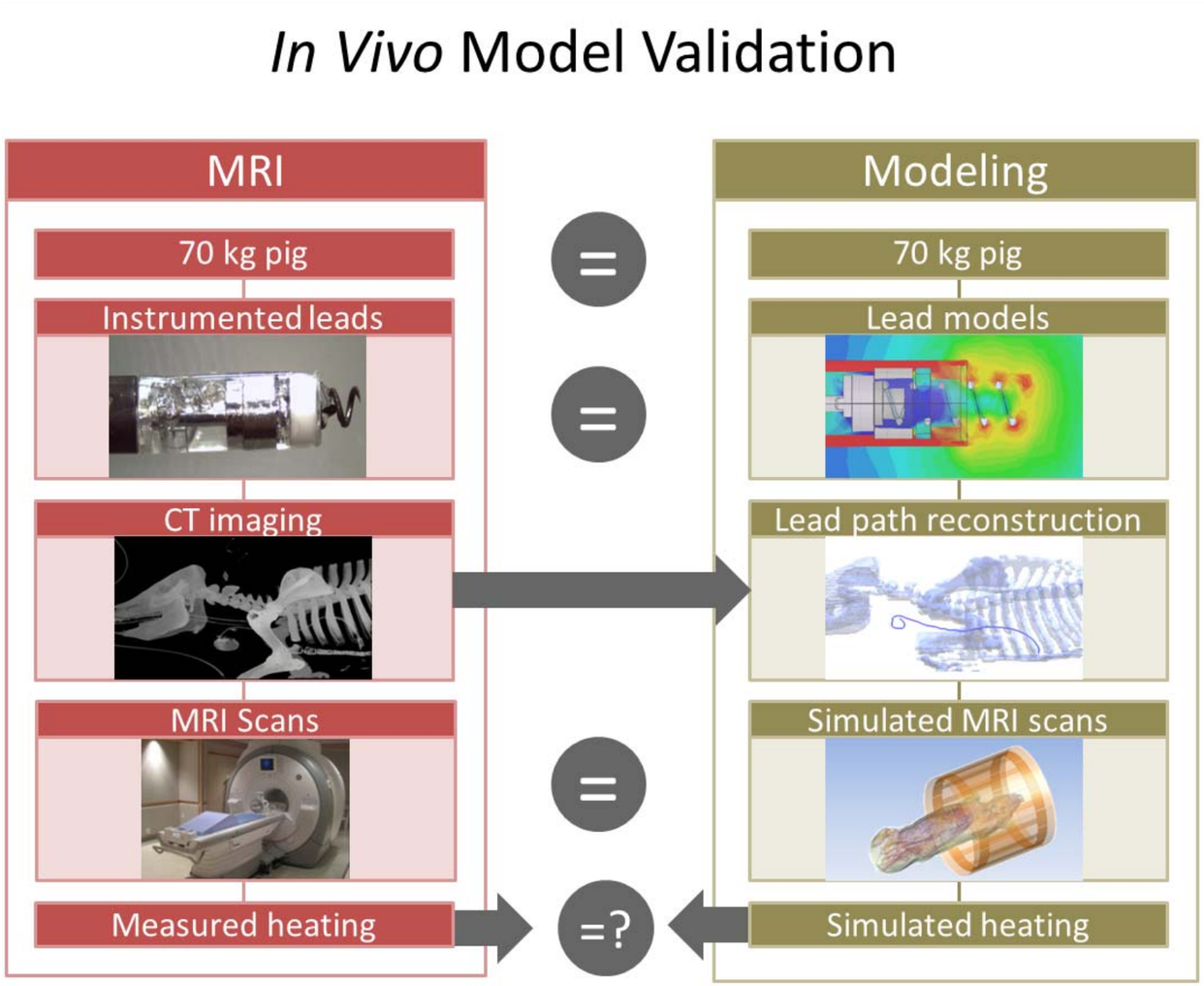


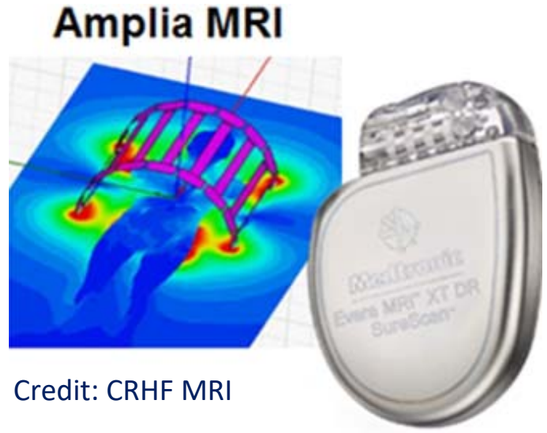


Courtesy MDIC

Digital Evidence in place of Clinical Evidence

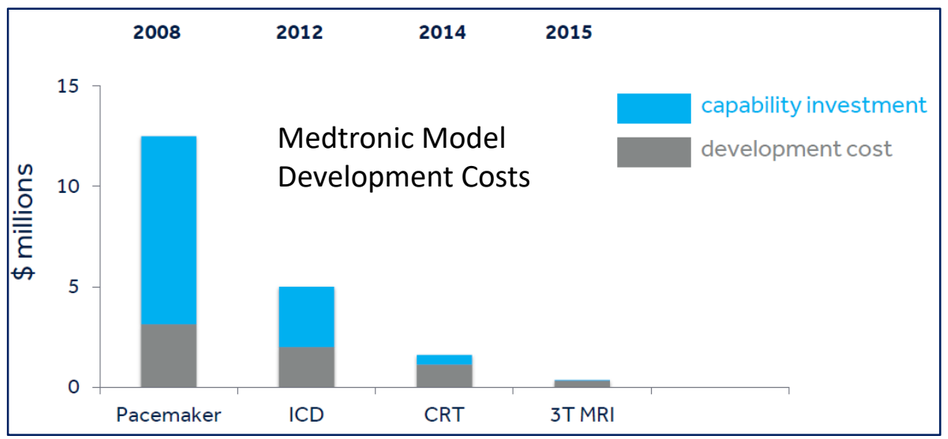
INDUSTRY EXAMPLE – Courtesy of Medtronic, Inc.





Credit: CRHF MRI

- Advisa SR pacemaker approved with digital evidence
- No clinical trial required for MRI



