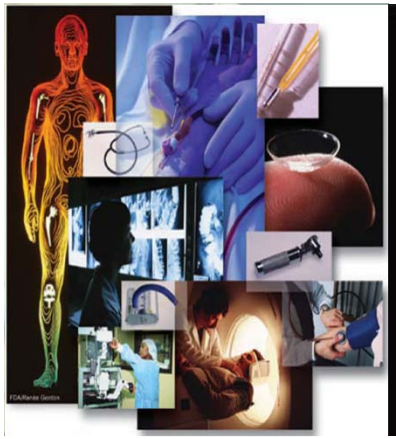
Center for Devices and Radiological Health
U.S. Food and Drug Administration



Regulatory Decision Making with Computational Modeling and Simulation

Tina Morrison PhD, **LT James Coburn MS**, Leonardo Angelone PhD
Jessica Hernandez MS, Donna Lochner

CDRH Mission

"The mission of the Center for Devices and Radiological Health (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.**"

Safety and Effectiveness

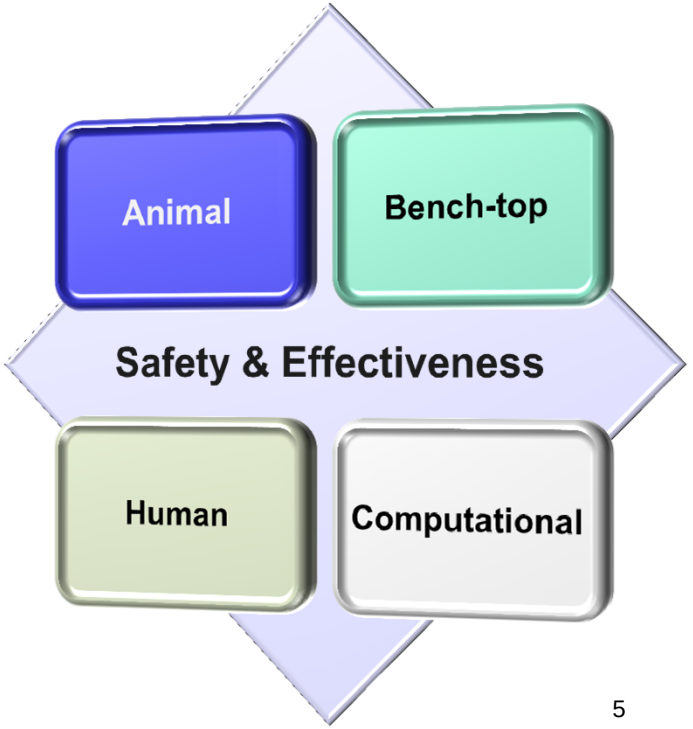
- There is **reasonable assurance that a device is safe** when it can be determined, **based upon valid scientific evidence,** that the ***probable benefits to health*** from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, ***outweigh any probable risks*.**

- There is **reasonable assurance that a device is effective** when it can be determined, **based upon valid scientific evidence,** that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, ***will provide clinically significant results*.**

Medical Device Evaluation

- Comprehensive evaluation of a marketing application for a therapeutic medical device is typically supported by a combination of **valid scientific evidence** from **four types of models**: animal, bench, computational, and human.

- Each model has its strengths and limitations for predicting clinical outcomes.



Models and Their Advantages

Adapted from Victor Krauthamer

	Cost	Time	Ability to vary parameters	Evaluation involving harm	Simplifying assumptions	Relevance to Clinical Use	Evaluating disease state	Experimental control	Ability to interpret data and predict clinical use
Animal	moderate	moderate	limited	restricted	moderate	species variability	difficult	relatively high	limited
Bench	low	short	limited	yes	many and always	limited	simplified states	high	limited
Human	very high	long	not easy	no, unethical	minimal	direct	yes	low	not easy
Computer	relatively low	short - to - moderate	high	yes*	many and always	variable	yes*	high	yes*

* CM&S in medical devices, as compared to other industries, is nascent and is the one method with the most potential for refinement and improvement because the other models have already matured.

