Towards Credible Modeling & Simulation for Regulatory Decision Making

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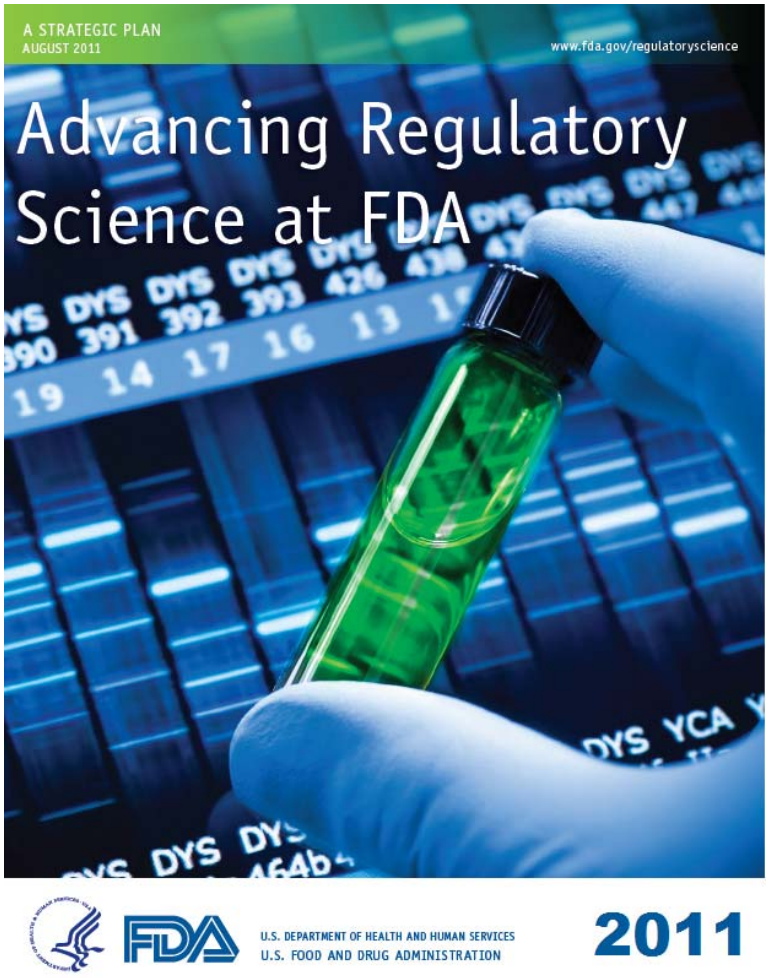
Joseph Pellettiere

FDA's Strategic Plan for Regulatory Science



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FDA's Strategic Plan for Regulatory Science

FDA has identified an important role for M&S in its strategic priorities.

Science Priority Areas

1. Modernize Toxicology

2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes

4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies

5. Harness Diverse Data through Information Sciences to Improve Health Outcomes

Proposed Methods/Approaches

- **(Q)SAR models to predict human risk**
- **Computer models of cells, organs, and systems to better predict product safety and efficacy**
- **Virtual physiologic patients for testing medical products**
- **Clinical trial simulations that reveal interactions between therapeutic effects, patient characteristics, and disease variables**
- **Knowledge building tools: data mining, sophisticated visualization, high throughput methods**
- **Mechanism for sharing data/models/algorithms**

