REAGAN-UDALL FOUNDATION FOR THE FDA

SEPTEMBER 2023

Good Simulation Practices/Computational Modeling & Simulation Cluster Summary Report

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Discussion Result – Summary of Findings from the Good Simulation Practices/Computational Modeling & Simulation Cluster

The Good Simulation Practices/Computational Modeling & Simulation (GSP/CM&S) cluster began by discussing whether there was a need for GSP guidelines that mirrored other "good practice" guidelines (e.g., Good Clinical Practice Guidelines, Good Laboratory Practice Guidelines).

Over the course of the cluster, however, participants concluded that, rather than a GSP document articulating regulatory expectations, the computer modeling & simulation field needed a document describing how the practices might be more thoroughly adopted in FDA-regulated product development and regulation. Approximately four primary documents exist to guide modeling and simulation practices, and adoption tends to be more limited within industry itself rather than by FDA. The audience for the document would be stakeholders who are in positions to advance the use of CM&S and disassemble current barriers to broader adoption of CM&S in FDA-regulated products.

The overall goal of the document is to communicate how CM&S is complimentary to other methods/mechanisms of evidence generation across FDA-regulated product areas. Cluster members identified elements missing from the current literature and outlined content areas for a document to address.

Outline for a Document to Help Drive the Adoption of CM&S in FDA-regulated Products

1. **Glossary**
   - Dynamic collection, with ongoing review and updating
     - Examples
       - DoD glossary https://ac.cto.mil/de-ms-glossary/
       - The Biologics Effectiveness and Safety (BEST) Initiative https://bestinitiative.org/
       - CPMS https://simtk.org/plugins/moinmoin/cpms/Glossary%20and%20Definitions

2. **Evidence Generation and Evaluation**
   - Use and implementation of modeling & simulation to support regulatory decision making
   - Overarching principles that should be applied to all sorts of evidence, whether it's from a test method, an in vivo study, or simulation (mechanistic simulation, physics-based simulation, statistical AI simulation)
   - Contextualize how CM&S contributes to the totality of the evidence.
     - CM&S is a piece of the puzzle that complements other parts of the system – an evidence generation system where interlocking pieces provide different bits of information; arguably modeling and simulation can fill in a lot of gaps that you can't get elsewhere. (visual representation)

A. Evidence Generation
    1) How modeling & simulation fits into the ecosystem of evidence generation according to Context of Use[1]
        a. Reduce, Refine, Replace
            i. Reduce – reduce the number of in vitro experiments or those involving living subjects (animals or humans), their duration, or the number of experimental subjects (animals or humans) involved in the experiment, or the number of measurements performed during the experiment.
            ii. Refine – revise the study design in order to eliminate or relieve the suffering of the animals involved, or the risks for the humans involved in the experiments; or to shift the experiment to non-animal species, in accordance with animal experimentation ethics.
            iii. Replace – replace entirely the experiment, whether in vitro, ex vivo or in vivo in animals or humans, with computational models and simulations.
        b. Preclinical In Vitro/Ex Vivo Experiments, Preclinical Animal Experiments, Clinical Human Experiments
    2) How modeling & simulation fits into the ecosystem of evidence generation at different stages of product lifecycle
        a. Required model maturity in relation to product lifecycle
        b. Connecting modeling & simulation workflow and lifecycle to the total product life cycle
            - Explicitly state why we think models are useful, and connect it to the whole lifecycle of a regulated product, models for accelerating design, development, deployment, and regulation of regulated products
        c. What constitutes a significant cohort to demonstrate efficacy/safety and uncertainty quantification?
        d. Emphasizing the need to develop and refine CM&S methods for applicability in the space of using models as a way to predict unmeasurable primary outcomes and use that for evidence evaluation to question, are we making the right inferences from the data?
    3) End-to-end modeling and simulation workflows from development, calibration, benchmarking, deployment and use, to communication, maintenance, retrofitting
    4) Medical product or modeling method-specific information and references
        a. The model serves as repository for a state of knowledge to quantify understanding.
    5) Acknowledgement that the evidence generation system is imperfect, and CM&S as part of that evidence generation system is a related component
    6) Barriers to evidence generation

B. Evaluation
    1) Evaluation of CM&S according to Context of Use
        a. Reference FDA draft document
        b. Example: biomarkers
    2) Evaluation of CM&S at different stages of product lifecycle

[1] Viceconti M, Emili L, Afshari, P, et. al. Possible Contexts of Use for In Silico Trials Methodologies: A Consensus-Based Review. IEEE J Biomed Health Inform 2021;25(10):3977-3982.

3) There needs to be a defined standard for equivalency between the model and the real world.
4) Barriers to evaluation

3. Implementation (implementation/translational science) & Outcomes

A. Implementation
1) Identify barriers and consider an implementation plan to address these barriers, establishing where such barriers are and can be addressed in M&S lifecycle and total product lifecycle
2) Design of longitudinal studies that point to improvement in product reliability/performance that is (presumably) correlated with increasing use of CM&S encapsulating both M&S and total product lifecycle

B. Outcomes
1) How accurate did the models prove out to be? The purpose of this section could be to enhance confidence in predictive models.
2) Include longitudinal studies that point to improvement in device reliability/performance that is (presumably) correlated with increasing use of CM&S.

4. Showcase how modeling & simulation has been successfully used in the regulatory process

- Categorical examples for different stages in total product lifecycle
- For other regulated industries
  - Aerospace industry examples (highly regulated industry with human risk being a big factor in design)
  - Companies that are using CM&S to inform design (which may not be part of the FDA review)
- For FDA
  - Also include why companies have the M&S, but are not putting it in to applications (ex: Striker)
  - Identify companies that are making the investment in CM&S (using it in house), but are not using it in the regulatory context and submitting the documentation to FDA (where is the gap?)

5. Ethics of CM&S

- It would be unethical to **not** utilize CM&S that is capable of better informing safety, and potentially reducing animal use
- Inform CM&S and the stakeholders for FDA-regulated Products, regarding the safety and biases for Good Simulation Practices (GSP)
- Liabilities, i.e., who is responsible when a model goes wrong
- Responsibilities of the stakeholders: (a) modelers, (b) medical product developers, (c) regulatory agencies, (d) funding agencies, (e) healthcare providers, (f) patients, (g) society, essentially developers, communicators, and audience of M&S and digital evidence

6. Economics of CM&S

- Cost of modeling and simulation
- Perceived financial value in comparison to alternatives

7. Other documents that currently support/guide CM&S

- Model-Informed Drug Development (MIDD) and Complex Innovative Designs (CID) pilots are implementations of CM&S in drug development where simulations are used to evaluate trial characteristics based on methods that don't lend themselves to closed form analytics solutions.
- In Silico toxicology protocols
- Complex Innovative Trial Design
- Connecting current regulatory work and other documents that drive it
    - Reference some good simulation practices so they are not lost

Background and Processes

To meet regulatory science goals and objectives that serve stakeholders in the FDA-regulated ecosystem for emerging technologies, the FDA's Office of the Chief Scientist's (OCS) Office of Regulatory Science and Innovation (ORSI), in partnership with the Reagan-Udall Foundation for the FDA (the Foundation), created the Regulatory Science Accelerator (RSA). The RSA is intended to create collaboration space for sharing information regarding emerging technology that FDA centers will encounter in the near future.[2]

Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science (FARS) report

The Regulatory Science Accelerator, using the FARS report as its guide, represents opportunities for FDA to efficiently prepare for new science and technology that Agency staff will likely encounter in the regulatory process. In addition, RSA activities can positively influence the way science is conducted in the focus areas of regulatory science by stakeholders in the FDA-regulated ecosystem. Outcomes from that science (applied and translational) can be efficiently vetted by FDA (i.e., qualified) and more readily implemented into the regulatory review process with minimal delay, while improving the quality and integrity of FDA's regulatory decisions.

The RSA is intended to provide additional insight into:

- emerging science and technology that centers need to provide future regulatory review,
- the opportunities and pitfalls associated with new science and technologies, and
- exploring potential next steps to meet the anticipated regulatory science to help speed innovation.

Clusters

Guided by the 2022 update to the Advancing Regulatory Science at the FDA: Focus Areas of Regulatory Science Report,[3] the ORSI/Foundation collaboration identified two discrete cross-cutting issues (clusters) stemming from the FARS report warranting continued investment – In Silico Alternative Methods and GSP/CM&S. In the 2022 update, active areas of interest using CM&S include, but are not limited to, maternal health, complex generic drug products, and model-informed product design. Figure 1 illustrates how CM&S aims to modernize

[2] Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Building a National Framework for the Establishment of Regulatory Science for Drug Development: Workshop Summary. Washington (DC): National Academies Press (US); 2011. 2, Defining Regulatory Science. Available from: https://www.ncbi.nlm.nih.gov/books/NBK54399/

[3] Commissioner of the FDA. Focus Areas of Regulatory Science Report. U.S. Food and Drug Administration. Accessed September 7, 2023. https://www.fda.gov/science-research/advancing-regulatory-science/focus-areas-regulatory-science-report.

development and evaluation of FDA-regulated products according to the FARS framework. This report is a summary of the activities of the second cluster, GSP/CM&S.