Advancing Regulatory Science at FDA

FDA has identified an important role for CM&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

- (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
- Methods to verify, store, share

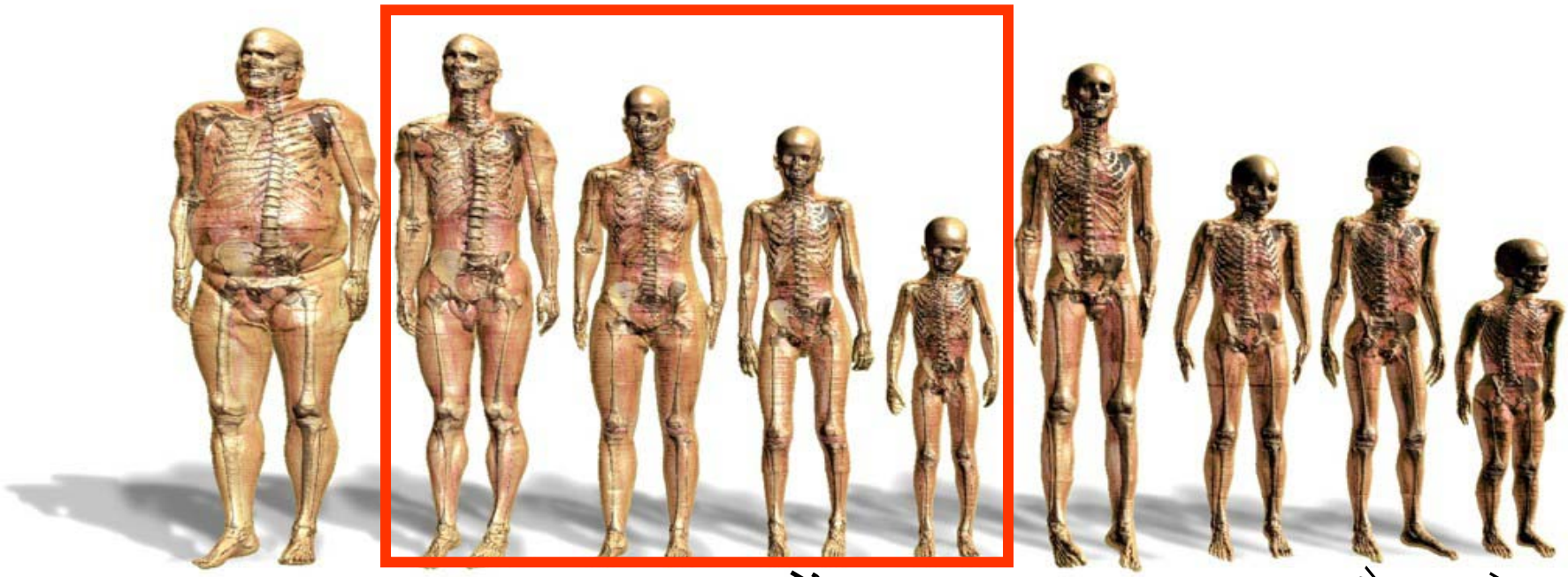
http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf

Areas of Active Research at CDRH

- **Computational Solid Mechanics**
  - Stents, Heart Valve Frames, Occluders, Vena Cava Filters
  - Spine and Joint Implants
- **Computational Fluid Dynamics and Acoustics**
  - Blood Pumps, Heart Valves, Endovascular Grafts
  - Drug Eluting Stents, Virus and Aerosol Transport
  - Ultrasound Propagation
  - Heat Transfer and Thermal Bioeffects
- **Computational Toxicology**
  - (Q)SAR models to predict human risk
- **Computational Electromagnetics**
- **Virtual Clinical Trials**

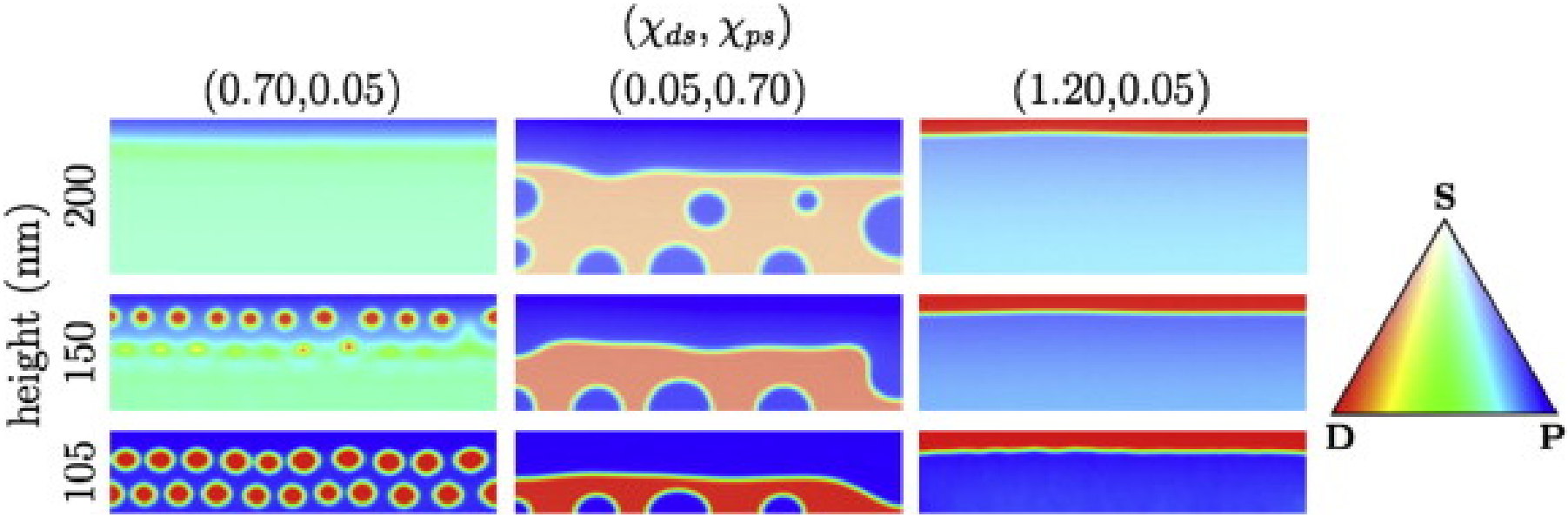
Computational phantoms Virtual Family (FDA & IT'IS Foundation)

