The FDA is Leading In Silico Medicine in the U.S.

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In Vivo, In Vitro, In Silico:
Why computer modelling is the next evolution of the healthcare sector
EU Parliament
4 September 2018

U.S. Department of Health and Human Services

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FDA protects and promotes public health …

…and facilitates healthy innovation.

Healthy Innovation, Safer Families: FDA's 2018 Strategic Policy Roadmap

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January 11, 2018

I am delighted to share FDA's 2018 Strategic Policy Roadmap, the product of a close collaboration among the Agency's centers. This document provides an overview of some of the key priorities we will pursue together to advance FDA's public health mission.

Read the 2018 Strategic Policy Roadmap

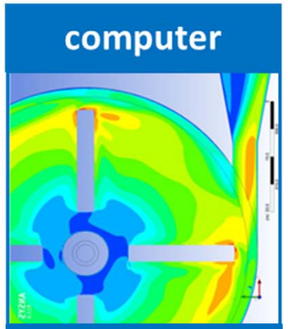
Many of these efforts are already underway, and will be further advanced in 2018, while other policies outlined in this document will be initiated during the coming months.

Reliance on Evidence from Different Models

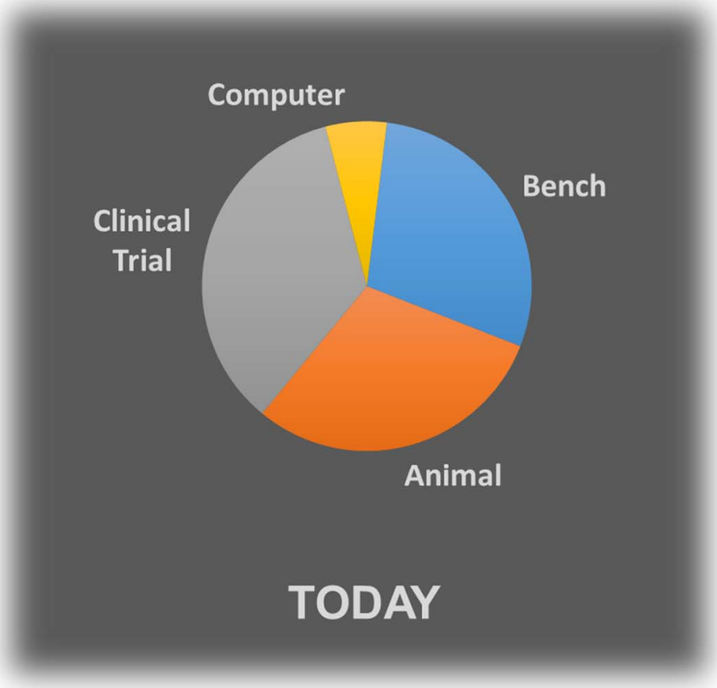
in vivo

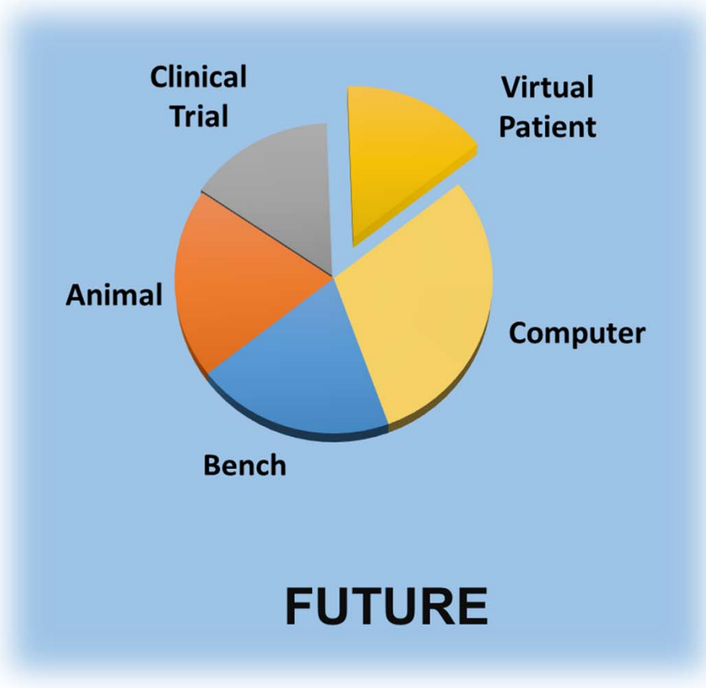
in vitro

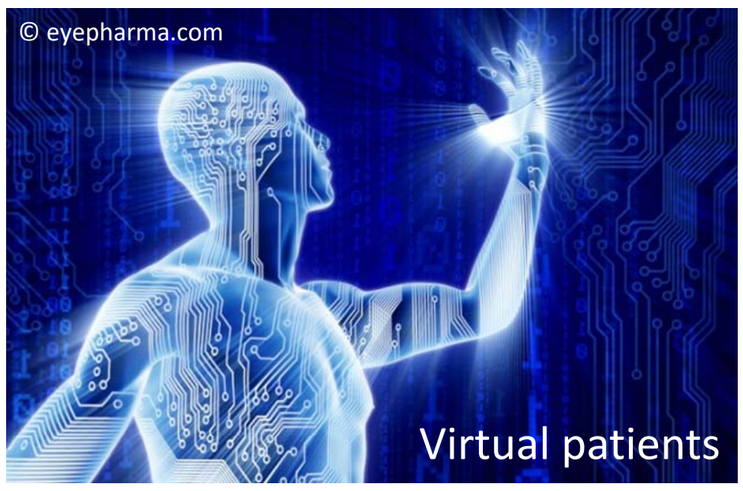
in vivo

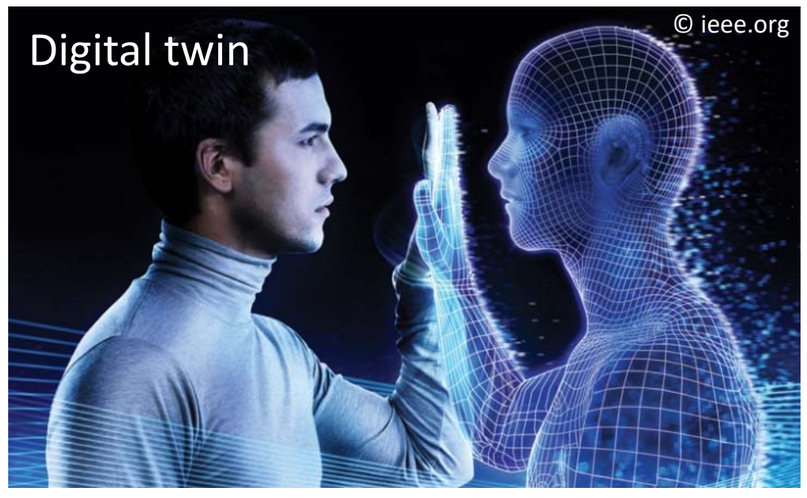


in silico









21st Century Cures

The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, is designed to help ***accelerate*** medical product development and ***bring new innovations and advances*** to patients who need them faster and more efficiently.

In Silico Methods and In Silico Clinical Trials

FDA Fiscal Year 2019 Budget

DEPARTMENT of HEALTH and HUMAN SERVICES

Fiscal Year 2019

Food and Drug Administration

Justification of Estimates for Appropriations Committees

18. In Silico Clinical Trials

The Committee appreciates FDA's interest in in silico medicine and directs the Office of the Chief Scientist to enter into an affiliation agreement with an academic institution with expertise in physiological modeling for the purpose of bridging the gaps between genetics and clinical practice with in silico clinical trials, allowing the development of personalized medicine and optimizing the regulatory process, pursuant to the goals set forth in the Critical Path Initiative.

In addition, FDA has a Memorandum of Understanding with the Avicenna Alliance, an association comprised of industry and academic partners, to seek actionable ways to harness in silico clinical trials. The existing grant from the Office of the Chief Scientist to the Stanford/UCSF Center of Excellence in Regulatory Science and Innovation, provides another opportunity to pursue physiological modeling in conjunction with the Precision Medicine Initiative-focused projects.