Figure 1: Focus Areas of Regulatory Science (FARS) Framework[4]

I. Modernize development and evaluation of FDA-regulated products

A. Alternative Methods
B. Advanced Manufacturing Approaches
C. Analytical and Computational Methods
D. Biomarker Tools
E. Clinical Outcome Assessment
F. Complex and Novel Clinical Trial Design
G. Methods for Assessing Behavioral, Economic, or Human Factors
H. Approaches to Incorporate Patient and Consumer Input
I. Methods to Assess Real-World Data to serve as Real-World Evidence
J. Methods to Assess Data Source Interoperability

II. Strengthen post-market surveillance and labeling of FDA-regulated products

A. Methods to Assess Real-World Data to Support Regulatory Decision-Making
B. Using and Validating Artificial Intelligence Approaches
C. Novel Clinical Trial Design, Statistical and Epidemiologic Methods
D. Automated Reporting Tools for Adverse Events and Active Surveillance
E. Methods to Improve Communication About Risk to Patients and Consumers
F. Approach to Expand Data Capacity, and Increase Data Quality and Use
G. Efforts to Harmonize Existing and Emerging Data Standards

III. Invigorate public health preparedness and response of the FDA, patients, and consumers

A. Reinforce Medical Countermeasures Initiative (MCMi)
B. Mitigate Antimicrobial Resistance
C. Strengthen Patient and Consumer Engagement and Communication
D. Understand Substance Use and Minimize Misuse
E. Apply Population Approaches to Precision Medicine
F. Expand One Health Approaches
G. Identify and Harness Relevant Emerging Technologies
H. Strengthen Global Product Safety Net

[4] Office of Regulatory Science and Innovation – Program Office and Office of Acquisitions and Grants – Contracting Office. Welcome to the FDA's Broad Agency Announcement Day. December 6, 2022. https://www.fda.gov/media/164126/download

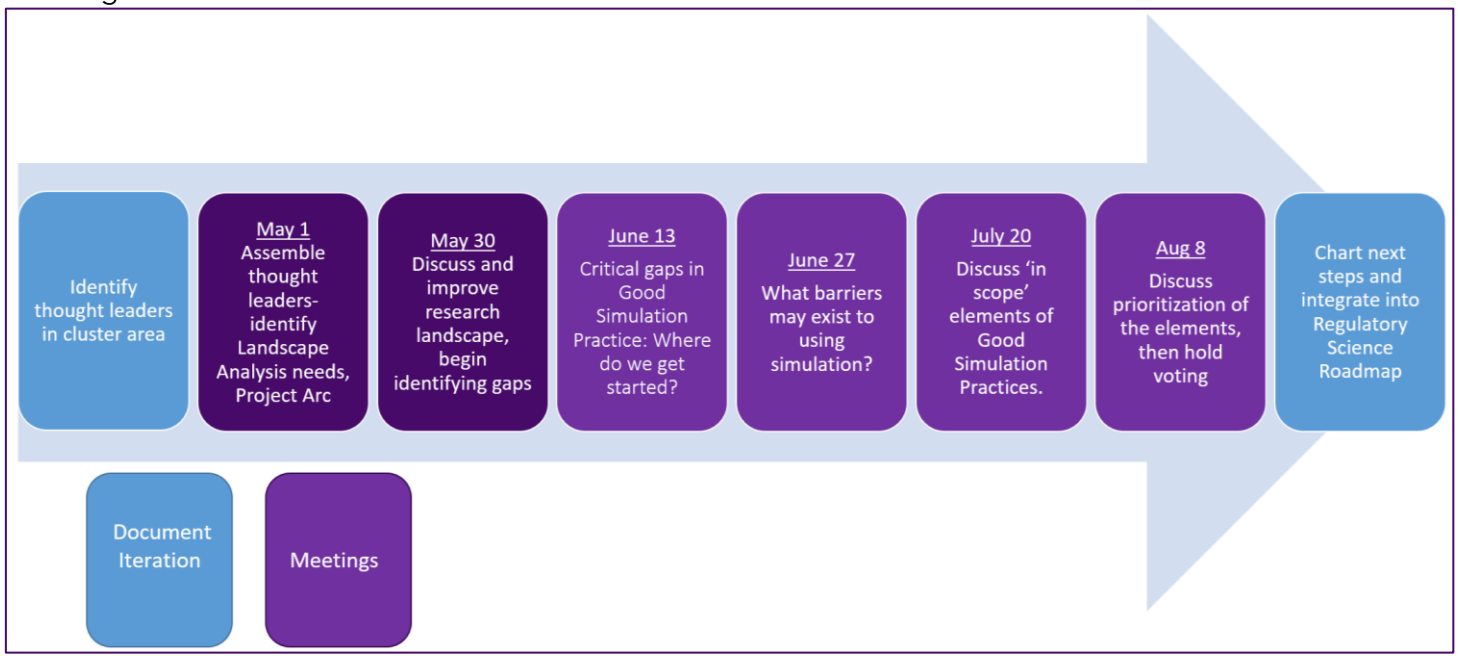
Good Simulation Practices/Computational Modeling & Simulation (GSP/CM&S) Cluster

Subject matter experts were identified to serve as an Advisory Group for the cluster (Appendix A). Membership for the cluster was selected using a questionnaire seeking input about good simulation practices (Appendix C). Four interactive webinars were held to determine the need for a GSP document, overarching principles that should be applied to CM&S evidence generated in the regulatory space and barriers to its use in this setting.

Timeline

Figure 2 provides the timeline for the In Silico Alternative Methods cluster. The advisory group met three times prior to and in between the four cluster workgroup sessions.

Figure 2: Cluster Timeline



Membership and Registration Questionnaire Results

The registration questionnaire (Appendix C) was completed by 105 people. Approximately half of the respondents provided their employment affiliation and country of residence. Respondents resided primarily in the United States (76%) and represented FDA-regulated industry (53%), academia (11%), non-FDA-regulated industry 10%), other organizations (10%), not-for-profit organizations (8%), and governmental/public service (8%). 102 of the 105 respondents (97%) agreed that there is a need for the global medical product community to develop Good Simulation Practice guidelines similar to other existing "good practice" guidelines. Forty-one of 69 respondents (59%), answering question two, endorsed creating new guidelines rather than reframing the "good laboratory practice" guidelines to include a "virtual laboratory" by way of scientific computing section. Examples of critical gaps that need to be addressed for simulation to be more fully harnessed in product development and regulatory review were provided by 57% of the respondents.

Workgroup Meetings

Four workgroup meetings were held in 2023 on June 13, June 27, July 20, and August 8. In addition to the advisory group, approximately 55 community members attended each session (Appendix B). The first meeting provided a project overview and reviewed results from the membership questionnaire. Three presentations from advisory group members addressed the question "If there were to be good simulation practices, what are the existing and ongoing efforts that can be used to kickstart this effort?" (Appendix D)

- Presentation #1: Ten Rules for Credible Practice of Modeling & Simulation in Healthcare
- Presentation #2: Introduction to the consensus book on the Good Simulation Practice
- Presentation #3: ASME V&V 40 & Complementary FDA draft guidance

During the second workgroup meeting, cluster members heard six presentations describing barriers to using modeling and simulation within their discipline. (Appendix E) Presenters were asked to:

1. Describe a situation where you wanted to move forward with using an in silico approach but you didn't or couldn't;
2. Describe what would have encouraged you/allowed you to pursue the in silico approach; and
3. Describe what a Good Simulation Practices document could have done/should have contained to support the use of your approach for that situation.

Potential barriers to utilizing CM&S was further discussed during the third workgroup meeting, shifting the conversation away from the need for a GSP guideline document to how to advance the use of CM&S in industry and regulatory science. Cluster members identified where CM&S is currently being used and could be used more frequently in the total product life cycle (TPLC) of drugs and biologics, devices, and food and cosmetics. Following the annotated exercise (Figures 3-5), cluster members discussed how to address existing barriers in order to use CM&S more frequently.