- **9 different models available, more than 200 organs and 43 tissues,**
- **direct import and automatic material assignment, voxel import of models**



Microstructure Modeling of a Drug Eluting stent

- **TheraPy – Available on MatForge**
  - Diffuse interface theory
  - Determine the microstructure of a drug inside a polymer coating



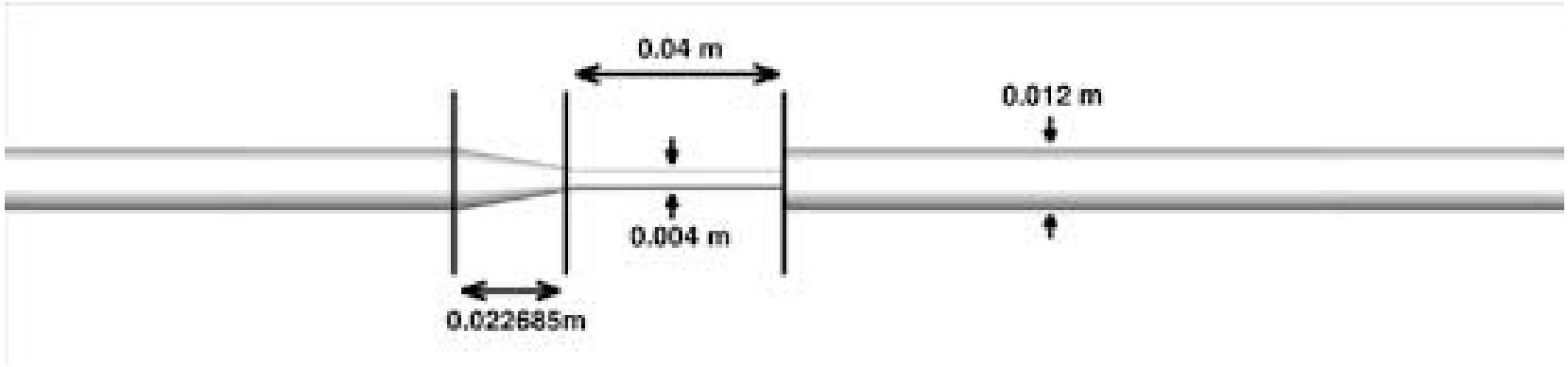
FDA Idealized Medical Device (Nozzle)

Assessment of CFD Performance in Simulations of an Idealized Medical Device: Results of FDA's First Computational Interlaboratory Study

SANDY F. C. STEWART,[1] ERIC G. PATERSON,[2] GREG W. BURGREEN,[3] PRASANNA HARIHARAN,[1] MATTHEW GIARRA,[4] VARUN REDDY,[2] STEVEN W. DAY,[4] KEEFE B. MANNING,[2] STEVEN DEUTSCH,[2] MICHAEL R. BERMAN,[1] MATTHEW R. MYERS,[1] and RICHARD A. MALINAUSKAS[1]