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FDA Centers

CBER: Center for **Biologics** Evaluation and Research

CDER: Center for **Drug** Evaluation and Research

CDRH: Center for **Devices** and Radiological Health

CFSAN: Center for **Food Safety** and Applied Nutrition

CTP: Center for **Tobacco** Products

CVM: Center for **Veterinary** Medicine

NCTR: National Center for **Toxicological** Research

OC: of the Commissioner

ORA: Office of Regulatory Affairs

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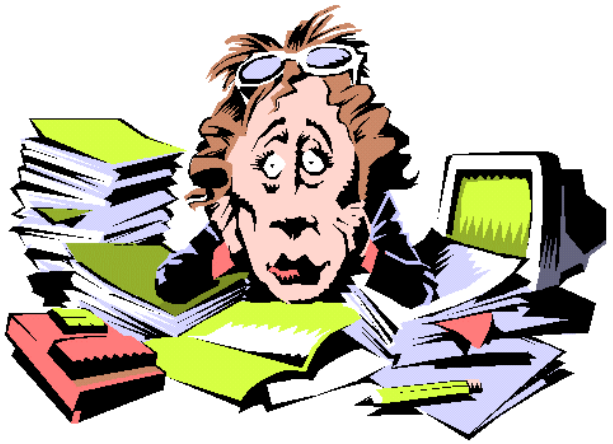
Different Perspectives

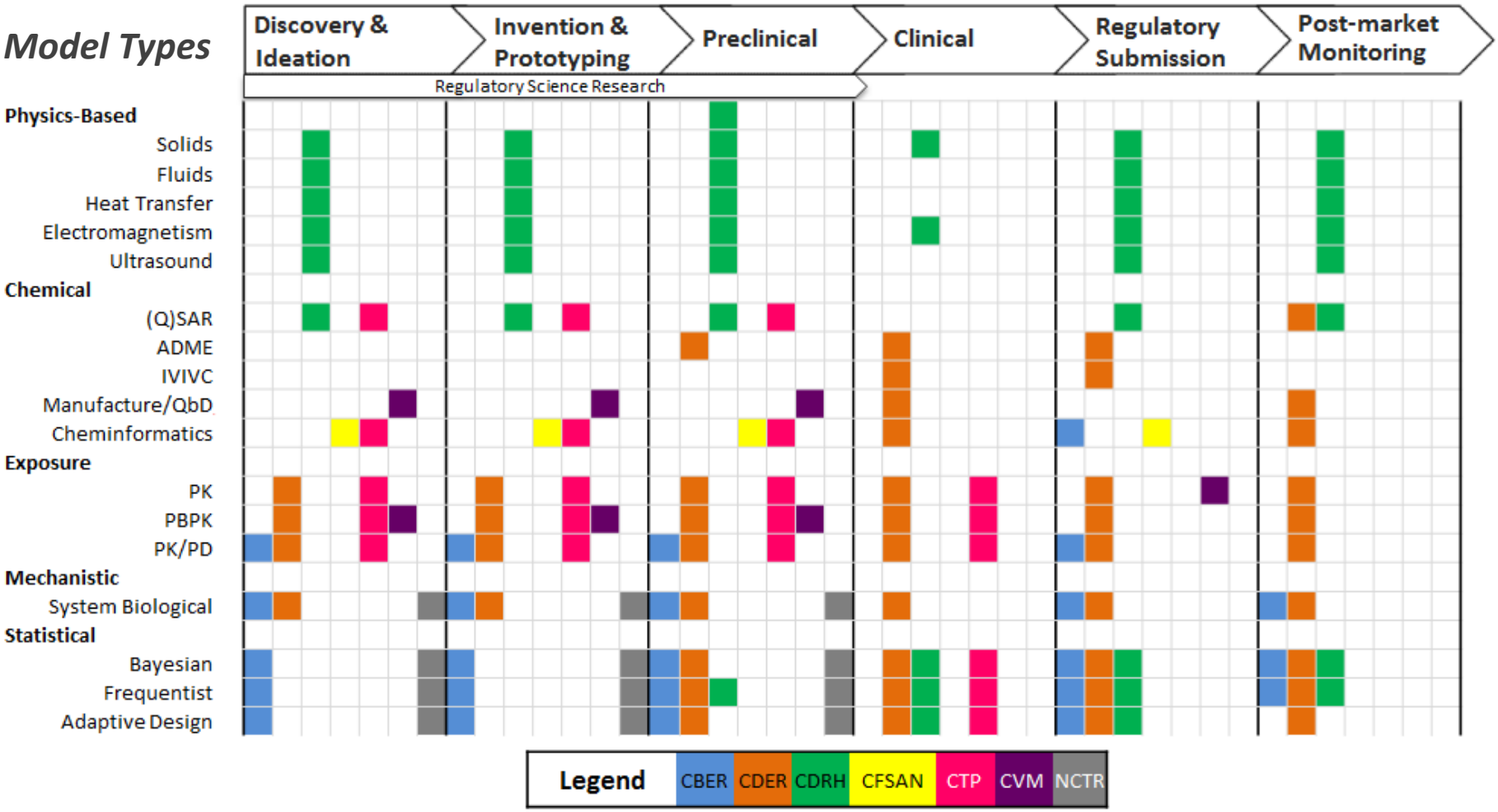
Some FDA scientists develop M&S for regulatory science and decision-making