Figure 3: CM&S in the Drug/Biologics TPLC

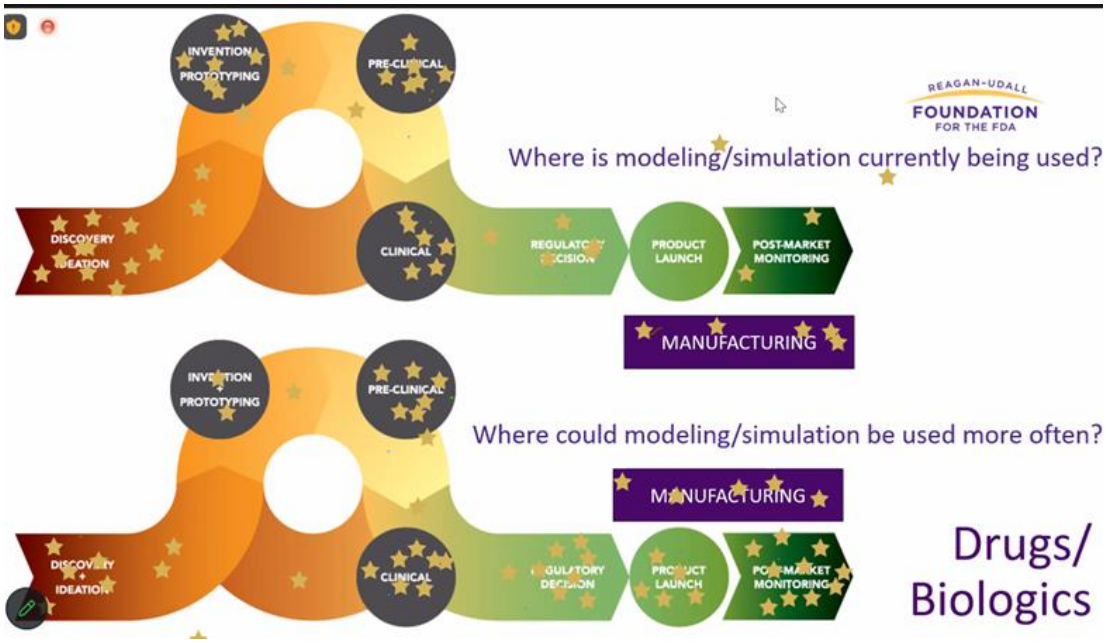


Figure 4: CM&S in the Device TPLC

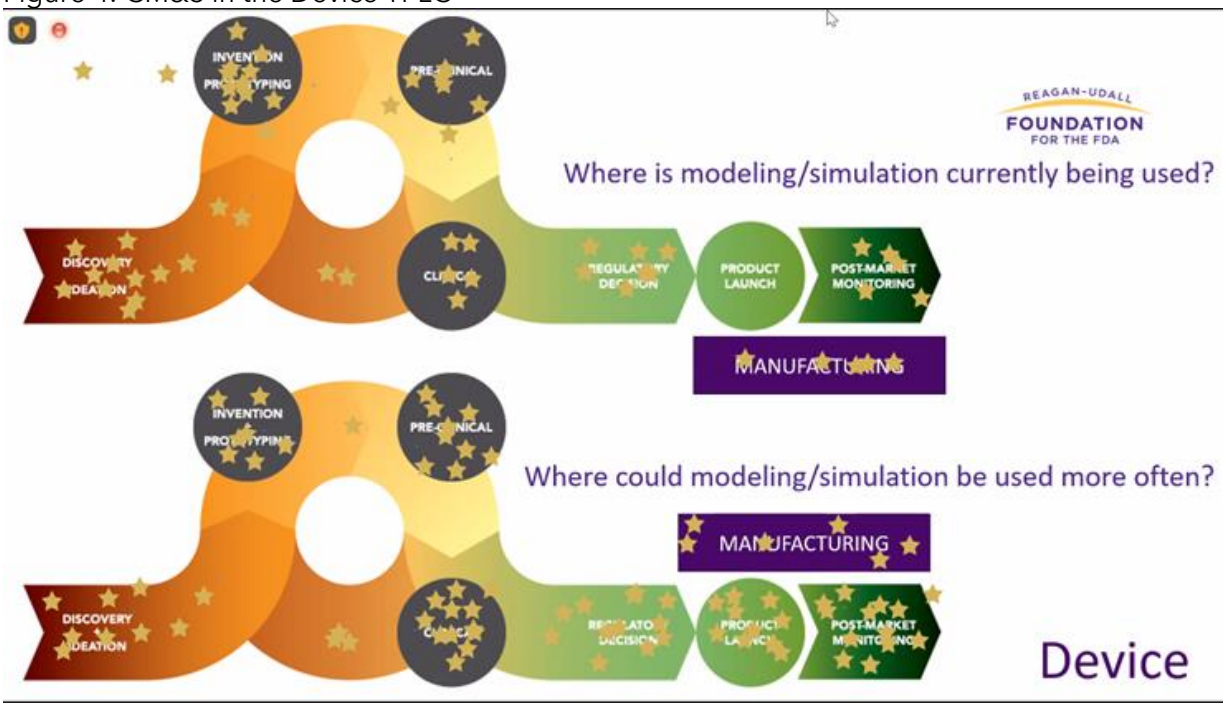
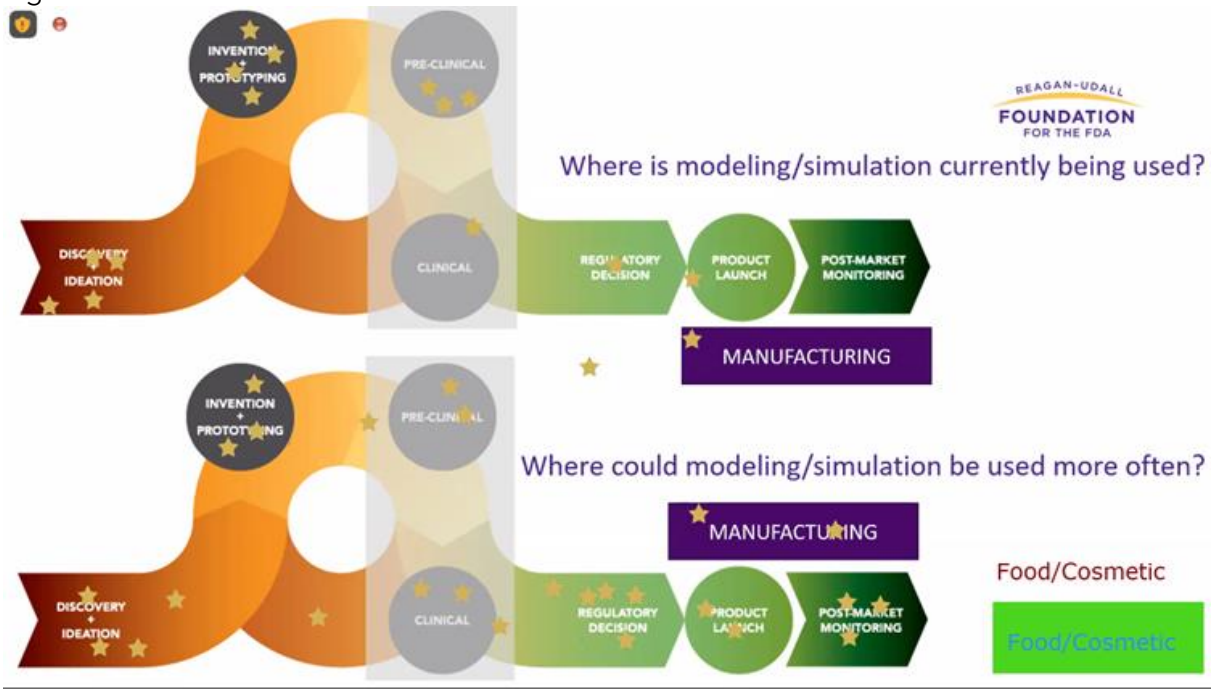


Figure 5: CM&S in the Food and Cosmetic TPLC



During the final cluster meeting, workgroup members began to outline a list of recommendations for content of a document to help drive the adoption of modeling and simulation in FDA-regulated products. The final outline constructed by the FARScc GSP/CM&S cluster members is presented in the "Discussion Result – Summary of Findings from the Good Simulation Practices/Computational Modeling & Simulation Cluster" section above.

Next Steps

The RSA will continue working toward creating a document to help drive the adoption of CM&S in FDA-regulated products. Next steps include:

1. Finalize a working outline for the document
2. Identify FARScc members who wish to assist in authoring the document
3. Publish a document to help drive adoption of CM&S

Future clusters will continue to focus on a strategy to drive acceptance of CM&S in the regulatory arena, identify barriers to adoption and devise strategies to disassemble current barriers to broader adoption of CM&S in FDA-regulated products.

Appendices

Appendix A: Advisory Group

Payman Afshari, PhD, Senior Principal Engineer, DePuy Synthes, Johnson & Johnson

Jeff Bischoff, PhD, Senior Director, Biomechanics, Zimmer Biomet

Ahmet Erdemir, PhD, Director, Computational Biomodeling (CoBi) Core, Lerner Research Institute

Marc Horner, PhD, Distinguished Engineer, Ansys

Mark Palmer, MD, PhD, Senior Chief Technologist for Healthcare, Ansys

Rajanikanth Vadigepalli, PhD, Professor, Department of Pathology & Genomic Medicine, Thomas Jefferson University

Appendix B: GSP/CM&S Working Group Participant List

Michael Ambrose, USP
Pat Baird, Philips
Arianna Bassan, Innovatune
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Miguel Bosch, IDX20 Inc.
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Suqin Cai, Illumina Inc.
Tejas Canchi, ResMed Ltd.
Helen Chow, Bigfoot Biomedical
Murat Cirit, Javelin Biotech
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Aaron Crowley, Genesis Research LLC
Nach Dave, Lumanity
Kristian Debus, Thornton Tomasetti
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Ash Peterson, Thornton Tomasetti
Yuri Peterson, MUSC
Elsje Pienaar, Purdue University
Bohdana Ratitch, Bayer
Bharatvaaj Ravi, Biocon Biologics Limited
Ehsan Samei, Carl E. Ravin Advanced Imaging Labs
Gilbert Shanga, Haleon
Lisa Sweeney, UES, Inc.
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Lixia Wang, Vaxxinity Inc
Paul Watkins, UNC
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Ahmet Erdemir, Lerner Research Institute
Marc Horner, Ansys
Mark Palmer, Ansys
Rajanikanth Vadigepalli, Thomas Jefferson University

FDA Observers
Khaled Bouri
Tracy Chen
Michele Ferrante
Miguel Lago
Michael Santillo
Paul Schuette

Appendix C: Membership Questionnaire

We aim to kick-start a conversation about the need for the global community to come together and develop Good Simulation Practice. We invite you to be a part of the conversation through this Regulatory Science Accelerator. To join the discussion, please provide us with the following information:

1. Do you think there is a need for the global regulated product community to develop Good Simulation Practice guidelines, a framework that mirrors the other "good practice" guidelines?
   a. You answered yes. What are three critical aspects that need to be the initial focus?
   b. You answered no. What do you think is needed to support the advancement of simulation in medical product development and evaluation?