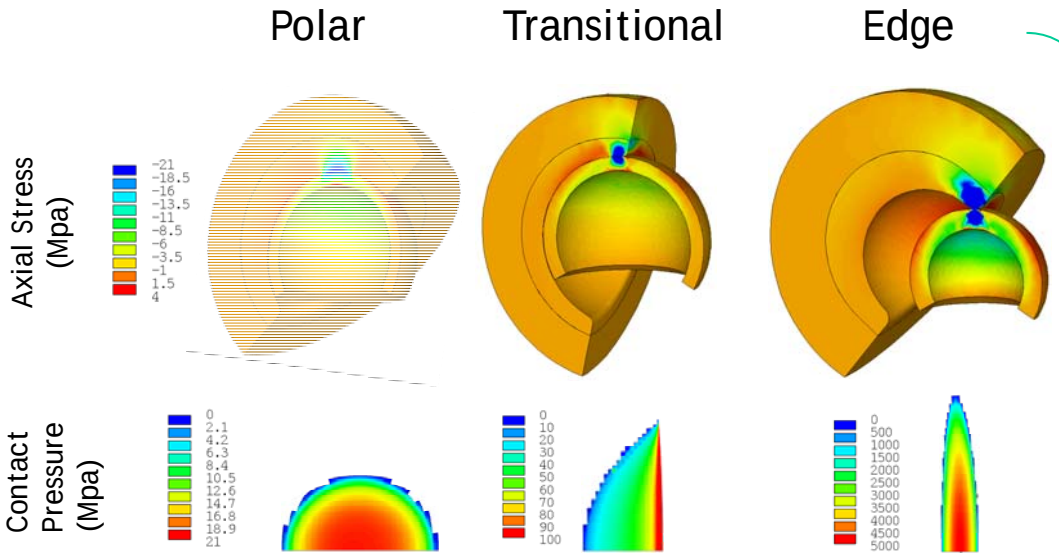
[1]Office of Science and Engineering Laboratories, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg 62, Rm 2210, Silver Spring, MD 20993, USA; [2]Pennsylvania State University, University Park, PA, USA; [3]Mississippi State University, Starkville, MS, USA; and [4]Rochester Institute of Technology, Rochester, NY, USA

(Received 19 October 2011; accepted 11 February 2012; published online 28 February 2012)

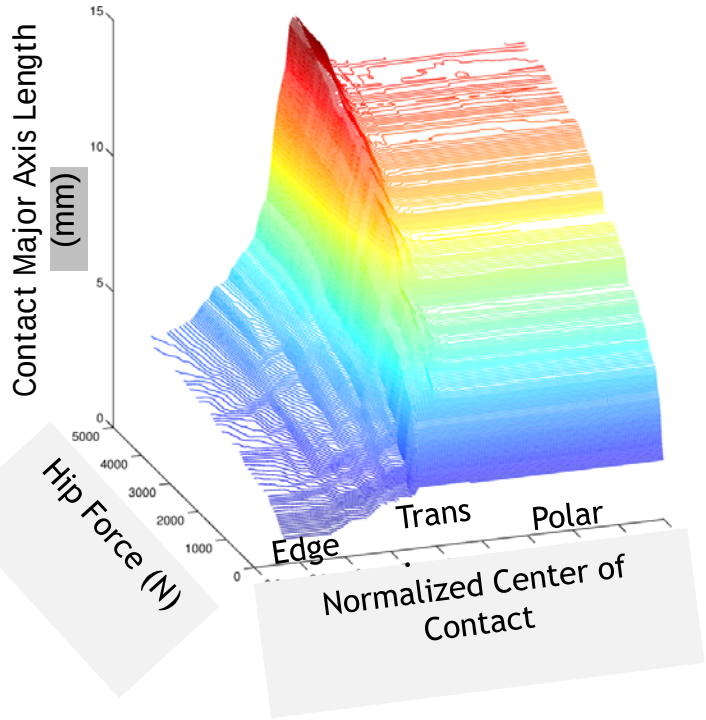


Stochastic Finite Element Model and Metamodel of Hip Contact Pressure

Finite Element Analysis - # simulations = 5000.



Metamodel response surface (10 dimensional)



Solution times for 1 gait cycle:

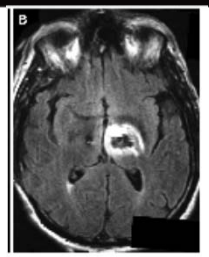
FEA = 20-30 hours = 70,000 – 110,000 seconds

Metamodel = 0.1 seconds

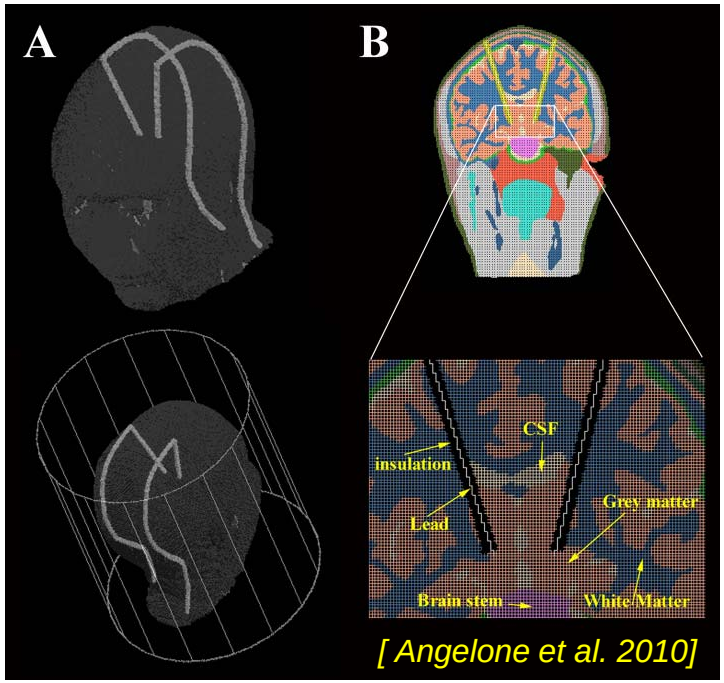
Accuracy: within 10% of contact patch dimensions and pressure