Some scientists review M&S submitted to FDA in regulatory submissions



Modeling and Simulation at FDA

Stages of product lifecycle



Brief Summary of M&S at FDA

Some interesting differences

- A majority of M&S used at the different Centers are developed internally; CDRH has some internal development but a majority of M&S is created externally by sponsors for regulatory submissions
- CBER, CDER and CTP have advisory committees to assess M&S, mainly for assessing the validity and appropriateness of models used in regulatory decision-making
- CBER also has some external review

Some similarities

- M&S has a role in numerous internal and external collaborations
- No clear strategy or tool for assessing credibility; M&S review are subjective and without formal guidelines for regulatory decision making
  - CDRH is developing draft guidance for a Credibility Strategy for M&S
- There is (broad) interest in (and opportunity for) having M&S play a larger role in regulatory decision making, and the future evaluation of products

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Towards Credible Modeling & Simulation for Regulatory Decision Making

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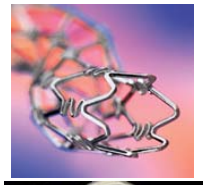
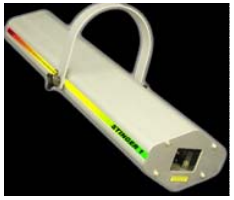
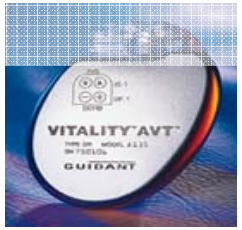
Center for Devices and Radiological Health



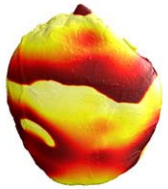


"The mission of CDRH is to **protect and promote the public health**. …We facilitate **medical device innovation by advancing regulatory science**, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and **assuring consumer confidence in devices marketed in the U.S.**"



Medical Devices

Pathmanathan



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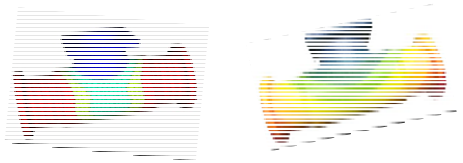
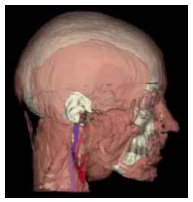
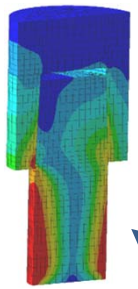


Iacono



Donaldson



of anatomy

of physiology

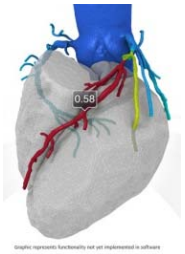
that becomes a 3D Printed Device

of the device

M&S

is the device

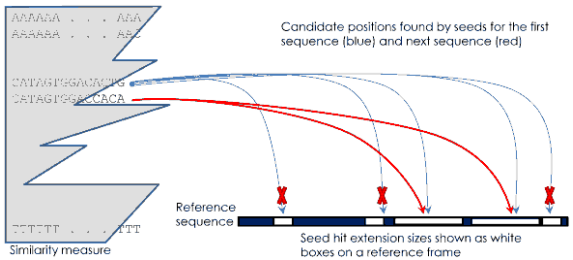
Heartflow



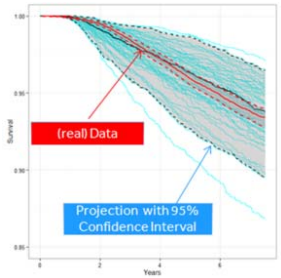
from big data

to predict treatment effects

embedded in the device



Simonyan



Haddad

diabetesforecast.org

Modeling & Simulation Disciplines

- Control Systems
- Electromagnetics and Optics
- Fluid Dynamics and Mass Transport
- Heat Transfer
- Physiology
- Solid Mechanics
- Ultrasound and X-ray