2. Instead of creating new guidelines, do you think the "good laboratory practice" guidelines might be reframed to include "virtual laboratory" by way of scientific computing?
   a. You answered yes. What do you think would be needed to accomplish that?

3. Do you know of any on-going activities and/or organizations doing work that aligns with the aspects of good simulation practice?
   a. You selected yes. Please provide links or references for those activities.

4. What critical gaps need to be addressed for simulation to be more fully harnessed in product development and regulatory review?

5. What have we not asked but you would like to share regarding "good simulation practice" guidelines?

Appendix D: Working Group 1 Presentations June 13, 2023

Presentation 1

Ten Rules for Credible Practice of Modeling & Simulation in Healthcare

Committee on Credible Practice of Modeling& Simulation inHealthcare

Publication: https://doi.org/10.1186/s12967-020-02540-4
Website: https://simtk.org/home/cpms
E-Mail: cpmsinhealthcare@gmail.com

1

MOTIVATION

In modeling & simulation ***common practice guidelines do not exist*** to ensure that appropriate credibility processes are followed

Practice focused
not just models or predictions

Lifecycle (end-to-end)
not just verification& validation
also development, exchange,communication

Agnosticism
to domain o M&S application & intentions

2

HISTORY

2003
Interagency Modeling and Analysis Group
2004
Funding opportunities in multiscale modeling
2006
Multiscale Modeling Consortium
2008-2011
Challenges in appreciation of M&S
2011-2012
Scoping for reproducibility and reuse
2013
Committee on Credible Practice of Modeling & Simulation in Healthcare (CPMS)

IMAG & Multiscale Modeling (MSM) Consortium

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ABOUT THE COMMITTEE

CPMS Goal
Reliable application of M&S in healthcare and research

- Establish credible practice guidelines
- Consistent terminology
- Demonstrate workflows
- Support new areas of research
- Promote good practice
- Rotating membership
- Bringing in trainees

Circa - 2018

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GETTING TO TEN RULES - DEFINITIONS

Credible: Dependable, with a desired certainty level to guide research or support decision-making within a prescribed application domain and intended use; establishing reproducibility and accountability.

Practice: Any activity involving the development, solution, interpretation and application of computational representations of biological, environmental and man-made systems and their interaction thereof.

Modeling: Virtual, in silico, representation of system(s) of interest in a usable form in order to provide descriptive and predictive metrics for timely and systematic exploration of said system(s).

Simulation: Computational solution of models that quantify descriptive and predictive metrics of system(s) of interest, including related post-processing efforts to calculate these metrics from raw analysis results.

Healthcare: Any activity involving development, maintenance, advancement, or administration of medical care, including research, diagnosis, risk assessment, prevention, therapy, rehabilitation, surgery, intervention design, and regulation.

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GETTING TO TEN RULES - PROCESS

- Started with 26 proposed rules of good practice from the Committee
- Committee estimated proximity to clinical applications:
  - mathematics and computation
  - vested interest in the end-use of M&S
  - standards, guidance, evaluation and regulation
- Discussions among and between Committee subgroups to identify priorities
- An international public survey to curate a spectrum of perspectives in healthcare M&S
- Ranking of committee and survey findings identified the top 10 rules
- Evaluation and refinement of rules in the IMAG community and through open access
- Scholarly publication

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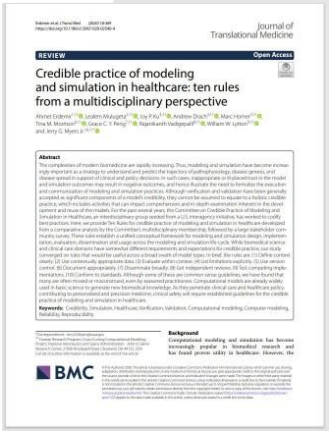
GETTING TO TEN RULES - OUTCOME


Journal of Translational Medicine

REVIEW Open Access

Credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective

BMC

Erdemir A, Mulugeta L, Ku JP, Drach A, Horner M, Morrison TM, Peng GCY, Vadigepalli R, Lytton WW, Myers JGJr. *Credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective*. J Transl Med 18, 369 (2020).

https://doi.org/10.1186/s12967-020-02540-4

A common operational framework to provide a practical basis for the design, deployment, assessment, and communication of modeling & simulation studies used for scientific and clinical decisions.

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TEN RULES - IN BRIEF

Ten Rules	
R1 - *Define context clearly*	**R6** - *Document adequately*
R2 - *Use appropriate data*	**R7** - *Disseminate broadly*
R3 - *Evaluate within context*	**R8** - *Get independent reviews*
R4 - *List limitations explicitly*	**R9** - *Test competing implementations*
R5 - *Use version control*	**R10** - *Conform to standards*

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TEN RULES - DETAILS

Rule 1 – Define context clearly - document the subject, purpose, and intended use(s) of the model or simulation

- Domain of Use
- Use Capacity
- Strength of Influence

Rule 2 – Use contextually appropriate data - Employ relevant and traceable information

- Data used in development, operation, and evaluation of the M&S traceable to their original source
- Data's relevance to the stated Context of Use is well articulated
- The Domain of Use Subject Matter Expert understands which and how the data is applied
- Findable, Accessible, Interoperable, Reusable (FAIR)

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TEN RULES - DETAILS

Rule 3 – Evaluate within context - accomplished with respect to the reality of interest and intended use

- Verification - determine computational M&S accurately represents the underlying mathematical model and its solution
- Validation - determine the degree to which the model is an accurate representation of the real world from the perspective of its Context of Use
- Uncertainty quantification - characterize the pertinent variability in the model and comparator and to quantify their effect on the simulation outcomes
- Sensitivity analysis - establish the degree to which the uncertainty in the model output(s) can be attributed uncertainty in the model inputs

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TEN RULES - DETAILS

Rule 4 – List limitations explicitly - Restrictions, constraints, or qualifications

- Assumptions that are application-specific, limits generalizability
- Clearly identify the conditions under which their M&S cannot be relied upon

Rule 5 – Use version control - Implement a system to trace the time history of M&S activities

- Version control for all model, software, data, and documentation files
- Tracking changes between versions
- Associating specific modifications to the creator/developer
- Including annotations/comments/notes with each version

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TEN RULES - DETAILS

Rule 6 – Document appropriately - Maintain up-to-date informative records of all activities, including simulation code, model mark-up, scope and intended use, and users guide

- Providing the information needed for to assess the credibility of the M&S activity planned and probably Context of Uses
- Providing the information needed to understand the nuances of reproducing and using/reusing the associated code and model

Rule 7 – Disseminate broadly - Publish all components of M&S activities

- Sharing of knowledge via publications and the sharing of M&S assets
- Methods sections of scholarly publication is generally not sufficient to embed all the details needed to meet rule 6 and 7

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TEN RULES - DETAILS

Rule 8 – Get independent reviews - M&S activity reviewed by nonpartisan third-party users and developers

- Independent "third-party" reviews by end-users or peers evaluating the activity in its entirety - Evaluate rules 2-6, 9 & 10 wrt 1
- Mechanism should be a thoughtful, impartial evaluation predicated on accepted guidelines and requirements
- Peer reviews of manuscripts should not be the sole form of third-party review

Rule 9 – Testcompeting implementations - Use contrasting M&S execution strategies to check conclusions

- Understanding of model behavior WRT familiar standards of performance
- Insight deriving from weighing the pros andcons of competing approaches

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TEN RULES - DETAILS

Rule 10 – Conform to standards - Adopt applicable procedures, guidelines, and regulations accepted as best practices withinsupporting disciplines

- When consistently applied, represent a means of providing requirements, specifications, and guidelines that establish that the M&S materials and products fit the intended purpose
- May vary depending on the institution or discipline
- Importance will vary with the development stage of the M&S application
- Improved insight into and adoption of M&S follows from adherence tostandards which promote transparency

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REMARKS

- Grounding the practice with the model's Context of Use
  - Intensity of the tasks are defined by the Context of Use.
  - E.g., exploratory models vs clinical diagnosticmodels.
- Comprehensive view of the whole practice of modeling & simulation
  - Inclusive of verification, validation, uncertainty quantification, and sensitivity analysis.
  - Capturing the workflow from start to end: design, development, calibration, benchmarking, use, reuse, exchange and communication.
  - Bridging M&S practitioner's implementation with end-users expectations.
- Supported by examples and early adoption
  - Leveraged by the Committee and IMAG/MSM toreview M&S practices.
  - Adopted by repositories (e.g., SPARC)and journals (e.g., Physiome) as a rating/review tool.
- Customizable to tailor domain of application and intent
  - Mechanistic modeling focused but extensible to data-driven/hybrid modeling modalities
  - Applicable to diverse biomedicalsciences and clinical disciplines
  - Accommodatingstate of development and stakeholder communities

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DIRECTIONS

- Utilization of Ten Rules and conformance rubric in supporting review of practices and reuse of models
  - E.g., outreach capability to domain-specific M&S practitioners, application domain experts, broader community, and public
- Specialization of Ten Rules for depth (conformance thresholds and criticality) based on categorical contexts of use
  - E.g., Good Simulation Practices for development and regulation of medical products
- Training tool for upcoming generation of M&S practitioners
- Exploring transferability of Ten Rules and experiences from mechanistic modeling to data-driven / hybrid modeling
  - E.g. Linking to trustworthiness in AI
- Jumping board of science research in credible practices of M&S

34

INQUIRIES

Committee on Credible Practice of Modeling & Simulation in Healthcare

Publication: https://doi.org/10.1186/s12967-020-02540-4
Website: https://simtk.org/home/cpms
E-Mail: cpmsinhealthcare@gmail.com

Slides provided by Ahmet Erdemir, erdemira@ccf.org on behalf of the Committee.

