DISCLAIMER

• I worked for 12 years in the Center for Devices and Radiological Health (CDRH):
  • 7 years as a lead review of cardiovascular implants, and served as an expert consultant on computer modeling and bench testing
  • 5 years as a lead researcher on computational modeling approaches for medical devices, and formed a “credibility assessment” program
    • Led the development of a consensus standard, and two FDA guidances

• I am currently in the Office of the Chief Scientist, not representing CDRH.
Slides are available now on FigShare.

Additionally, you can find related publications on my Google Scholar Profile.
Just a reminder ...

... these are all models!
The Role of Computational Modeling and Simulation in the Total Product Life Cycle of Peripheral Vascular Devices

Tina M Morrison, Maureen L Dreher, Sridhri Nagaraja, Leonardo M Angelone, Wolfgang Kainz

Affiliations + expand
PMID: 29479395  PMC: PMC5823268  DOI: 10.1115/1.4035866

Fig. 2  Four different models (top row) can be used for regulatory evaluation of peripheral intervention and vascular surgery devices. The shading represents our interpretation of how well the models can be used for different aspects of performance, as listed in the left column. Note that while cost and time are not attributes of performance, they are important factors to consider when selecting a model for use as scientific evidence.
The Need for a Credibility Assessment Framework

• Medical device companies wanted to use computer modeling and simulation to advance product development and evaluation

• Companies either
  o developed computational models of their devices, of test set-up, or representative anatomical (surrogate patient) models
  OR
  o “borrowed” models developed by a third party (e.g., simulation companies, academia, test labs)

• Many sources of variability across the industry (below is a just snapshot):
  o Materials (e.g., metals (like shape memory alloys), polymers, surface coatings)
  o Geometry (e.g., shape, sizes, implant configurations)
  o Boundary conditions (e.g., cardiac pulsatility, gross deformations)
  o Blood contacting or non-blood contacting
  o Short-term (e.g., IVC filter, pedical screw) long-term implant (e.g., heart value, stent)
  o Modeling approaches
The Need for a Credibility Assessment Framework

• FDA’s need
  o How do we evaluate all these different models and simulations?
  o How do we determine and communicate validation requirements?

• Industry’s need
  o How will we know that FDA will accept our models and simulations?
  o What are validation requirements if we use computer modeling and simulation?
  o How do we package our data to streamline the review?
It Depends …

… on how the output from the model will be used in the regulatory process.

Need to dig deeper ➔

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>TAXONOMY OF THE POSSIBLE CONTEXTS OF USE OF IN SILICO TRIAL METHODOLOGIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce</td>
<td>Refine</td>
</tr>
<tr>
<td>Preclinical</td>
<td>Reduce the number or duration of in vitro/ex vivo experiments</td>
</tr>
<tr>
<td>In Vitro/Ex Vivo Experiments</td>
<td></td>
</tr>
<tr>
<td>Preclinical</td>
<td>Reduce the number of animals involved in the experiment, or its duration</td>
</tr>
<tr>
<td>Animal Experiments</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>Reduce the number of humans involved in the experiment, or its duration</td>
</tr>
<tr>
<td>Human Experiments</td>
<td></td>
</tr>
</tbody>
</table>

**Possible Contexts of Use for In Silico Trials Methodologies: A Consensus-Based Review.**

Vicentini, Marco; Emili, Luca; Alshari, Payman et al.

2021 - In *IEEE Journal of Biomedical and Health Informatics*, 25 (10), p. 3977-3982

Peer Reviewed verified by ORBi
Context of Use – intended use of the tool/model

**FDA’s Development Tool Programs**

- **Medical Device Development Tools (MDDT) Program**
  - COU is a statement that fully and clearly describes the way the MDDT is to be used and the medical device development-related purpose of the use.

- **Drug Development Tools (MDDT) Program**
  - The COU statement should describe all the elements characterizing the tool’s purpose and manner of use; defines the boundaries within which the available data adequately justify its use.

- COU is not static and may evolve over time with the appropriate data.
Why is the context of use important?

Typically, there are many evidence sources on the table informing regulatory decisions.