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CDRH's Role in Advancing M&S

- **Collaboration with stakeholders**

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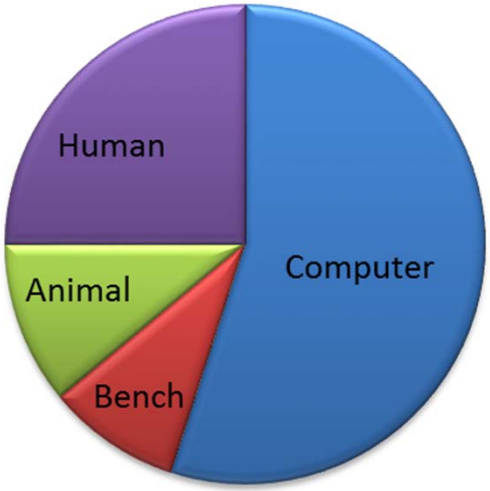
Medical Device Innovation Consortium

501(c)3 Public-Private Partnership
Members include FDA/CDRH, CMS, NIH, and Medical Device Industry

Computer Modeling and Simulation Project Vision

Quick and **Predictable** access for **Patients**
to **Innovative** technologies enabled by
Computation Modeling and Simulation as
Evidence of safety and performance



The Future of Evidence

- Increase Evaluation Confidence
- Faster Market Clearance
- Decrease Cost

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"The Gray Sheet"

Replacing Test Subjects With Computer Models Will Take Cooperation

By Reed Miller / Email the Author / View Full Issue
Top Stories / Word Count: 983 / Article # 01150518009 / Posted: May 14 2015 4:00 PM

Executive Summary

More collaboration between device companies and with FDA will be needed to employ sophisticated "virtual patient" computer models to reduce the number of patients needed in clinical trials, says Medtronic statistician Tarek Haddad.

Sophisticated computer models, or virtual patients, that can simulate how a device will function in a patient, could eventually cut the cost and time of device clinical trials, but manufacturers will have to cooperate with each other and regulatory agencies to reach that goal, according to Medtronic statistician Tarek Haddad.

"Even at a big company like Medtronic, we still don't have the resources to do everything so if we really want to make modeling a big part of this industry, different companies are going to have to come together," Haddad said at the Design of Medical Devices conference at the University of Minnesota in Minneapolis last month.

To learn more, see the webcast: MDICx Series at http://mdic.org/mdicx/

CDRH's Role in Advancing M&S

- **Actively engaged with the ASME Verification & Validation Standards Committee**
  - **ASME V&V 10 – Subcommittee on Solid Mechanics**
  - **ASME V&V 20 – Subcommittee on Fluid Dynamics and Heat Transfer**
  - **ASME V&V 40 – Subcommittee on M&S for Medical Devices**

    Completed second ballot of the standard guide on the Risk-informed Credibility Assessment Framework in Spring 2016

    More details on FigShare:
    https://dx.doi.org/10.6084/m9.figshare.3468962.v1

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CDRH's Role in Advancing M&S

- **Collaboration with stakeholders**
  - Medical Device Innovation Consortium
  - ASME V&V Committee
  - **Numerous** academic/industry partnerships
- **FDA Guidance**

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CDRH's Role in Advancing M&S

- **Drafted guidance document on reporting M&S studies in regulatory submissions;**
  - **FDA DRAFT Guidance on *Reporting of Computational Modeling Studies in Medical Device Submissions* – published Jan 2014**
    - **To be final in September 2016**
  - Main body discusses the purpose of computational modeling and simulation in regulatory submissions
  - Main body presents recommendations for ***reporting*** different elements of the computational modeling study
  - There are five subject specific appendices
    - Fluid & Mass Transport, Solid Mechanics, Electromagnetism, Thermal Transport, and Ultrasound
  - ***Does not address sufficiency of evidence***