U.S. Senate Appropriations Committee

Numerous Modeling and Simulation Approaches at FDA

Chemical

- Structure-activity relationship (SAR)
- Quantitative structure-activity relationship (QSAR)
- Molecular docking
- Structural alerts and rule-based models
- Chemical category, or Read-Across
- Quality by Design
- Cheminformatics
- Chemical and chemical-toxicity databases

Mechanistic

- PK/ADME
- PBPK
- PK/PD
- In vitro-in vivo extrapolation and correlation
- Reduced order
- Lumped parameter
- Systems modeling
- Quantitative Systems Pharmacology (QSP)

Statistical

- Stochastic
- Bayesian & Adaptive
- Dynamic models
- Hierarchical models
- Factor analysis
- Monte Carlo models
- Population Modeling
- Dynamical system: stochastic system of equation
- Social network analysis
- Topic modeling

Big Data & Knowledge Bases

- Next gen sequencing
- Data-driven models
- Data visualization
- Network models
- Data & database modeling
- Document Modeling
- Metamodeling
- Ontological Modeling
- Business Process Modeling
- Natural language processing
- Machine learning and AI tools

Physics

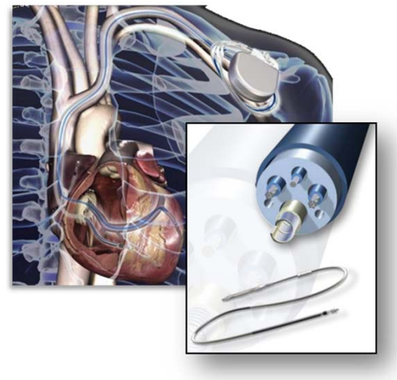
- Acoustics
- Electromagnetics
- Fluid dynamics
- Heat transfer
- Optics
- Solid mechanics
- Photon transport
- Control systems

Risk-Assessment

- Probabilistic Risk Estimation
- Agent-Based
- Whole Genome Sequencing
- Risk Ranking & Prioritization
- Quantitative Benefit-Risk Modeling
- Reverse Dosimetry
- High-throughput Risk Prioritization
- Nonlinear Mixed Effects
- Benchmark Dose
- Biologically Based Dose-Response

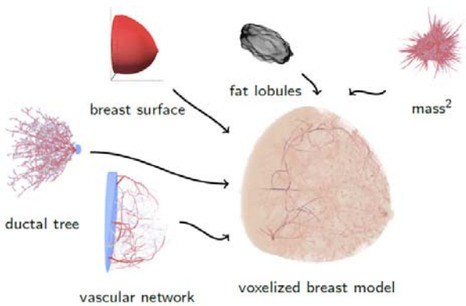
3 Examples of In Silico Methods Impacting Medical Products

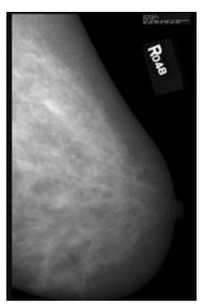
1. Reducing the clinical trial size for a new pacemaker lead
   - ***From*** traditional study of 450 patients
   - ***To*** a study of approx. 400 patients with about 50 virtual patient



2. Optimizing the dosing for regimens not tested in clinical study
   - ***From*** limited scope of drug regimens and patient populations
   - ***To*** additional regimens and dosing to broad patient population

3. Completely *in silico* evaluation of a new imaging system
   - ***From*** 400 patient study with 30 radiologists, 4+ years
   - ***To*** 1000 virtual patient study, no radiologists, 3 months