Each source of evidence is not necessarily weighed equally; depends on its role; depends on its scope; depends on risk.
Briefly Introduce ASME V&V40

Examples to showcase the question of interest and context of use
ASME V&V 40 Standard
A standard for a broad range of modeling disciplines

Guides a team through the risk-informed credibility assessment framework, to determine **HOW MUCH** verification and validation (V&V) is necessary to support using a computational model for a context of use (COU).

Trust

Understands V&V evidence

Can I trust this model?

Courtesy: Jeff Bodner, Medtronic
ASME V&V40 History

2008-2011
- ASME V&V committee members traveled to conferences (e.g., NIH-NSF-FDA Workshops) to recruit members
- Signed Charter

2011-2013
- Intensive V&V literature review – what’s missing for medical devices?
- Developed new concepts: RAM/CAM
- FDA Public Meeting on formational ideas

2013-2016
- Revamped RAM/CAM based on important feedback from public meeting
- Many companies tested framework and offered critical feedback

2016-2017
- Prepared 6 device-specific examples
- Five internal ballots (thousands of comments from 43 voting members)
- Public Comment in November 2017
  - 26 persons requested copies
  - 36 comments

2018
- V&V 40 Industry Day
- V&V 40 is Published!
- 1st V&V 40 Introductory Training – more to come
- Established 5 new work items for standards subcommittee

ASME V&V 40 Charter, Signed January 2011
Provide procedures to standardize verification and validation for computational modeling of medical devices

Motivating factors
- Regulated industry with limited ability to clinically validate computational models
- Increased emphasis on modeling to support medical device safety and/or efficacy
- Use of modeling hindered by lack of V&V guidance and expectations within medical device community
ASME V&V 40 Membership
http://go.asme.org/VnV40Committee

Chair, Tina Morrison, US FDA*
Vice Chair, Marc Horner, ANSYS, Inc.*
Vice Chair, Jeff Bischoff, Zimmer Biomet
Secretary, Ryan Crane, ASME

P. Afshari, Depuy-Synthes Spine
B. P. Baillargeon, Dassault Systemes Simulia Corp
D. Bardot, Medical Device Innovation Consortium
A. Bestelmeyer, BD Technologies
J. P. Bodner, Medtronic Corp
S. Cheng, Alere San Diego, Inc.
B. D. Choules, Embry-Riddle Aeronautical University
R. Chow, Boston Scientific
C. Corrales, Baxter Healthcare Corporation
K. K. Debus, Siemens PLM Software
M. Dharia, Zimmer Biomet
S. Eswaran, Abbott Vascular
C. Funkhouser, Baxter Healthcare Corporation
K. Genc, Synopsys, Inc.
M. Goodin, SimuTech Group
I. Gulier, Boston Scientific Corporation
A. Gupta, Google Inc.
W. Hary, HeartFlow
H. Jin, Medtronic, Inc.
A. Kiapour, 4WEB Medical Inc.
L. Knudsen, Syncroness, Inc.
S. Kulkarni, VEXTEC Corporation
D. Levine, Zimmer Biomet
X. Li, Abbott Structural Heart
X. Liu, Stryker Orthopaedics
B. A. Lurie, W.L. Gore & Associates
R. Martinescu, Smith & Nephew
J. Mast, Hill-Rom, Inc.
L. Mulugeta, InSilico Labs, LLC
W. A. Olson, Ethicon Endo-surgery
C. Popeler, Southwest Research Institute
A.C. Rau, Exponent, Inc.
T. L. Rossman, Mayo Clinic
P. Saffari, Engage Medical Device Services, Inc.
C. Scotti, W.L. Gore & Associates
R. Swift, Cook Research Inc.
P. Tomaszewski, DePuy Synthes Joint Reconstruction
T. Zhao, Edwards Lifesciences
P. Harirahan, Alternate, US Food and Drug Administration
J. C. Coburn, Alternate, US Food and Drug Administration
P. Brian, Alternate, Exponent, Inc.
C. Basciano, Alternate, BD Technologies
N. Rebelo, Alternate, Dassault Systemes Simulia Corp

* Standards Committee representative

From 2018

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- Charlie Yongpravat
- Zane Wyatt
FDA complements standard with guidance
Credibility is the trust, through the collection of evidence, in the predictive capability of a computational model for a context of use.