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Avicenna Alliance
Association for Data Driven Medicine

In Silico World
Community of Practice

VPH Institute
Building the Virtual Physiological Human

Introduction to the consensus book on the Good Simulation Practice

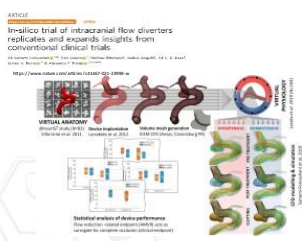
Marc Horner
Ansys, Inc.

What are GxP documents?

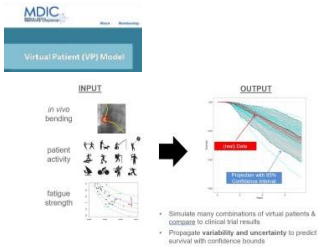
- GxP documents are quality guidelines developed and enforced for a variety of regulated industries, incl. food, drugs, medical devices, and cosmetics.
- GxPs help to ensure that products are safe and meet their intended use. They also guide quality in manufacturing.
- GxP documents are developed through a consensus process.

The stakes are rising

- Computational modeling and simulation continues to grow in importance in areas of patient care and regulatory decision-making.



in silico Clinical Trials
- to de-risk a clinical trial



Virtual Patients
- to replace patients in clinical trials

Digital Twins
- to continually remind us to behave

Who are we?

VPH Institute
Building the Virtual Physiological Human

International not-for-profit organisation incorporated in Belgium representing the academics working on *In Silico* medicine technologies. Founding member of the Avicenna Alliance

Avicenna Alliance
Association for Predictive Medicine

International not-for-profit organisation incorporated in Belgium representing the companies that operate as providers or users of *In Silico* medicine technologies

In Silico World
Community of Practice

Online Community of Practice operated by the EU-funded *In Silico* World project coordinated by Prof. Viceconti, which offers to any practitioner of *In Silico* Medicine a discussion platform aimed to develop best practices.

Confidential 40

The In Silico World Community of Practice

- Open and free to anyone with a professional or educational interest in In Silico Medicine
  - To join: https://insilico.world/community/
- 618 experts to date, including individuals from:
  - **Large biomedical companies** such as Medtronic, Smith & Nephew, Pfizer, Johnson and Johnson, Innovative Medicine Initiative, CSL Behring, Ambu, RS-Scan, Corwave EN, Zimmer Biomet, Novartis, Bayer, ATOS, Biogen, Agfa, Icon PLC, Amgen, ERT, Exponent, etc.
  - **Biomedical SMEs** such as Nova Discovery, Lynkeus, Obsidian Biomedical, Quibim, Mediolanum Cardio Research, Voisin Consulting, CRM-Microport, Mimesis srl, H. M. Pharmacon, MCHCE, etc.
  - **Independent Software Vendors** such as Ansys, In Silico Trials Technologies, 3DS, KIT, ASD Advanced Simulation & Design GmbH, Kuano-AI, Aparito, Chemotargets, Digital Orthopaedics, ExactCure, Materialise, BioCFD, Matical, FEOPS, 4RealSim, Exploristics, Synopsis, Virtonomy, Cad-Fem Medical, etc.
  - **Regulators and standardisation bodies** such as FDA, DIN, BSCI China, NICE, Critical Path Institute, ACQUAS, etc.
  - **Clinical research institutions** such as Istituto Ortopedico Rizzoli, Sloan Kettering Cancer Center, Royal College of Surgeons Ireland, Gratz University Hospital, Charite Berlin, Centre Nacional Investigacio Nes Oncologicas, Aspirus Health, Universitätsklinikum des Saarlandes, European Society for Paediatric Oncology, etc.

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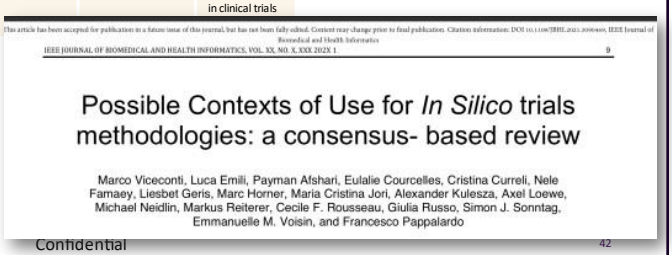
Step #1: Identify possible CoUs for *In Silico* Trials

	Reduce	Refine	Replace
Preclinical In Vitro/Ex Vivo Experiments	Reduce # or duration of *in vitro* testing		
Preclinical Animal experiments			
Clinical Human experiments			Replace humans in clinical trials

- 46 CoUs
- 31 with ref.



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Step #2: Develop GSP position paper

- Establish a grassroot consensus process using the In Silico World_CoP, open to any practitioner worldwide, to develop a Position Paper to inform a future Good Simulation Practice standardisation effort
- Submit drafts to the Avicenna Alliance GSP Task Force
- GSP Task Force revises drafts in light of the feedback we are receiving from experts working at EU EMA and US FDA
- Final Position paper to be published as Open Access book by Nature Springer

Step #2: GSP Index

1. Glossary
2. Introduction
3. Theoretical foundations of Good Simulation Practice
4. Model development
5. Model credibility
6. Possible qualification pathways for In Silico methodologies
7. Possible Health Technology Assessment pathways
8. Ethical review of In Silico Trials
9. Sponsor
10. Investigator: modellers and analysts

Step #2: GSP Chapter 5 – Model Credibility

5.1 Introduction

5.2 Model credibility in existing regulatory guidelines

5.3 A standard framework: ASME VV-40:2018

5.4 Verification

5.5 Validation

5.6 Applicability of the validation activities

5.7 VVUQ considerations for data-driven models and agent-based models

5.8 Final credibility

5.9 Essential Good Simulation Practice recommendations

Step #2: GSP Chapter 5 – Model Credibility

5.1 Introduction

5.2 Model credibility in existing regulatory guidelines

5.3 A standard framework: ASME VV-40:2018

5.4 Verification

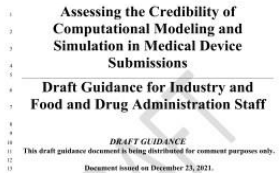
5.5 Validation

5.6 Applicability of the validation activities

5.7 VVUQ considerations for data-driven models and agent-based models

5.8 Final credibility

5.9 Essential Good Simulation Practice recommendations



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Step #2: GSP Chapter 5 – Model Credibility