Partnerships

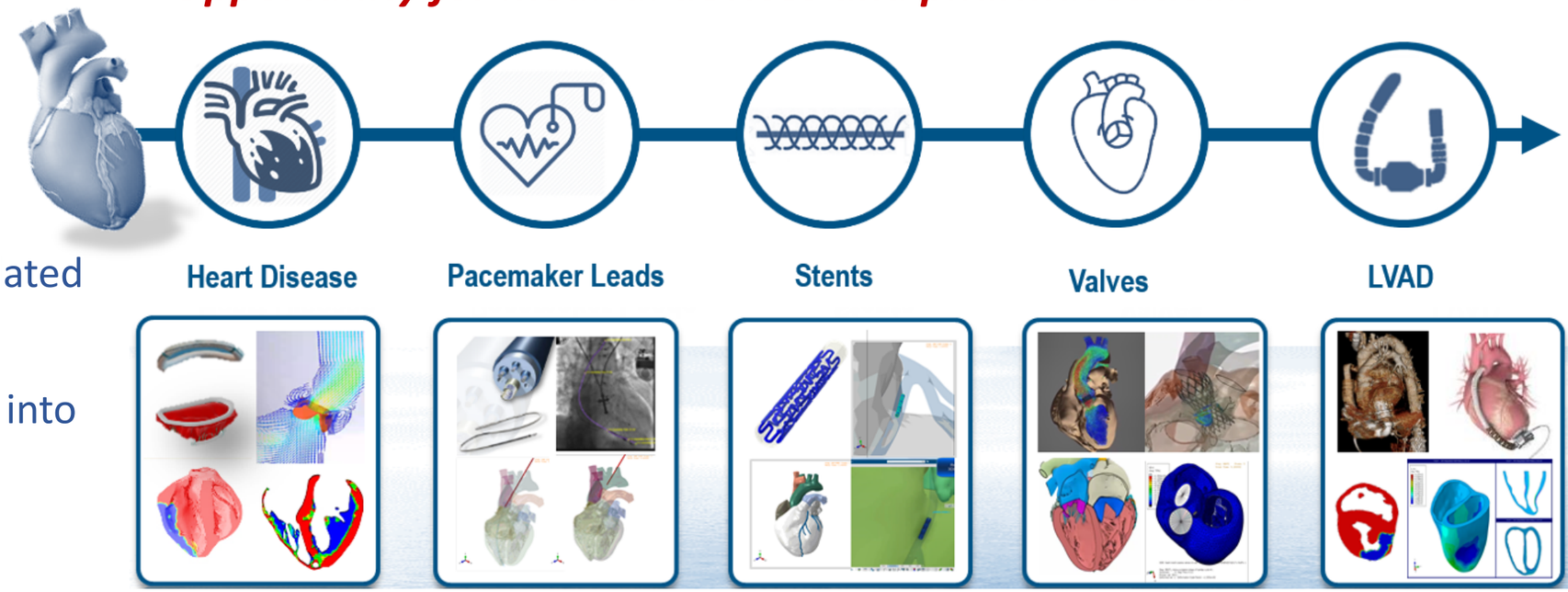
Dassault Systèmes

The ***Living Heart Project*** from Virtual Human Simulation Group

- Large collaboration with researchers, medical industry, regulators and clinicians
  - FDA is a formal partner with D.S. via research collaborative agreement

Living Heart Applications: Virtual Design & Testing of Cardiovascular Devices

Opportunity for medical devices and pharmaceuticals



Mission:

Advance the development of safe & effective cardiovascular products and treatments by

- **Uniting** engineering, scientific, & biomedical experts to deliver validated models and
- **Translating** simulation technology into improved patient care.

Partnerships

ASME Standards

What is the “bar” for digital evidence?

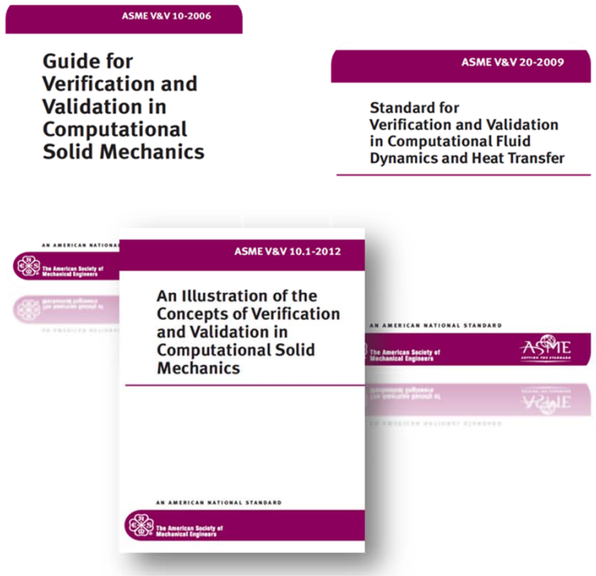
- FDA training slides on guidance and ASME V&V40 Standard:

https://doi.org/10.6084/m9.figshare.5018783.v1

ASME Verification &Validation Committee

CHARTER	**Coordinate, promote, and foster the development of standards that provide procedures for assessing and quantifying the accuracy and credibility of computational models and simulations.**

V&V 10	Computational Solid Mechanics
V&V 20	Computational Fluid Dynamics and Heat Transfer