MR-induced heating (FDA & Collaborators)

Public Health Impact: **Patient with Deep Brain Stimulator (DBS) leads undergoing Magnetic Resonance Imaging (MRI) for back-pain. Right hemiparesis developed upon removal from MR scanner** ***[Henderson et al. Neurosurgery 2005]***



Methods to assess risks and ensure safety of patients with active implants (e.g. DBS system) undergoing MRI



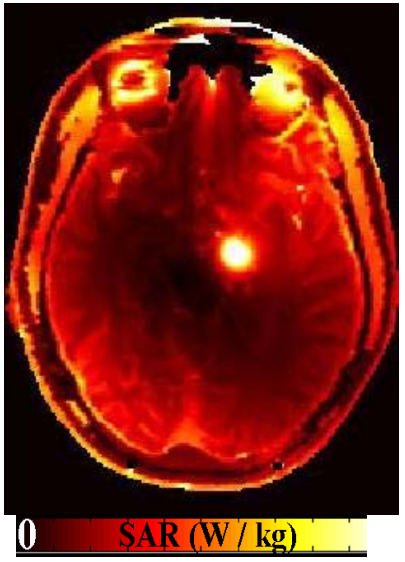
[Angelone et al. 2010]

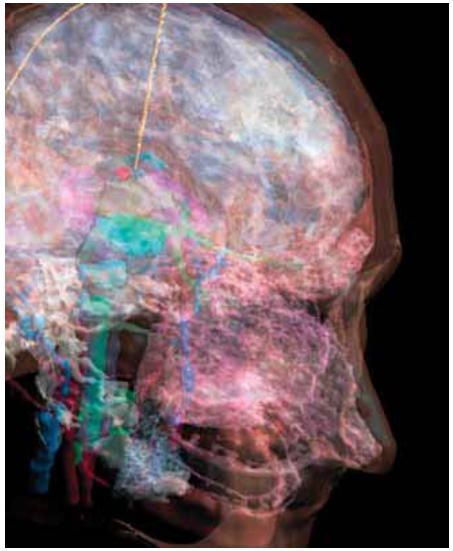
NIH – U01

Massachusetts General Hospital

Risk assessment:

Map of energy in patient





[Cabot et al. 2012]

IT'IS Foundation, ETH *Zurich*

Some of the challenges with current practice …

… have led us to address the need for:

- standards on documentation and reporting CM&S results in pre-market submissions;
  - FDA DRAFT Guidance on *Reporting of Computational Modeling Studies in Medical Device Submissions* – published Jan 2014[1]
- systematic assessment and understanding of device-use conditions;
  - Critical Path Initiative[2]
  - FDA Library of Models and Simulation[3]
  - Medical Device Innovation Consortium[4]

1, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm371016.htm
2, http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm
3, http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm346375.htm
4, http://mdic.org/projects/computer-modeling/

FDA *DRAFT* Guidance

Reporting[1] Computational Modeling Studies in Medical Device Regulatory Submissions (DRAFT)[2]