Key Objectives of the Working Group

Office of the Chief Scientist

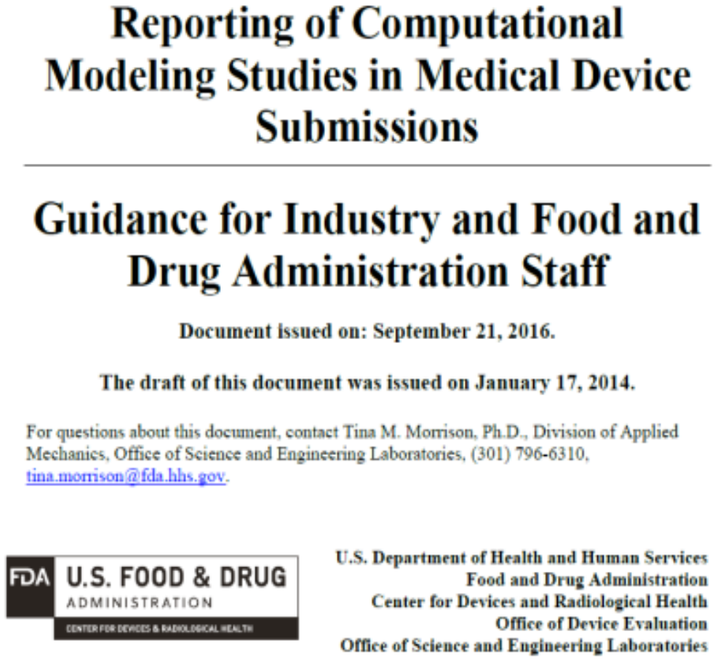
200 Scientists FDA-Wide

- **Raise awareness** about M&S to advance regulatory science for public health
- Foster **enhanced communication** about M&S efforts among stakeholders
- Serve as a **scientific resource** on M&S and emerging technologies for the FDA
- **Collaborate** with national and international organizations pursuing similar activities.
- Establish **Good Simulation Practices** for advancing in silico medicine

Visit with U.S. Senator Cochran

I. FDA Final Guidance

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



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.

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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

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

II. 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.

http://go.asme.org/VnV40Committee

ASME V&V 40-2018

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

September 2018

An International Standard

The American Society of Mechanical Engineers

Initiating a Clinical Trial with Simulation and Digital Evidence

FDA Critical Path Project Underway

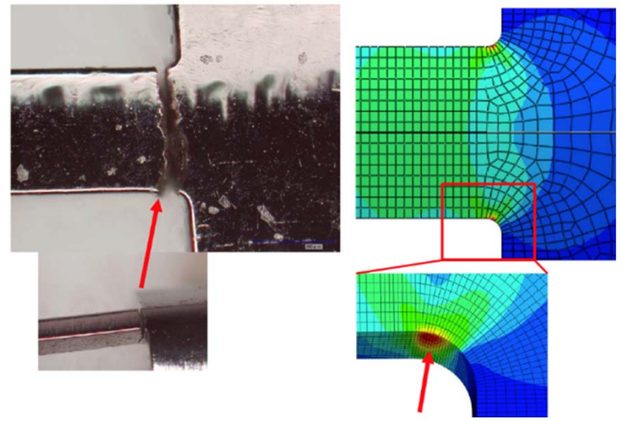
<u>Mock Submission Team</u>:

Industry: four medical device companies and one medical device manufacturer: expert modeler & regulatory affairs from each

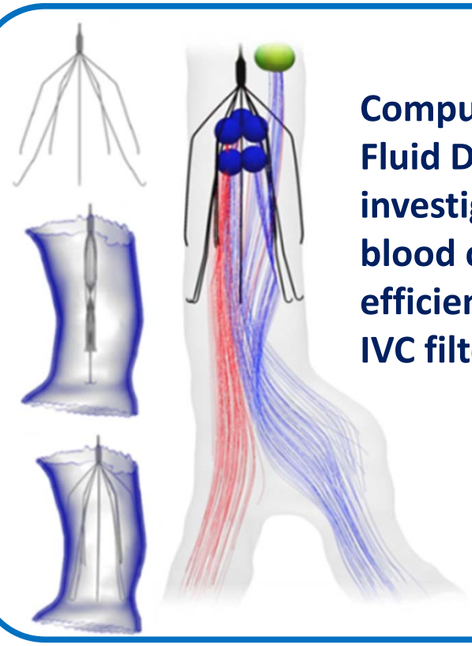
FDA: expert modelers, experimentalists and regulatory

<u>Key Objectives</u>:

1. Generate & demonstrate "regulatory-grade" digital evidence for a mock IDE submission
2. Prepare mock IDE submission using FDA reporting guidance & ASME V&V40 Standard
3. Conduct independent FDA review of mock IDE submission
4. Assess & improve regulatory review process for computational modeling
5. Share content and develop training materials for industry & FDA staff



Finite Element Analysis to determine the potential for fracture due to fatigue

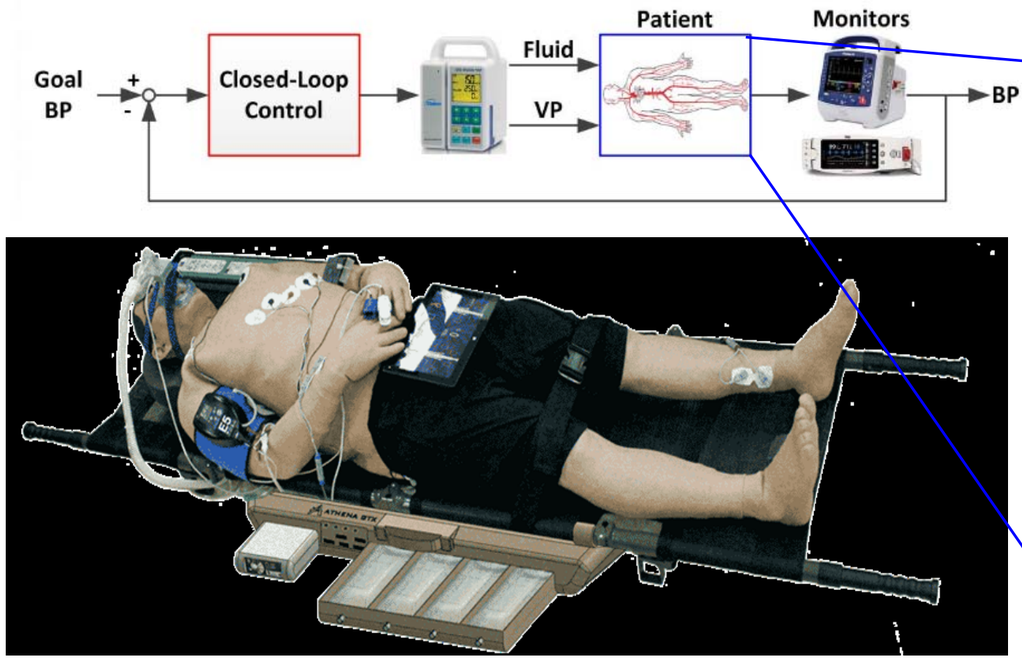


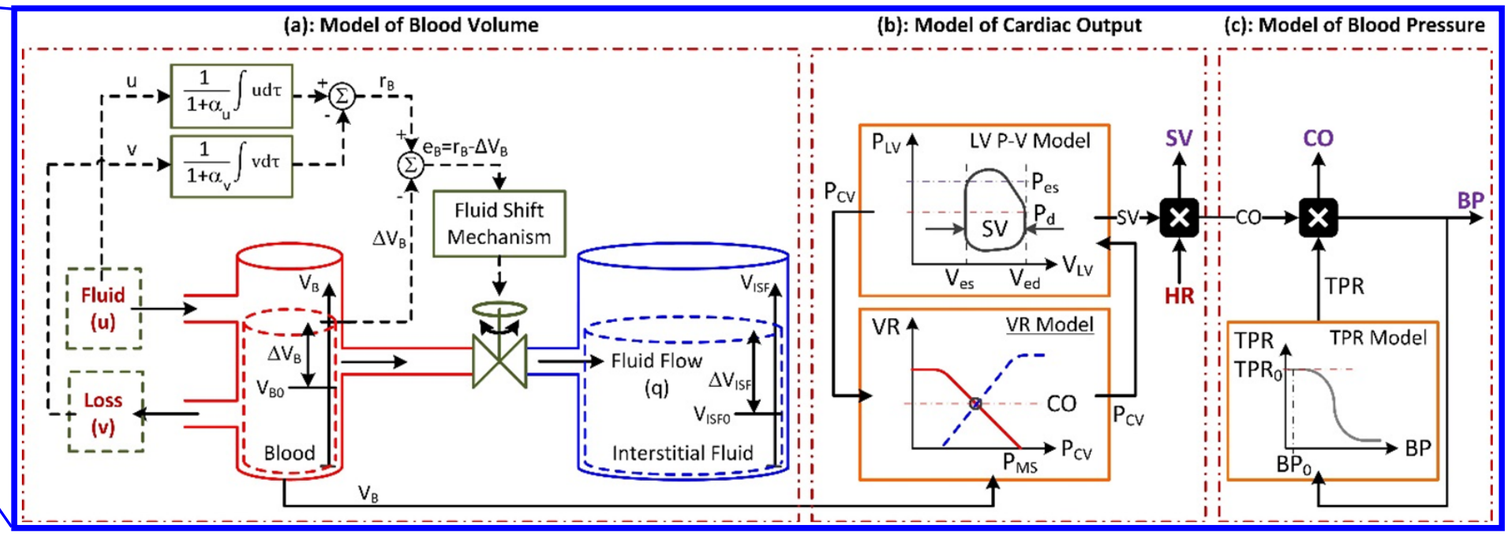
Computational Fluid Dynamics to investigate blood clot trapping efficiency of the IVC filter