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CDRH's Role in Advancing M&S

- ***Drafting*** **guidance document on a credibility strategy that can be used to help sponsors determine the level of verification and validation needed to support the use of their M&S in regulatory submissions.**
  - **Draft to be published in Winter 2017**
  - **Focuses on implement the risk-informed credibility assessment framework developed by the ASME V&V40 subcommittee**

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CDRH's Role in Advancing M&S

- **Collaboration with stakeholders**
  - Medical Device Innovation Consortium
  - ASME V&V Committee
  - Numerous academic/industry partnerships
- **FDA Guidance**
  - Reporting on the M&S studies
  - How to use the "Risk-informed Credibility Assessment Framework" in regulatory submission
- **Applicability Framework**

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Applicability Framework

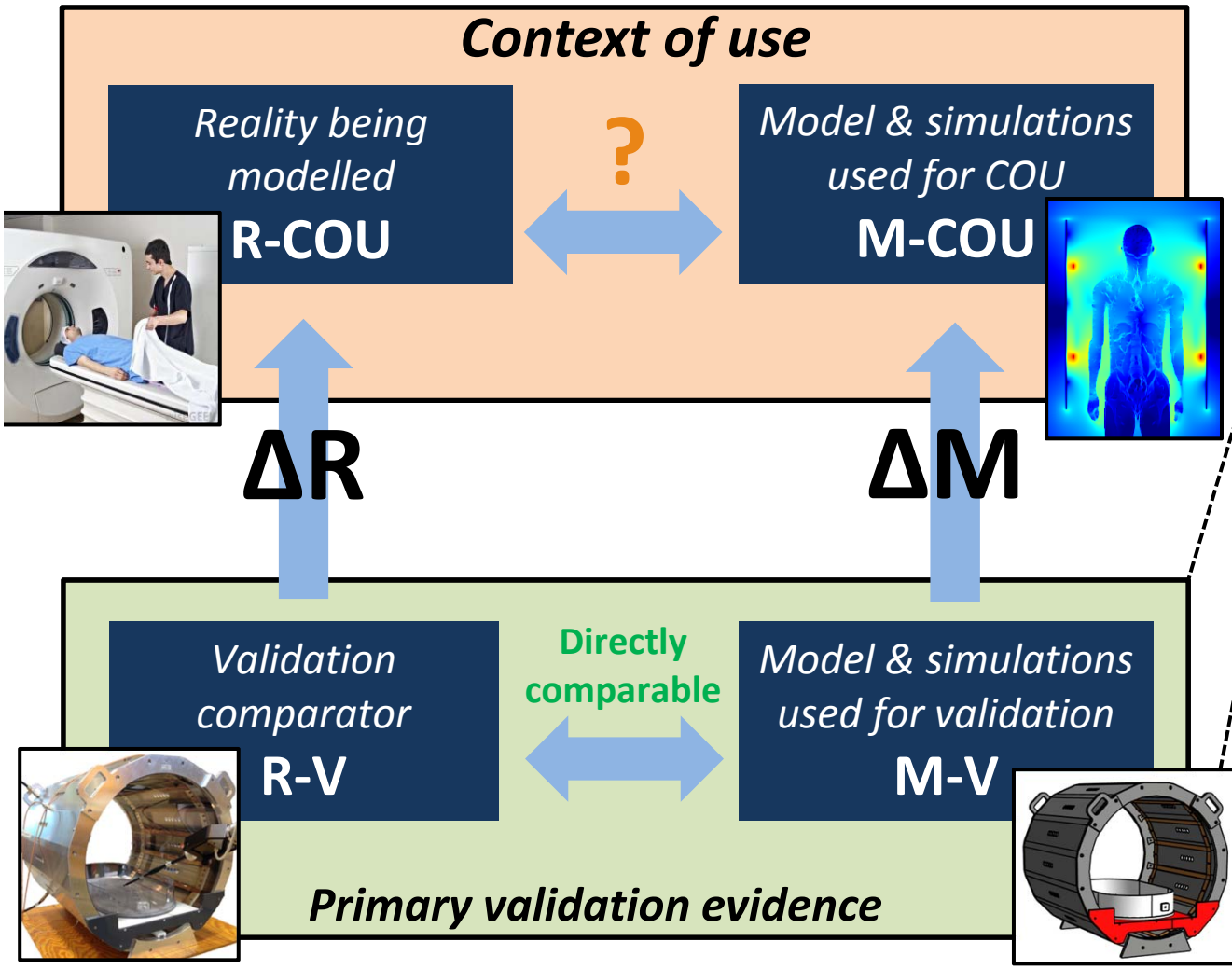
- **The *context of use* of M&S for medical products usually involves the clinical setting and/or patients**
- **The inability to perform direct validation hinders the broader acceptance and reliability of computational modeling.**