For CISM: (complex in silico model)
Verification: Did you solve the underlying mathematical model correctly?
Validation: Does the underlying mathematical model correctly represent the reality of interest?

For CIVM: (complex in vitro model)  “Tina’s translation”
Verification: Is the CIVM performing as intended?
Validation: Does the CIVM correctly represent the reality of interest?
1. State the **decision or question of interest** that is being informed by the computational model.

2. Define the **context of use (COU)** for the computational model, which defines the specific role and scope of the model to address the question of interest.
   - *This is important because there are likely going to be other sources of evidence to inform the decision being made.*

3. Assess **model risk**, which represents the possibility that the use of the computational model leads to a decision that results in patient harm and/or other undesirable impacts.
Context of Use (COU)

• COU describes how the model will be used to address the question of interest, i.e., the specific role and scope.
  o Alongside it should be a description of additional data sources that will also be used to inform the question of interest (e.g., in vivo data).

• In our experience, ambiguity in the question of interest and COU can result in
  (i) reluctance to accept model in a given drug development or regulatory review scenario or
  (ii) An undesirably protracted dialogue between drug developers and regulators on the data requirements needed to establish model credibility.

• It is, therefore, critical to **unambiguously** and **explicitly state the question of interest** and **how the proposed modeling approach will address the COU**.
Developing a COU – where should I start?

• Define the Question of Interest (QOI)
  o Are patients with a metallic coronary stent able to safely undergo MRI scan?

• What types of models will inform the QOI?
  o Heating data from patients with similar type of device
  o Physical testing of stent in a phantom model
  o Tissue data from animal study of a sheep implanted with coronary stent that then received an MRI
  o Computational model of the stent in different configurations under different heating conditions to mimic the radiofrequency of an MRI machine

• What is the specific ROLE of the model of interest?
  o E.g., use the computational model to determine the worst-case condition; then test in the physical phantom; then conduct animal study, then conduct confirmatory patient safety study

• What is the specific (regulatory) SCOPE of the model of interest?
  o In the beginning, patients with metallic stents could not receive an MRI \( \rightarrow \) MRI Unsafe
  o Then broad range of testing was conducted for devices to be MRI Conditional
  o Clinical data provided evidence to inform the patient labeling as MRI safe
    ▪ Current paradigm – many devices receive MRI safety label from computational models\(^1\)
  1: DOI: 10.1056/NEJMra1512592

DISCLAIMER: Summary from my regulatory experience – not current practice
Developing a COU: SUGGESTED STEPS

Answering these could help define the COU for any model

• Define the Question of Interest (QOI)
  o E.g., question at a critical stage in the regulatory process

• Identify the different models that can/will inform the QOI?
  o CIVM
  o Data from multiple animal species
  o Data from tox modeling
  o Data from similar molecule

• What is the specific ROLE of the model to address the QOI?

• What is the specific (regulatory) SCOPE of the model to the QOI?
Three Examples

• Coronary stent – determine if patients with the implant can safely undergo MRI testing

Depending on time:

• Blood pump – identify operating conditions that put the pump at risk for hemolysis (damage to red blood cells)
• Small molecule drug – determine dosing for adult population, and starting dose for pediatric population
Device of Interest – Coronary Stent
ASME V&V40 Framework: **Potential heating of a stent from radiofrequency (RF) energy when a patient undergoes MRI.**

1. State the **decision or question of interest** that is being informed by the computational model.

**Coronary Stent (CS) Geometry**

CS vary in length and diameter

**Question of Interest:** Are patients implanted with a coronary stent able to safely undergo MRI scan procedures?
2. Define the context of use (COU) for the computational model, which defines the specific role and scope of the computational model used to address the question of interest.