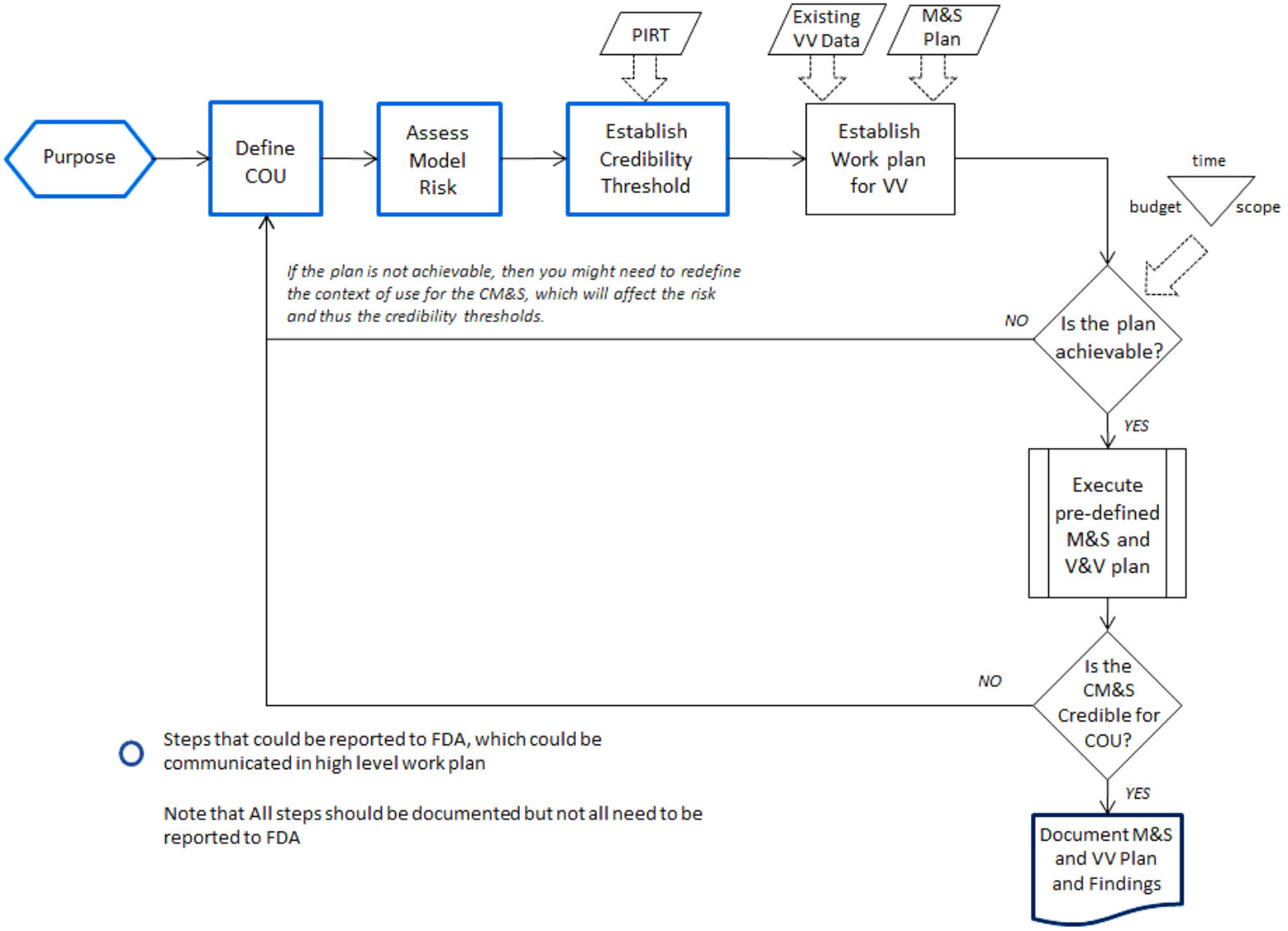
- Main body discusses the purpose of computational modeling and simulation in regulatory submissions
- Main body presents recommendations for reporting different elements of the computational modeling study
- There are five subject matter appendices
  - Fluid & Mass Transport, Solid Mechanics, Electromagnetism, Thermal Transport, and Ultrasound

- Public comment period closed – final guidance coming soon

1, Erdemir, Guess, Halloran, Tadepalli, Morrison, J Biomech. 2012 February 23; 45(4): 625–633
2, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm371016.htm

DRAFT Credibility Strategy

Similar to NASA-STD-7009



DRAFT Credibility Strategy

Similar to NASA-STD-7009

Numerical Implementation

Computational Model

- Code Verification
- Solution Verification
- System Configuration
- System Properties
- Boundary Conditions
- Governing Equations

Experimental Comparator

- Sample Characterization
- Control Over Test Conditions
- Measurement Uncertainty

Outputs

- Discrepancy of Inputs/Outputs
- Rigor of Output Comparison

Applicability to Context of Use

- Applicability to Context of Use

CDRH is getting ready to launch a pilot program to expand the current uses of CM&S in regulatory submissions, and to implement the Credibility Strategy

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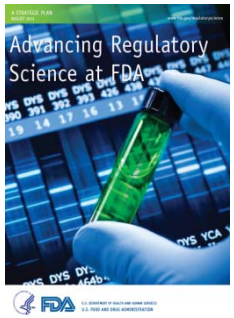


1, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm371016.htm
2, http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm
3, http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm346375.htm
4, http://mdic.org/projects/computer-modeling/

Some of the challenges with current practice …

… have led us to address the need for:

- methodologies to experimentally validate CM&S;
- sensitivity analyses and uncertainty quantification; and
  - CDRH is 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 CM&S for Medical Devices
- better elicitation of the consequence of the CM&S being incorrect.
  - CDRH is getting ready to launch a pilot program to expand the current uses of CM&S in regulatory submissions, and to implement the Credibility Strategy

Library

- Message RE library – V&V of models and we want the library to be a “promotional” tool for academia to know tools, models that are appropriate for regulatory use; want to have community review of the models – external experts (e.g. academia) – the library will be stronger through the community review, in an open source capacity.
- Linking to the BAA with the MAPS from Thor!
- Details on infrastructure/framework and maybe ideas on early examples for library.