5.1 Introduction

5.2 Model credibility in existing regulatory guidelines

5.3 A standard framework: ASME VV-40:2018

5.4 Verification

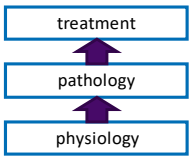
5.5 Validation

5.6 Applicability of the validation activities

5.7 VVUQ considerations for data-driven models and agent-based models

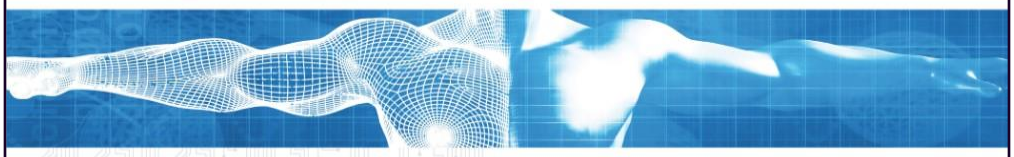
5.8 Final credibility

5.9 Essential Good Simulation Practice recommendations



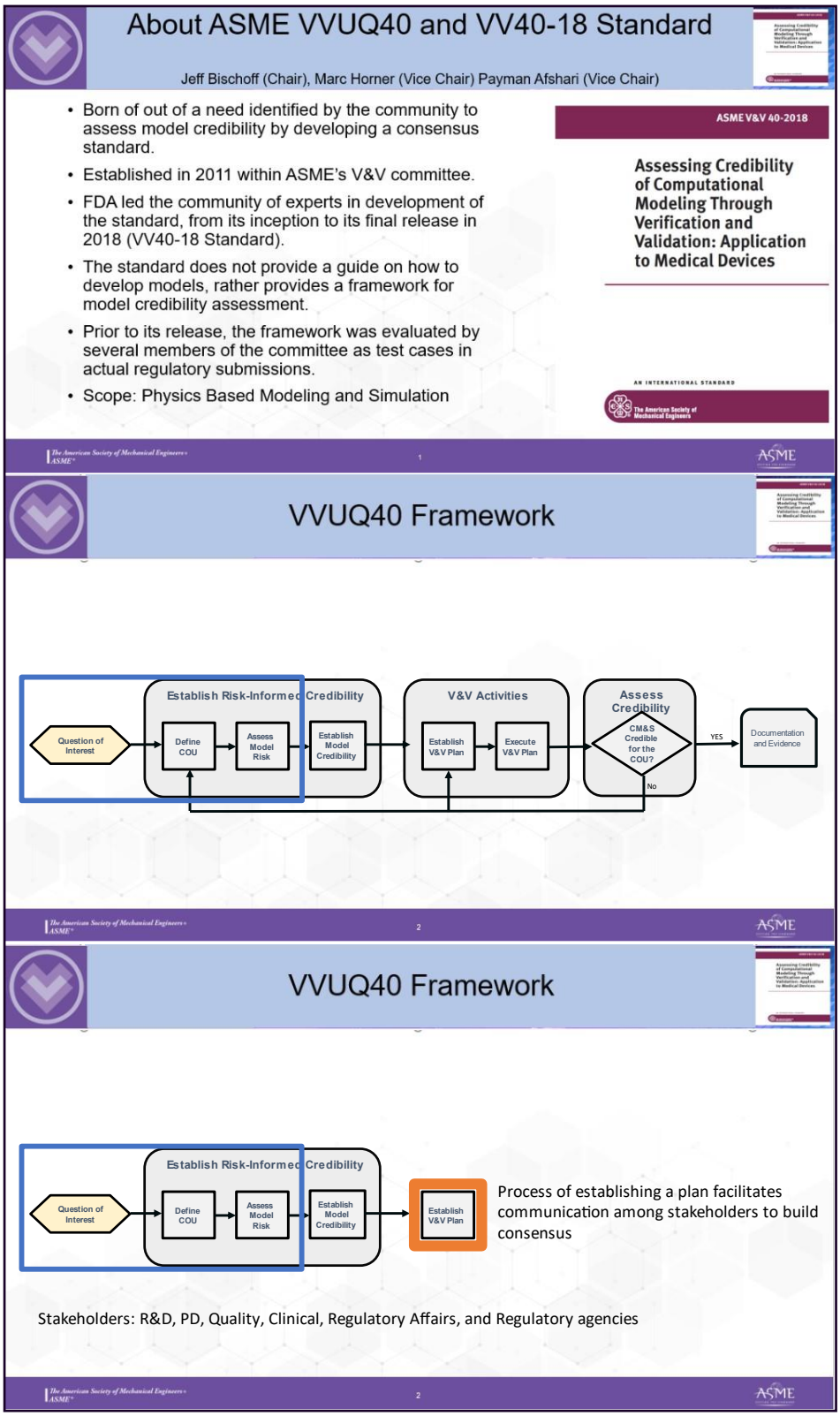
Technical vs. Clinical Validation

Confidential 47



THANK YOU

Presentation 3




VVUQ40 Framework
Credibility
Question of Interest
Define COU
Assess Model Risk
Establish Model Credibility
Describing The Framework Elements
Question of Interest
Describes the specific question, decision or concern that is being addressed.
COU
Defines the specific role and scope of the computational model used to inform that decision.
Model Risk
Is the possibility that the model may lead to a false/incorrect conclusion about device performance, resulting in adverse outcomes.
Model Credibility
Process of establishing model trustworthiness for the COU and its ability to address the question of interest.
The American Society of Mechanical Engineers
ASME
3
VVUQ40 Model Risk
Establish Risk-Informed Credibility
Question of Interest
Define COU
Assess Model Risk
Establish Model Credibility
Establish V&V Plan
Assess Model Risk
Is the possibility that the model may lead to false/incorrect conclusion about device performance, resulting in adverse outcomes.
Model risk level is established using 2 independent factors: Model Influence and Decision Consequence.
- Model influence is the contribution of the computational model to the decision relative to other available evidence.
- Decision consequence is the significance of an adverse outcome resulting from an incorrect decision.
E=MC²
4
ASME V&V 40
Verification and Validation Workshop
Establish Risk-Informed Credibility
V&V Activities
Assess Credibility
Verification
Did you solve the underlying mathematical model correctly?
Mathematical Evidence
Validation
Does the underlying mathematical model correctly represent the reality of interest?
Experimental Evidence
Uncertainty Quantification
What is the uncertainty in the inputs (e.g., parameters, initial conditions), and what is the resultant uncertainty in the outputs?
Statistical Evidence
Applicability
How relevant is the validation evidence to support using the model in the context of use?
Engineering Judgement
Credibility
Based on the available evidence, is there trust in the predictive capability of the computational model for the context of use?
Engineering Judgement
Activities
Credibility Factors
Verification
Code
Software Quality Assurance
Numerical Code Verification
Calculation
Discretization Error
Numerical Solver Error
Use Error
Validation
Computational Model
Model Form
Model Inputs
Comparator
Test Samples
Test Conditions
Assessment
Equivalency of Input Parameters
Output Comparison
Applicability
Relevance of the Validation Activities to the COU
Relevance of the Quantities of Interest
5

ASME V&V 40
Verification and Validation
Workshop

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

Contains Nonbinding Recommendations

Table of Contents

ASME V&V 40
Verification and Validation
Workshop

Contains Nonbinding Recommendations

Draft – Not for Implementation

Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on December 23, 2021.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Office of Science and Engineering Laboratories (OSEL), by email at OSEL_CDRH@fda.hhs.gov, or at (301) 796-2530, or Pras Pathmanathan at (301) 796-3490 or by email pras.pathmanathan@fda.hhs.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Table 1: Ten categories of credibility evidence. Categories 1, 4 and 5 are explicitly within the scope of ASME V&V 40.

	Category	Definition
1	Code verification results	Results showing that a computational model implemented in software is an accurate implementation of the underlying mathematical model.
2	Model calibration evidence	Comparison of model results with the same data used to calibrate model parameters.
3	General non-COU evidence	Calculation verification and/or validation evidence gathered for the model under conditions that are broad and not specific to the COU.
4	Evidence generated using bench-top conditions to support the current COU	Calculation verification and/or validation evidence using bench-top conditions, that was explicitly planned and generated to support the current COU.
5	Evidence generated using *in vivo* conditions to support the current COU	Same as previous category except using *in vivo* conditions.
6	Evidence generated using bench-top conditions to support a different COU	Calculation verification and/or validation evidence using bench-top conditions, that was planned and generated to support a different COU.
7	Evidence generated using *in vivo* conditions to support a different COU	Same as previous category except using *in vivo* conditions.
8	Population-based evidence	Statistical comparisons of population-level data between model predictions and a clinical data set. (Note: individual-level comparison between model predictions and a clinical dataset falls under Category 5.)
9	Emergent model behavior	Evidence showing that the model reproduces phenomena that are known to occur in the system at the specified conditions but were not pre-specified or explicitly modeled by the governing equations.
10	Model plausibility	Evidence that supports the validity of the governing equations, model assumptions, and input parameters only.