V&V 30	Computational Simulation of Nuclear System Thermal Fluids Behavior
V&V 40	**Computational Modeling of Medical Devices**
V&V 50	Computational Modeling for Advanced Manufacturing
V&V 60	Computational Modeling for Energy Systems



Ethicon Endo-Surgery

SIMULIA

MAYO CLINIC

SimuTech Group

FDA

SYNOPSYS®

ANSYS®

Baxter

stryker

Edwards

MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM

GORE

BD

Exponent®

Google

VEXTEC

COOK® RESEARCH

Abbott Vascular

4WEB

ASME
SETTING THE STANDARD

ZIMMER BIOMET

Medtronic

Alere™

DePuy Synthes
SPINE
COMPANIES OF Johnson & Johnson

HeartFlow®

smith&nephew

FDA U.S. FOOD & DRUG ADMINISTRATION

Siemens PLM Software
SIEMENS

SwRI®

Boston Scientific

InSilico Labs

syncroness™
complex problems inspired solutions

EMBRY-RIDDLE AERONAUTICAL UNIVERSITY

ENDOLOGIX

ASME V&V 40 Standard

Credibility: the trust, obtained through the collection of evidence, in the predictive capability of a computational model for a context of use

- Focus is on ***HOW MUCH*** V&V is necessary to support using a computational model for a context of use.
  - should be commensurate with model risk; the concept of "model risk" has been also been used by NASA[1].