Direct validation is a validation study with a comparator that has been closely designed to match to the COU.

Indirect validation is a validation study with a comparator for which there are significant differences to the setting of the COU.

Overview of applicability framework

https://dx.doi.org/10.6084/m9.figshare.3409294.v2



CDRH's Role in Advancing M&S

- **Collaboration with stakeholders**
  - Medical Device Innovation Consortium
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  - Numerous academic/industry partnerships
- **FDA Guidance**
  - Reporting on the M&S studies
  - How to use the "Risk-informed Credibility Assessment Framework" in regulatory submissions
- **Applicability Framework**
  - Systematic evaluation of the applicability of a computational model for a proposed COU given a set of validation evidence

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For medical products, we envision a future of

Digital Patients: Designers **download** anatomic and physiologic computer **models** of (dozens, hundreds, thousands, …) of patients with a given disease.

Virtual Clinical Trials: New product concepts are "deployed/tested" in virtual patients and performance is simulated leading to more effective bench testing, animal studies and (actual) clinical trials, possibly augmenting real-world clinical trials.

Discover "Soft Failures"

Personalized Medicine: Physicians use simulation to **predict** safety and effectiveness of a given medical product for an individual patient.

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To realize that future, we need

- to raise awareness regarding the capability and limitations;
- a systematic assessment and understanding of use conditions;
- guidance for documentation and reporting M&S studies;
- methodologies for verification, validation, sensitivity analyses and uncertainty quantification for medical applications;
- methodologies for credibility assessment;
- framework(s) for determining the level of evidence needed to support the use of M&S; and
- better elicitation of the consequence if the M&S is incorrect to improve decision making.

Lots to do.

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- **Extra Slides**

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Models and Their Advantages

	Animal	Bench	Human	Computer
Predict clinical outcomes relevant to patients	Fair	Poor	Good	Fair
Predict clinical performance of the device	Fair	Fair	Good	Fair
Predict beyond Indications for use	Fair	Good	Poor	Good
Represent disease state	Fair	Fair	Good	Good
Adaptable for patient specificity	Poor	Fair	Fair	Good
Rely on simplifying assumptions	Fair	Poor	Fair	Poor
Maintain experimental control	Fair	Good	Fair	Good
Ability to vary parameters	Poor	Fair	Poor	Good
Cost	Fair	Fair	Poor	Good
Time	Poor	Good	Poor	Good