FDA/MDIC Digital Library of CM&S

The vision is that the Library will be a mechanism for curating public open-use models and simulations in a non-competitive space to foster collaboration and advance research, development and evaluation of medical devices.

- Serve as a reference for access to state-of-the-art CM&S and data related to medical products
- Mechanism for FDA to transparently communicate utility and expectations of CM&S in a regulatory setting
- Being a space for companies to share their “smaller datasets”, e.g., pediatric population, to create a “larger datasets”

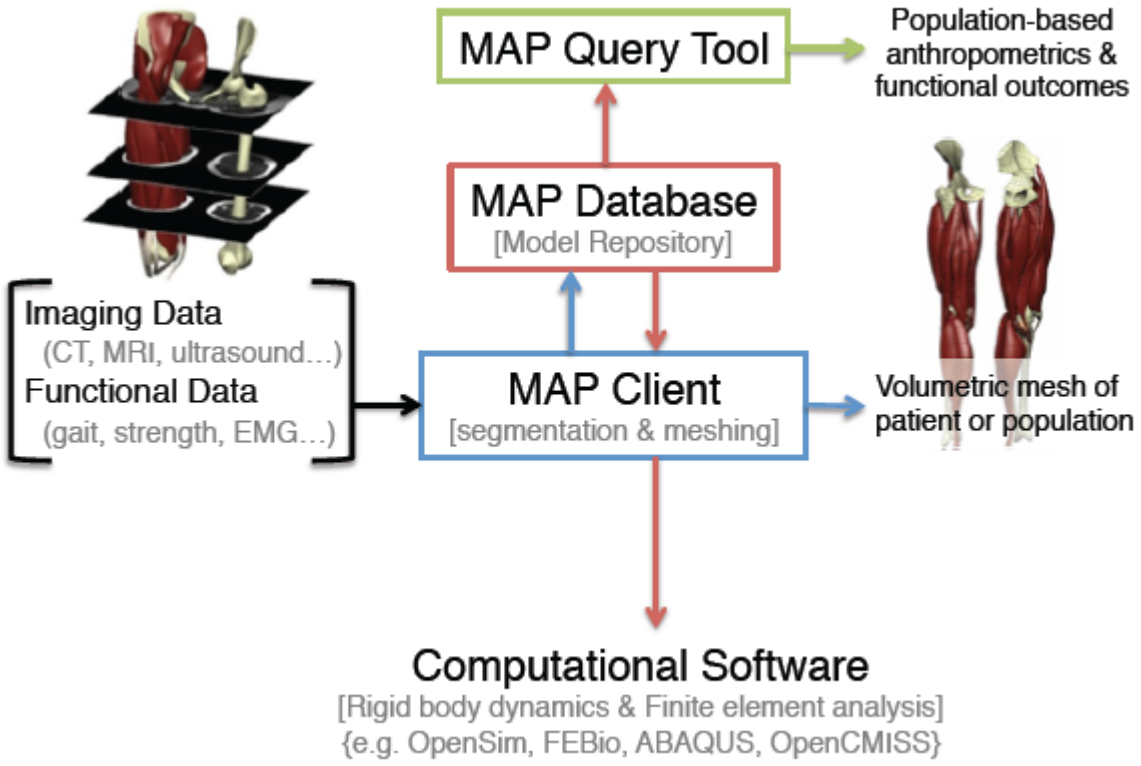
FDA/MDIC Digital Library of CM&S

- Hosted public workshop in June 2013 to introduce concept and openly discuss the Library
- Developed key aspects of the infrastructure and framework for use of the Library
- Anticipate initially that the Library will be used for curating DATA for creating models and validating simulations, and reference problems
- Collaborating with industry and academia to host and maintain the library

digital.library@fda.hhs.gov

The Musculoskeletal Atlas Project (MAP) -

An anatomical and functional population model of the musculoskeletal system to facilitate virtual clinical trials