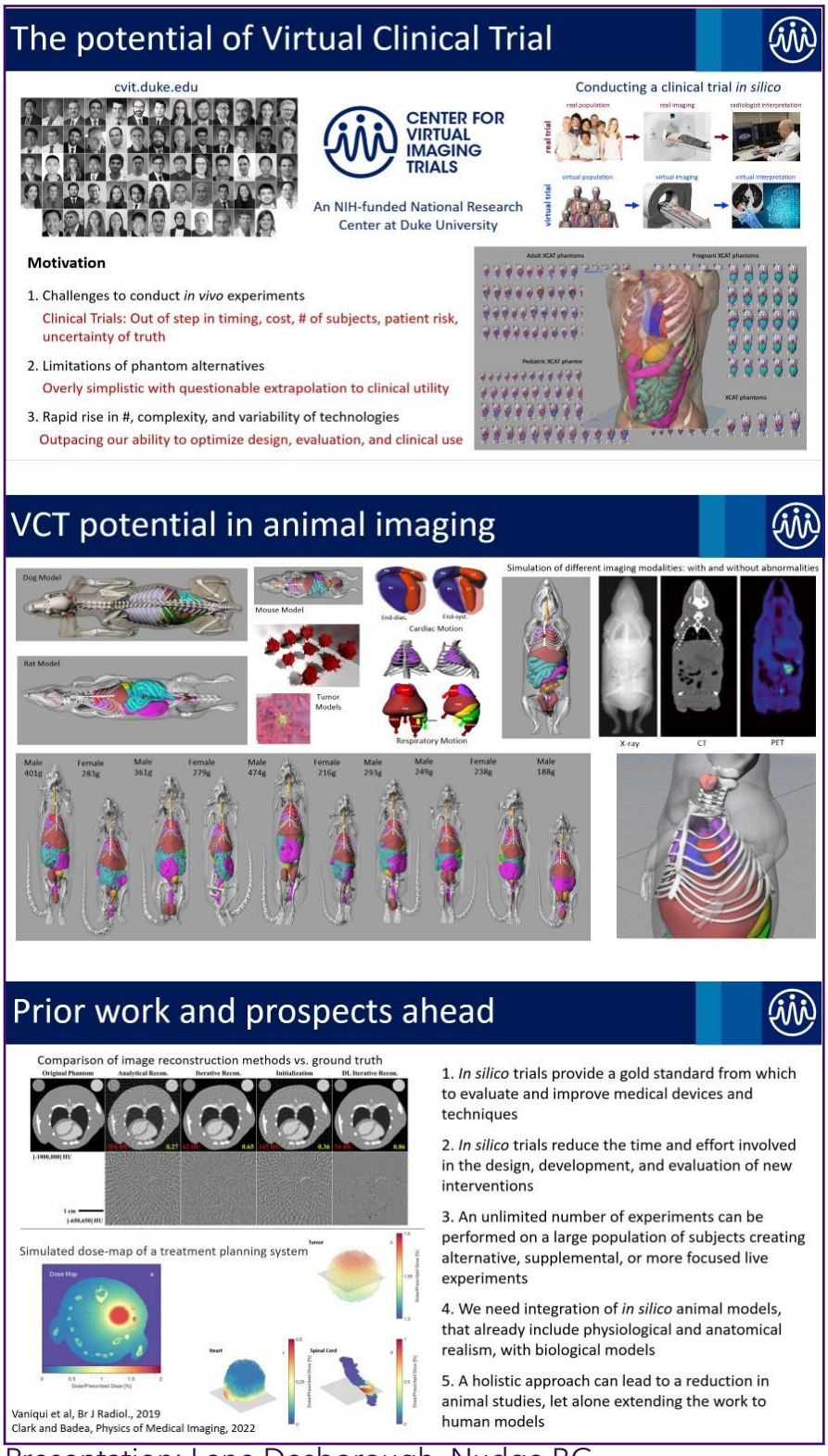
ASME V&V 40-2018

ASME V&V 40-2018

ASME V&V 40-2018

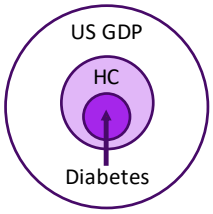
Appendix E: Working Group 2 Presentations June 27, 2023

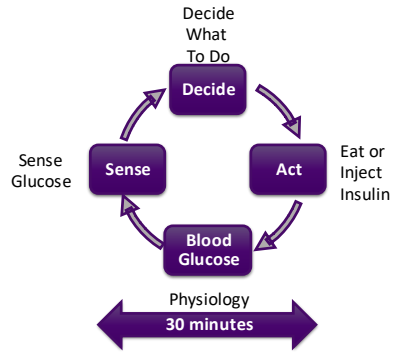
Presentation: Dr. Ehsan Samei, Duke University



Presentation: Lane Desborough, Nudge BG

Situation: insulin label change





Medtronic
For People with Diabetes

bigfoot BIOMEDICAL

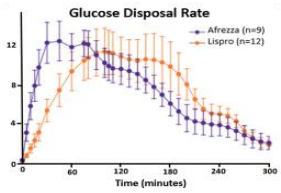
NUDGE

1. National Health Expenditure share of the US Gross Domestic Product is 20%
2. The Health and Economic Benefits of Diabetes Interventions,
3. Palerm, C.C., Lintereur, L., Monirabbasi, S. and Desborough, L., 2014, February. Virtual Trial Predicts Clinical Trial Outcomes -Accelerating Development and Reducing Risk Through Model -Based Design. In Diabetes Technology & Therapeutics (Vol. 16, pp. A43 -A44). 140 Huguenot Street, 3rd fl, New Rochelle, NY 10801 USA: Mary Ann Liebert, Inc.
4. Desborough, L, Naylor, R, Block, J, Buckingham, B, Pinsker, J, Wadwa, P, Forlenza, G, O'Brien, R, Lum, J, and B. Mazlish, "Leveraging Modeling and Simulation in the Development of the Bigfoot Biomedical Automated Insulin Delivery System", Poster, DTM 2017, Bethesda, MD.

NUDGE

in silico approach

2014
mannkind
afrezza



Injected Mealtime Insulin Dose	AFREZZA® Dose
up to 4 units	4 units
5-8 units	8 units
9-12 units	12 units
13-16 units	16 units
17-20 units	20 units
21-24 units	24 units

Injected Mealtime Insulin Dose	AFREZZA® Dose
up to 3 units	4 units
4-5 units	8 units
6-7 units	12 units
8-9 units	16 units
10-11 units	20 units
12-13 units	24 units

Mealtime AFREZZA Starting Dose Conversion Table

FDA U.S. FOOD & DRUG ADMINISTRATION
Model-Informed Drug Development Paired Meeting Program

NUDGE

1. Pfützner A, et al. Expert Opin Drug Deliv. 2005;2(6):1097-1106.
2. Potockaet al. Characterization of Metabolism Parameters Following Tl and Insulin Lispro. ADA Poster #1956, 2020.
3. https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program

Good Simulation Practices

Annals of Biomedical Engineering (© 2022 https://doi.org/10.1007/s10439-022-03062-4

BMES BIOMEDICAL ENGINEERING SOCIETY

S.I. : Modeling for Advancing Regulatory Science

Transforming Evidence Generation for Drug Label Changes: A Case Study

LANE DESBOROUGH,[1] KAREN JAFFE,[2] JOSEPH HANNA,[2] JOHANNA ULLOA,[2] and KEVIN KAISERMAN[2]

From	→	To
Explanatory	→	Predictive
Research	→	Development
Exploratory	→	Confirmatory
Early	→	Later
Big	→	Little
Incumbents	→	New entrants
Ambiguity	→	Certainty
Disincentives	→	Incentives
Defensive	→	Offensive

NUDGE

1. Desborough, L., Jaffe, K., Hanna, J., Ulloa, J. and Kaiserman, K., 2023. Transforming Evidence Generation for Drug Label Changes: A Case Study. Annals of Biomedical Engineering, 51(1), pp.137-149.
2. https://www.youtube.com/watch?v=AB9xAMtOvQ0 De risking and Accelerating Physiological Closed Loop Control Using Model Based Design, Desborough

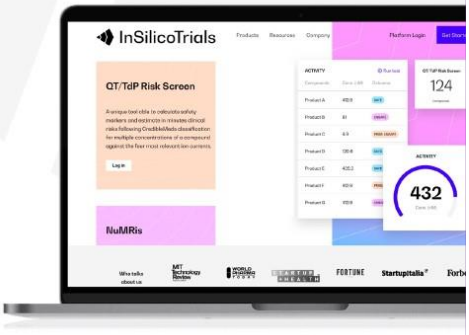
Presentation: Luca Emili, InSilicoTrials Technologies

InSilicoTrials

Hyper-accelerate
Drug & Medical Device
Development

June 2023

Private & Confidential



Describe a situation where you wanted to move forward with using an in silico approach but you didn't or couldn't.

The ICH S7B Q&A foresees a first evaluation of pharmaceuticals potential risk of causing delayed repolarization and QT interval prolongation by means of in vitro IKr/hERG and in vivo QT assay assessments. In case of positive signals, as part of an Integrated Risk Assessment strategy, follow-up studies should be performed including computational modelling.

The FDA modernization act 2.0 authorizes alternative methods to animal testing, including computer models.

Pharmaceutical companies test their compounds in vitro towards one channel, the IKr/hERG channel, and move directly afterwards into in vivo testing, as by guideline.

Several high quality in silico models of QT prolongation and TdP risk are available. They generally require in vitro data for up to 3 to 4 channels for reliable predictions. These models cannot be used in a first evaluation based on IKr/hERG only.

Describe what a Good Simulation Practices document could have done/should have contained to support the use of your approach for that situation.

The complementarity of in vitro and in silico should be emphasized by means of explanatory use cases.

Recommendations should be provided on how to implement combined in vitro-in silico techniques for early screening drug-induced cardiotoxicity compounds testing.

Describe what would have encouraged you/allowed you to pursue the in silico approach.

A guideline recommending to perform more in vitro (up to the four more relevant ion channels covering 95% of small molecules interactions with ion channels) and in silico screening and less in vivo testing.

Presentation: Dr. Steven Kreuzer, Exponent

Situation

- Describe a situation where you wanted to move forward with using an in silico approach but you didn't or couldn't

General Challenge		Result

• Patient anatomy and disease etiology are diverse and complex
  • Heart implants: variety of anatomy, fiber morphology, electrophysiology, systemic effects, etc.
• Physics-based simulation based on first-principles is powerful yet computationally expensive
  • Inclusion of all known sources of variability (regardless of importance) explodes model size
• Desired treatment of cohort-level safety data (fatigue, durability, etc.) motivates large data sets for statistical assessment
  • Context of Use: design of benchtop fatigue testing study
	⇨	Anticipated simplification of model judged to create conditions of unacceptable risk to acceptance
		
		Conservative assumptions made to create 'worst-case' model and test against predictions from conditions known to be unlikely

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Encouragement

- Describe what would have encouraged you/allowed you to pursue the in silico approach

General Challenge	Encouragement

• Patient anatomy and disease etiology are diverse and complex
  • Heart implants: variety of anatomy, fiber morphology, electrophysiology, systemic effects, etc.
• Physics-based simulation based on first-principles is powerful yet computationally expensive
  • Inclusion of all known sources of variability (regardless of importance) explodes model size
• Desired treatment of cohort-level safety data (fatigue, durability, etc.) motivates large data sets for statistical assessment
  • Context of Use: design of benchtop fatigue testing study
	1. Simplified model permitting rapid generation of large data set based on physics-based modeling
	  a) Identify distribution of metric(s)
	  b) Select extreme (but not overly conservative) metric(s) for testing
	2. Credible accounting for impact of simplifications on model predictions
	  a) Understand effect of simplifications
	  b) Communicate effect of simplifications

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Good Simulation Practices Document Contents

- Describe what a Good Simulation Practices document could have done/should have contained to support the use of your approach for that situation

1. Agreed-upon methods for identifying critical attributes and assessing effect of simplifications
   - Quantitative Phenomena Identification and Ranking Table (PIRT)
   - Fine v. coarse analyses; Physics-based v. Machine Learning models
2. Agreed-upon tools for quantifying uncertainty & propagation of uncertainty
   - Methods and key concepts for selecting between available approaches to UQ
3. Guidelines for acceptance criteria of uncertainty propagated through 'model form' decisions
   - Gradation of activities / rigor relative to model risk

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Presentation: Dr. Enrique Morales Orcajo, Ambu Innovation GmbH

Describe a situation where you wanted to move forward with using an in silico approach but you didn't or couldn't.