ASME V&V 40-2018

Assessing Credibility of Computational Models through Verification and Validation: Application to Medical Devices

Summer 2018!

http://go.asme.org/VnV40Committee

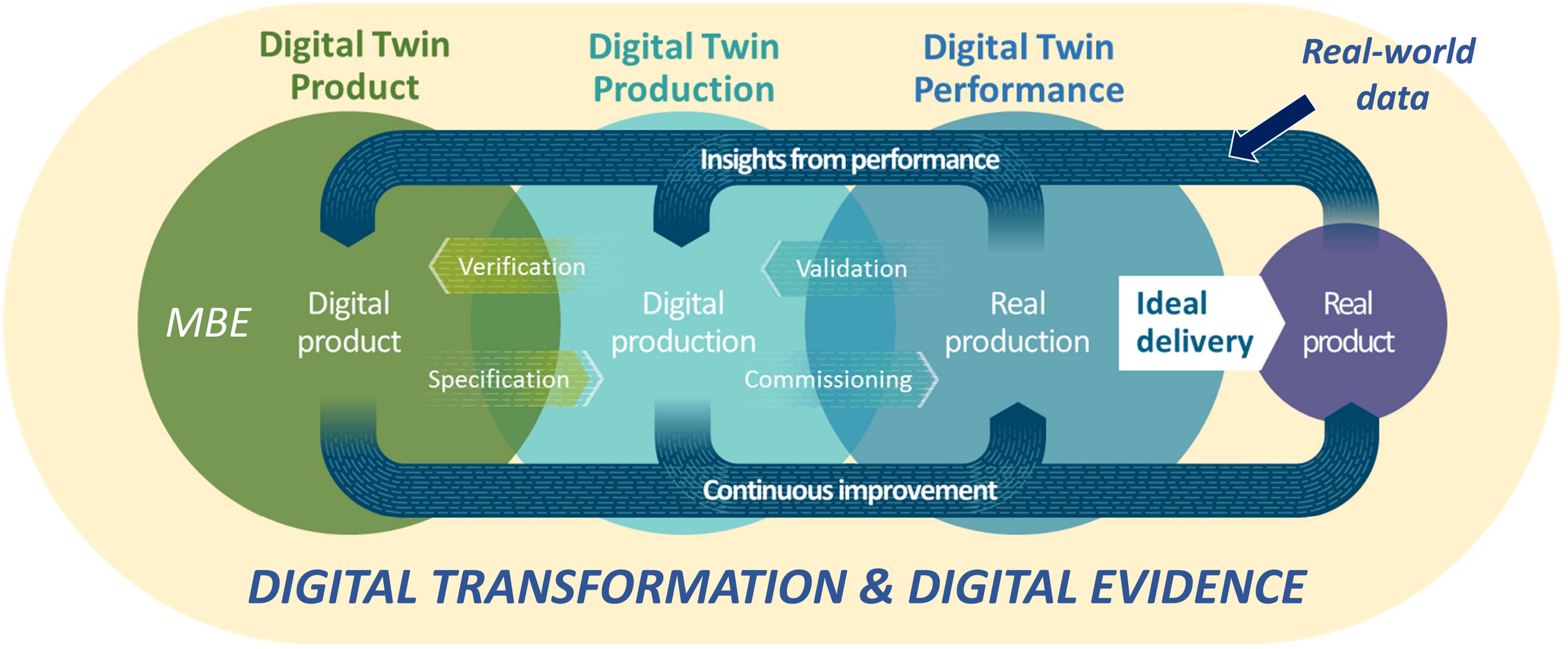
AN AMERICAN NATIONAL STANDARD

The American Society of Mechanical Engineers

1, NASA-STD-7009, https://standards.nasa.gov/documents/detail/3315599

Continuously Improve

Product and Production in the Real World



DIGITAL TRANSFORMATION & DIGITAL EVIDENCE

Closing comments

- ***Digital evidence*** is being used at CDRH to support regulatory submissions
- With the appropriate level of ***credibility***, digital evidence can reduce the burden on physical testing and *in vivo* studies, saving both animals and patients
  - 3 examples of digital evidence in place of clinical evidence
  - 4th example underway with Dassault Systèmes

Partnerships are key!

- Need to raise awareness to different communities, especially those unfamiliar with simulation, for broader adoption.