<table>
<thead>
<tr>
<th>Bench Testing</th>
<th>Existence of Previous Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>COU1</td>
</tr>
<tr>
<td>Worst Case</td>
<td>COU2</td>
</tr>
<tr>
<td></td>
<td>COU3</td>
</tr>
<tr>
<td></td>
<td>COU4</td>
</tr>
</tbody>
</table>
2. Define the **context of use (COU)** for the computational model, which defines the specific role and scope of the computational model used to address the question of interest.

### KEY ELEMENTS OF THE COUs

<table>
<thead>
<tr>
<th>COU2</th>
<th>COU3</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No previous device data available</td>
<td>• Previous device data available</td>
</tr>
<tr>
<td>• Computational electromagnetics and thermal modeling will be used to identify the maximum temperature rise for all device configurations ($\Delta T_{\text{max}}$).</td>
<td>• Computational framework thoroughly validated against the predicate device.</td>
</tr>
<tr>
<td>• <em>In vitro</em> testing will be performed to confirm the worst-case heating predicted by the computational model.</td>
<td>• Computational electromagnetics and thermal modeling will be used to determine the maximum temperature rise for all device configurations ($\Delta T_{\text{max}}$).</td>
</tr>
<tr>
<td></td>
<td>• The computational model results will be used to predict the clinical outcome for safety for the new design, i.e. no <em>in vitro</em> testing will be performed.</td>
</tr>
</tbody>
</table>
3. Determine **model risk**, which represents the possibility that the use of the computational model leads to a decision that results in patient harm and/or other undesirable impacts.

**KEY ELEMENTS OF THE COUs**

<table>
<thead>
<tr>
<th>COU2</th>
<th>COU3</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Final labelling decision will be based on <em>in vitro</em> testing of the worst-case stent dimensions, as identified by the model.</td>
<td>• The labelling decision will be based solely on the computational model, which was validated against a predicate design.</td>
</tr>
<tr>
<td>• No predicate device data available.</td>
<td></td>
</tr>
</tbody>
</table>
Back-up
1. State the **decision or question of interest** that is being informed by the computational model.

**Question of Interest**: Are the flow-induced hemolysis levels acceptable for the intended use?
2. Define the **Context of Use** for the computational model.

**KEY ELEMENTS OF THE COUs**

<table>
<thead>
<tr>
<th>COU1</th>
<th>COU2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cardiopulmonary Bypass Device</td>
<td>• Ventricular Assist Device</td>
</tr>
<tr>
<td>• Class II Indication for Use</td>
<td>• Class III Indication for Use</td>
</tr>
<tr>
<td>• CFD model* will identify pump operating conditions at risk for hemolysis</td>
<td>• CFD model* will identify pump operating conditions at risk for hemolysis</td>
</tr>
<tr>
<td>• Final hemolysis assessment will be made with <em>in vitro</em> testing only</td>
<td>• Final hemolysis assessment will be made with <em>in vitro</em> testing &amp; computational predictions</td>
</tr>
</tbody>
</table>

*CDF model includes the Eulerian power-law model*
3. Determine **model risk**

### KEY ELEMENTS OF THE COUs

<table>
<thead>
<tr>
<th>COU1</th>
<th>COU2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Final hemolysis assessment will be made with <em>in vitro</em> testing only</td>
<td>• Hemolysis assessment will be made with <em>in vitro</em> testing and computational results</td>
</tr>
<tr>
<td>• Class II Indication for Use</td>
<td>• Class III Indication for Use</td>
</tr>
</tbody>
</table>
Hypothetical PBPK Example – set-up

A small molecule drug is in clinical development for the treatment of a chronic, non-life-threatening symptomatic condition that affects people of all ages. Planned clinical studies include assessment of PK and long-term safety and efficacy in adults, adolescents, and children.

The drug is primarily eliminated by cytochrome P450 (CYP) 3A4 and has a broad therapeutic window. Clinical drug–drug interaction (DDI) studies in adults demonstrate that drug PK are affected by strong CYP3A4 modulators such that patients require altered dosing.

The PBPK model will be developed, refined, and modified throughout the clinical development program to predict (i) PK changes that result from DDIs with CYP3A4 modulators and (ii) PK profiles in children (6–11 years of age) and adolescent (12–17 years of age) patients.
Hypothetical PBPK Example – Questions & COU

Because the drug model will serve multiple purposes, there are two questions of interest, each with a different COU.