Model's ability to represent aspects of device performance: Good | Fair | Poor

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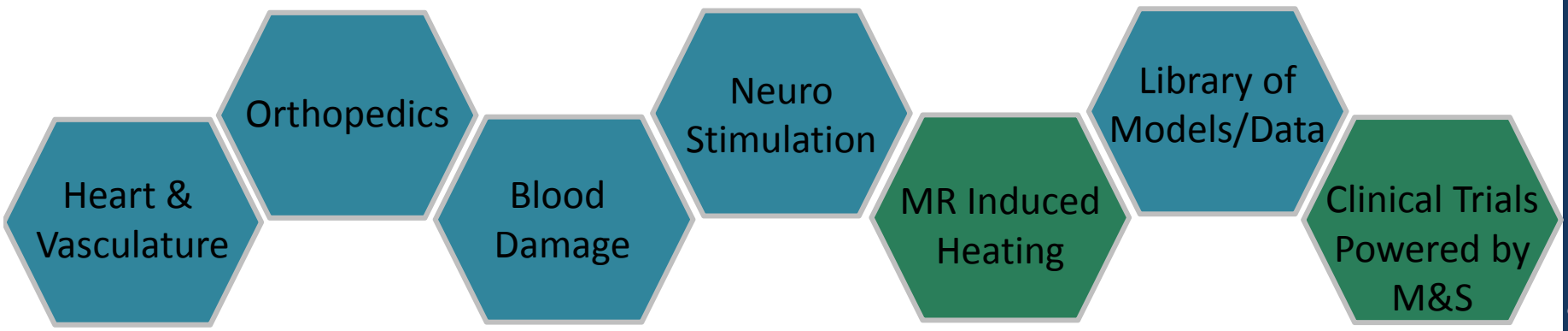
Terminology

	Definition	Status
Verification	Did you solve the underlying mathematical model correctly?	Methods are well established
Validation	Does the underlying mathematical model correctly represent the reality of interest?	Methods are well established, although for many applications (e.g., biological) data can be difficult to acquire
Uncertainty Quantification	What is the uncertainty in the inputs (e.g. parameters, initial conditions), and what is the resultant uncertainty in the outputs?	Methods are established but continue to evolve
Applicability	How applicable is the validation evidence to support using the model in the context of use?	New evolving area
Credibility	Based on the available evidence, is there belief in the predictive capability of the computational model for the context of use?	New evolving area

MDIC M&S Project Goals

1. Advance medical device innovation, and evaluate new and emerging technologies
2. Develop state of the art preclinical methods for assessing device safety and performance
3. Develop novel ways to use clinical data in evaluating medical devices
4. Define, standardize and educate the medical device community on validation requirements for the use of M&S in device development and regulatory submission



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Virtual Patient
with the Medical Device Innovation Consortium

Physical Modeling + Probabilistic Modeling → Clinically Relevant Predictions

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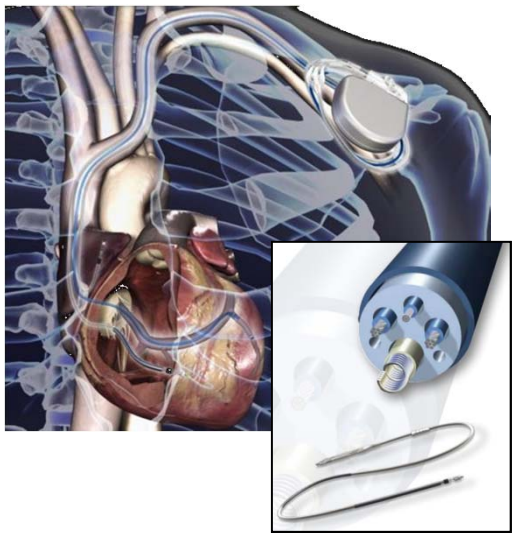

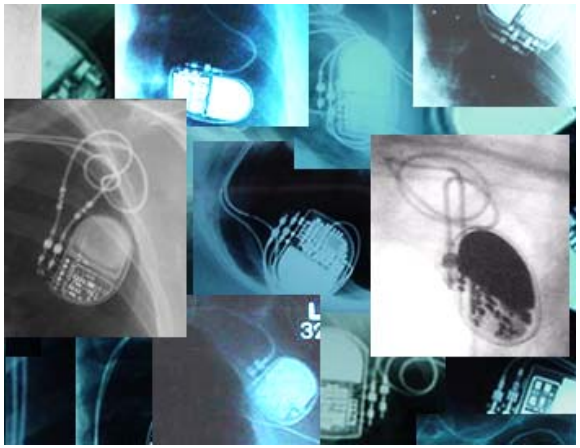

Credit: MDIC Modeling and Simulation Project