Start up MedTech company

Goal:
Develop an in silico solution
(organ digital twin for personalized surgery)

Problem:
- No clear regulatory pathway (pre-V&V40)
- No standards
- No internal expertise (in regulated industry)
- No industry examples (only academic examples)

Stablished medical device company

Goal:
Shorter Time-to-Market

Problem:
- Simulation not standardized in the company (no SOP)
- Management afraid of
  - ROI in simulation
  - acceptance of in silico evidence by the regulatory bodies.
- No industry example

Enrique Morales Orcajo, PhD 24

Describe what would have encouraged you/allowed you to pursue the in silico approach

Start up MedTech company

In silico solution

What would help?
- A regulatory framework (V&V40)
- GSP - how to develop an in silico solution
- Practical guidelines
- Industry examples

Stablished medical device company

Shorter Time-to-Market

What would help?
- Endorsement from regulatory bodies
- Standards
- Industry examples of products leveraging simulation

Enrique Morales Orcajo, PhD 25

Describe what a GSP document could have done/should have contained to support the use of your approach for that situation

My experience participating in the **GSP task force Aviccena Alliance:**

- Toward good simulation practice: best practices for the use of computational modelling & simulation in the regulatory process of biomedical products [https://insilico.world/community/good-simulation-practice-gsp-task-force/]
- Challenging the balance between a text broad enough to fit all in silico disciplines and narrow enough to give actionable guidance.

What **I would like to read in a GSP document:**

- Complete guide (from concept to archive)
  - e.g., NASA handbook for models and simulations [https://standards.nasa.gov/standard/nasa/nasa-hdbk-7009]
- Actionable advice (maybe necessary to create sub sections for specific disciplines)
  - e.g., How to get meaningful and correct results from your FE model [http://arxiv.org/abs/1811.05753]
- Industry examples (even if some examples are theoretical)
  - e.g., Possible Contexts of Use for In Silico Trials Methodologies: A Consensus-Based Review [https://pubmed.ncbi.nlm.nih.gov/34161248/]

Enrique Morales Orcajo, PhD 26

Presentation: Jesse Fishman, Apellis Pharmaceuticals

Disclaimer

The information contained in this presentation is being shared based on a prior experience and does not reflect the opinions of my current employer. Specific details on what specific development program cannot be shared and have been generalized for the purposes of this presentation which is intended for educational purposes only

Situation/Background

- A sponsor, intending on using the subpart H (accelerated) regulatory pathway, faced a common problem in rare disease development programs, as there was limited data to support the endpoints they selected to be part of their phase 3 trials
  - For the initial phase 3 trial (Trial 1) the trial endpoints used were surrogate outcome measures
  - The second phase 3 trial (Trial 2) to be submitted to regulators later, included both surrogate outcomes & longer-term outcome measures (e.g., mortality)
- During development meetings, regulators expressed interest in better understanding the relationship of the surrogate outcome measures from Trial 1 & the longer-term outcomes measures being studied in Trial 2
- The development team was unsure if the limited existing literature on the rare disease indication being studied would satisfy the regulators
- The team looked for approaches to supplement their NDA data package, which would initially include only Trial 1
- Although the use of the registry data alone might be sufficient for some evidence packages without the use of in silico modeling, the small population of data available lent itself to exploring modeling approaches that could project long term outcomes by providing additional estimates when compared to known outcomes
- One person on the development team proposed the use of in silico modeling using a small sample from an unpublished registry as a possible solution to develop the needed evidence for the NDA
- Modeling would be guided by working within the model informed drug development pathway (MIDD) to ensure it met the appropriate standards for acceptability

Background & What could have encouraged the use of in-silico modeling approaches

- The regulatory and clinical development leads were unfamiliar with the use of modeling and simulation within later stages of a development program
- The clinical development lead was aware of the MIDD program, but didn't have experience with it and thought the applications were only for trial simulation to plan studies and modeling dose responses in alternative populations (e.g. extrapolation)
- After reviewing the pubic presentations available about MIDD, the clinical program team agreed that MIDD could be used in later stages of clinical development but outside of working through this MIDD program they were unsure any modeled evidence would be acceptable to regulators
- The planned regulatory timelines were mapped to the potential timelines associated with working within the MIDD pathway and it was determined that these would cause delays in program development. Thus, modeling was not used for this submission need.
- In this case, what would have encouraged the use of modeling was having a clearer picture of how a sponsor can use both the MIDD pathway along side their planned regulatory pathway
- Additionally, understanding the anticipated evaluation process to be conducted by regulators would have facilitated use of in silico modeling to support a regulatory filing

What Good Simulation Practices Could have done

- In this case, the use of good simulation practices via in silico modeling could have provided the needed evidence to showcase the relationship of surrogate endpoints & longer term endpoints in a rare disease population
- This which was a needed piece of evidence in an NDA and this evidence was requested by regulators
- As a result of not knowing the best way to approach using multiple regulatory paths and the data evaluation process likely to be taken by regulators, this type of modeling was not used for the NDA file which instead relied on published data and expert opinions for their supportive evidence (in addition to Trial 1)

Appendix F: Resources

FDA Resources

2022 Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science (FARS) https://www.fda.gov/science-research/advancing-regulatory-science/focus-areas-regulatory-science-report.

Advancing New Alternative Methodologies at FDA https://www.fda.gov/media/144891/download?attachment

Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions

Complex Innovative Trial Design Meeting Program https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1

Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program

Model-Informed Drug Development Paired Meeting Program https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program

Reporting of Computational Modeling Studies in Medical Device Submissions https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-computational-modeling-studies-medical-device-submissions

Successes and Opportunities in Modeling & Simulation for FDA https://www.fda.gov/media/163156/download

Guidelines and GxP Documents

ASME VVUQ40 and VV40-18 Standard https://www.asme.org/codes-standards/publications-information/verification-validation-uncertainty

European Medicines Agency: Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf

OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring https://www.oecd.org/chemicalsafety/testing/oecdseriesonprinciplesofgoodlaboratorypracticeglpandcompliancemonitoring.htm

WHO Good Manufacturing Practices for Biological Products Annex 2, TRS No 999 https://www.who.int/docs/default-source/biologicals/gmp/annex-2-who-good-manufacturing-practices-for-biological-products.pdf?sfvrsn=995d5518_2&download=true

Erdemir, A., Mulugeta, L., Ku, J.P. et al. **Credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective.** J Transl Med 18, 369 (2020). https://doi.org/10.1186/s12967-020-02540-4

Organizations
Avicenna Alliance https://www.avicenna-alliance.com/
In Silico World Community of Practice https://insilico.world/community/
VPH Institute https://www.vph-institute.org/

Other Resource Documents
Myatt GJ, Ahlberg E, Akahori Y, et. al. **In Silico Toxicology Protocols**. Regul Toxicol Pharmacol. 2018 Jul;96:1-17. https://doi.org/10.1016/j.yrtph.2018.04.014

Srinivasan M, White A, Chaturvedula A, et. al. Incorporating Pharmacometrics into Pharmacoeconomic Models: Applications from Drug Development. Pharmacoeconomics. 2020 Oct;38(10):1031-1042. https://doi.org/10.1007/s40273-020-00944-0

Viceconti M, Emili L, Afshari, P, et. al. **Possible Contexts of Use for In Silico Trials Methodologies: A Consensus-Based Review.** IEEE J Biomed Health Inform 2021;25(10):3977-3982.

Morrison TM, Dreher ML, Nagaraja S, et. al. **The Role of Computational Modeling and Simulation in the Total Product Life Cycle of Peripheral Vascular Devices.** Journal of Medical Devices 2017;11:02503-1-02503-5.

BEST (Biomarkers, EndpointS, and other Tools) Resource
https://www.ncbi.nlm.nih.gov/books/NBK338448/
Framework for Defining Evidentiary Criteria for Biomarker Qualification https://fnih.org/wp-content/uploads/2023/06/Evidentiary-Criteria-Framework-Final-Version-Oct-20-2016.pdf
ISPOR Modeling Good Research Practices - Overview: Report 1 https://www.ispor.org/heor-resources/good-practices/article/modeling-good-research-practices---overview
NASA Handbook for Models and Simulations: An Implementation Guide for NASA-STD-7009 https://standards.nasa.gov/standard/NASA/NASA-HDBK-7009
TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6860463/