Physiological Closed-loop Control (PCLC) Medical Devices

Develop & Validate Computational Patient Model

- In silico methods for the design and evaluation of PCLC devices, a validated patient model for a specific context of use is needed.
  - Physiological, mechanistic-based model with ASME V&V40 approach
- Harness model-based engineering for *complete* in silico evaluation





doi: 10.1115/1.40338330

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

 Credit: Parvinian et al

Digital Evidence as External Evidence

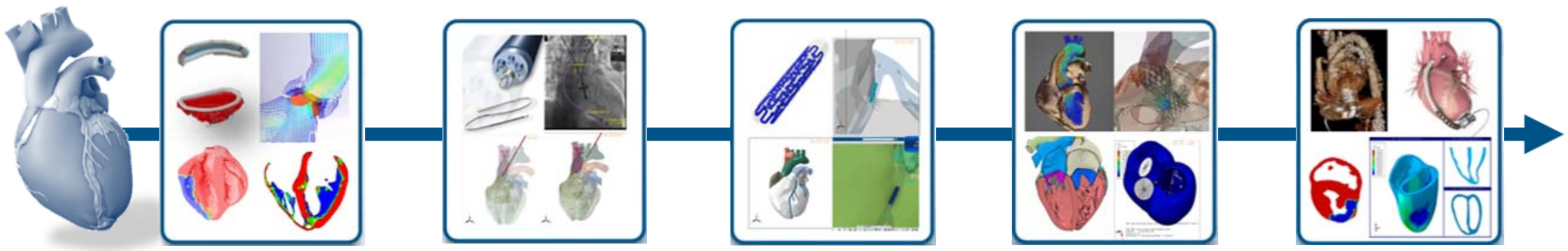
Implementing the Virtual Patient Model with Evidence from Simulations

NEW collaboration with Dassault Systèmes to develop a digital platform to:

- Use physics-based models with statistical models to demonstrate *virtual patients* from simulation
- Demonstrate the "submission of the future"
  - Develop a platform to incorporate digital, clinical and real-world evidence which supports product-lifecycle-management and continuous improvement
  - Create a new "review experience"

Living Heart Applications: Virtual Design & Testing of Cardiovascular Devices

Opportunity for medical devices and pharmaceuticals



Summary

- FDA is harnessing the power of *in silico* methods to U.S. public health.
- In silico methods impact regulatory decision-making at FDA.
- *In silico c*linical trials are underway at FDA. We are continuing to develop new mechanisms and pathways for using *in silico* methods in healthcare.
- New working group will continue to
  - raise awareness about the successes, challenges and opportunities for *in silico* medicine;
  - ***engage with national and international stakeholders to pursue harmonization efforts***; and
  - advance regulatory decision-making by establishing ***Good Simulation Practices*** to ensure the appropriate level of accuracy is attained.
    - Use FDA Guidance and ASME V&V40 as foundation material to get started!