Question of interest 1: How should the investigational drug be dosed when coadministered with CYP3A4 modulators?

• COU 1: The PBPK model will be used to predict the effects of weak and moderate CYP3A4 inhibitors and inducers on the PK of the investigational drug in adult patients. Simulated peak plasma concentration ($C_{\text{max}}$) and area under the plasma concentration-time curve (AUC) ratios of the investigational drug after a single dose and at steady state will be used to provide dosing recommendations for adults in labeling without the need for additional clinical DDI studies.

Question of interest 2: What is the optimal labeled dose for pediatric patients?

• COU 2: Relevant physiological parameters will be changed in the adult PBPK model to predict plasma concentration-time course and exposure metrics in adolescents and children. Predictions at steady state will be used to inform the starting dose for pediatric patients in a clinical trial assessing the PK, efficacy, and safety of the investigational drug. The results of the trial will determine the final labeled dose.
Let’s start with an example to discuss **Context of Use**

**Four different scenarios for the same simulation platform:**

1. Simulation is used to evaluate the performance of the stent graft for a medical device marketing application  
   E.g., **compute spring stresses and strains**

2. Simulation is used to conduct an *in silico* clinical trial to augment endpoint to assess freedom from fracture  
   Harness the [virtual patient model approach](#)

3. Simulation platform is used to evaluate different endovascular grafts for patient-specific surgical planning  
   [Software as a medical device](#)

4. Simulation platform is available as a tool for companies for design V&V and evaluation  
   [Medical device development tool](#)
1) Establish & assess credibility (ASME V&V40)

2) Implementing VVUQ (V&V10)

3) Prediction – applying the model to the Context of Use
1) Establish & assess credibility (ASME V&V40)

The question of interest presents the key question, concern, or decision of the study or development program. As such, the question of interest will likely be broader than the context of use of the model.
### Review Terminology

<table>
<thead>
<tr>
<th>Verification</th>
<th>Did you solve the underlying mathematical model correctly?</th>
<th>Mathematical Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation</td>
<td>Does the underlying mathematical model correctly represent the reality of interest?</td>
<td>Experimental Evidence</td>
</tr>
<tr>
<td>Uncertainty Quantification</td>
<td>What is the uncertainty in the inputs (e.g., parameters, initial conditions), and what is the resultant uncertainty in the outputs?</td>
<td>Statistical Evidence</td>
</tr>
</tbody>
</table>

#### V&V Activities
- Define conceptual model and establish V&V plan
  - Define mathematical model
    - Implement model
  - Design physical model
    - Implement model

#### Evidence
- Verify code
- Verify calculation
- Compare outcomes
- Validation metric

#### Evidence Types
- Mathematical Evidence
- Experimental Evidence
- Statistical Evidence

#### Activities
- Perform nominal simulation
- Perform experiments
- Quantify uncertainty
- Simulation outcomes
- Experimental outcomes
3) Prediction – applying the model to the Context of Use

- predict quantity of interest & uncertainty at application conditions
- quantity of interest at application conditions

- model credible for COU?
  - no
  - yes

- documentation and evidence

revise COU, model, and /or experiment

<table>
<thead>
<tr>
<th>Applicability</th>
<th>How relevant is the validation evidence to support using the model in the context of use?</th>
<th>Engineering Judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Credibility</td>
<td>Based on the available evidence, is there trust in the predictive capability of the computational model for the context of use?</td>
<td>Engineering Judgement</td>
</tr>
</tbody>
</table>
Formalized “Applicability”

Common approach in biomedical modeling

Develop a model → Perform validation → Alter model in some way → Run COU simulations

Applicability: the relevance of the validation activities for a computational model to support the use of the computational model for a context of use.

Pathmanathan P, Gray R, Romero V, Morrison TM, Demonstrating applicability of validation evidence for biomedical computational models, JVUQ, 2017
doi: 10.1115/1.4037671
The applicability analysis framework helps to qualitatively describe the “distance” from the validation domain to the COU domain.