FDA Grant – Broad Agency Announcement – Funding 2013

Interagency Modeling and Analysis Group

NIH National Institutes of Health

FDA

USDA United States Department of Agriculture

National Institute of Food and Agriculture

MITACS

IARPA BE THE FUTURE

- Multiscale Modeling Consortium
- 11 working groups

The Potential Benefit

- **Consortiums drive innovation**
  - Bluetooth Special Interest Group
  - *Medical Device Innovation Consortium*

Perceived short-term risk from sharing for…

Bluetooth®

LONG-TERM GAIN
AND
GREAT LEAPS FORWARD

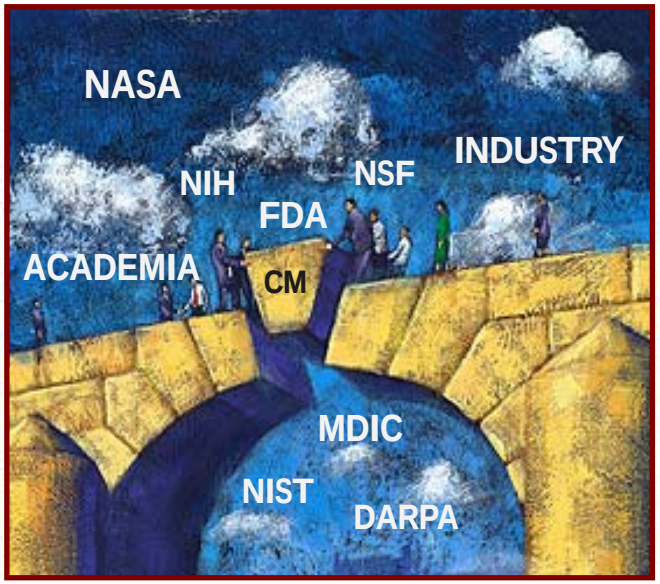
(Immediate) Future Directions

- **Provide feedback on the draft Reporting guidance and its use in reporting simulation results in premarket submissions**
- **We are hosting a pilot program to implement and evaluate the Credibility Strategy in premarket submissions**
- **The Credibility Strategy, once qualified as a Medical Device Development Tool[5], will be used to help determine which CM&S can be a part of the FDA Library of Models and Simulation**

5, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm374427.htm

Future Directions

- Digital Patients
- Virtual Clinical Trials
- Personalized Medicine



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Office of Device Evaluation

Current Uses of Modeling in Medical Device Applications

Extra Slides

Current Uses of Modeling in Medical Device Applications

Computational Solid Mechanics

Stents / Heart Valve Frames / Occluders / Vena Cava Filters / Annuloplasty Rings / Dental Implants / Spine & Joint Implants / Bone Plates & Screws / Surgical Tools

- Determine the implant size in a device family that is expected to perform the worst under simulated *in vivo* conditions
  - Reduces the amount of physical testing
  - Calculate Safety Factors for static and cyclic loads
- Evaluate the effect of manufacturing tolerances
- *Predicate Comparison*
- Demonstrate a modification (e.g., dimensional) is minor and has minimal affect on performance

Current Uses of Modeling in Medical Device Applications

Computational Fluid Dynamics

Ventricular Assist Devices / Total Artificial Heart / Blood pumps / Heart Valves / Endovascular Grafts / Drug Eluting Devices

- Characterize the flow field by identifying regions of high shear stress, wall shear stress, or areas of low flow or flow stagnation
  - especially in regions that cannot be visualized on the bench
- Determine blood damage, thrombosis potential, and drug transport using fluid flow properties

Current Uses of Modeling in Medical Device Applications

Computational Electromagnetism

Passive and Active Cardiology Implants / Peripheral Implants / Joint and Spinal Implants / Deep Brain Stimulators / MR-guided Interventional Devices

- Simulate the radiofrequency energy absorbed by patients undergoing magnetic resonance imaging (MRI)
  - Especially worst-case conditions that cannot be replicated in an animal model and cannot be tested ethically in humans
- Radiofrequency-induced currents and heating of (external) devices for electrophysiological recordings
- Simulate the electric/magnetic field generated by a device during use to provide evidence of effectiveness

Current Uses of Modeling in Medical Device Applications

Physiological Closed-Loop Controllers & Algorithms

Anesthesiology Devices / Artificial Pancreas / Neurodiagnostic Tools

- Use the simulation as an alternative validation method to demonstrate device performance and robustness
- *In silico* simulation model (control algorithm) of diabetes replaces *in vivo* animal testing for evaluating artificial pancreas
- Signal modeling (EEG source localizing software) for brain activity analysis

Current Uses of Modeling in Medical Device Applications

Computational Thermal Mapping

Ablation Devices

- Determine the thermal field distributions generated by tissue ablation devices (e.g., High Intensity Ultrasound, radiofrequency)
- Assess potential damage to surrounding tissue, organs and bones