FDA/MDIC
Symposium on Computational Modeling and Simulation

Generating Regulatory In Silico Evidence

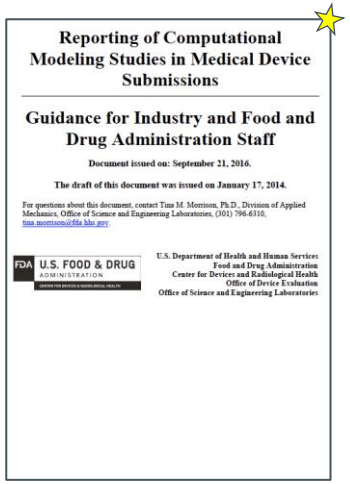
FDA/MDIC Pre-Symposium: FDA Reporting Guidance Training

Monday, April 15th
4:00 PM – 5:00 PM

Kenneth Aycock, PhD

Office of Science and Engineering Laboratories, CDRH, FDA

Research Scientist



Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

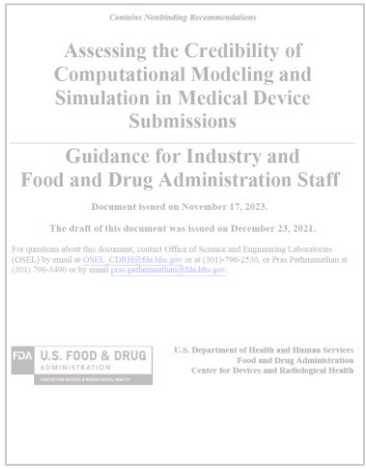
Document issued on: September 21, 2016.

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.

U.S. FOOD & DRUG ADMINISTRATION

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

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

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

The draft of this document was issued on December 23, 2021.

For questions about this document, contact 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) 796-1490 or by email pras.pathmanathan@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

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

#ModSim2024

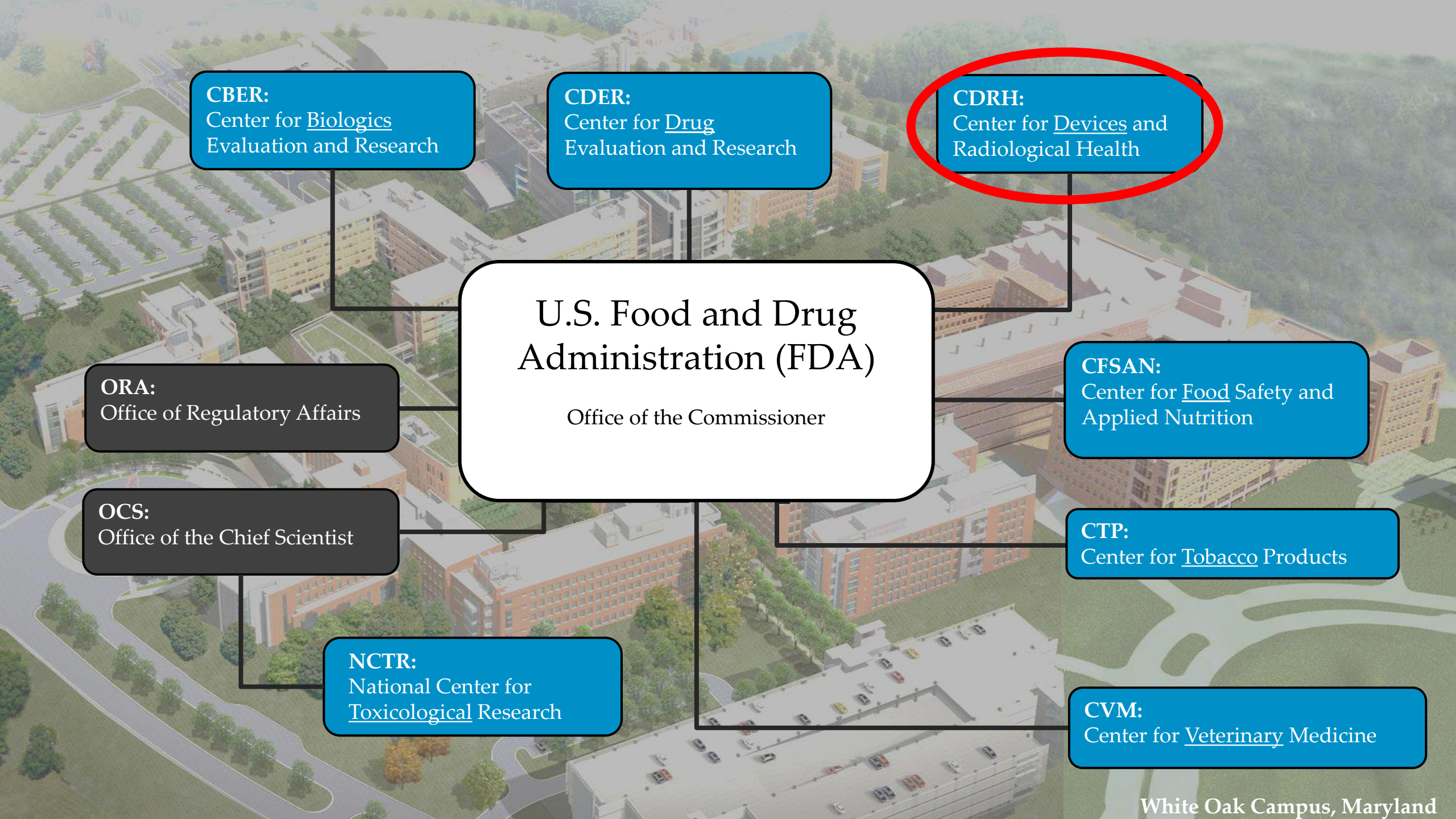
MDIC Medical Device Innovation Consortium

Disclosures

- I have no real or apparent conflicts of interest
- Any mention or representation of a product is for educational purposes only and does not convey endorsement

Outline

1. Compare & contrast credibility vs reporting guidance
2. Review reporting guidance body
3. Briefly review subject matter appendices
4. Address frequently asked questions


CBER:
Center for Biologics
Evaluation and Research
CDER:
Center for Drug
Evaluation and Research
CDRH:
Center for Devices and
Radiological Health
U.S. Food and Drug
Administration (FDA)
Office of the Commissioner
ORA:
Office of Regulatory Affairs
CFSAN:
Center for Food Safety and
Applied Nutrition
OCS:
Office of the Chief Scientist
CTP:
Center for Tobacco Products
NCTR:
National Center for
Toxicological Research
CVM:
Center for Veterinary Medicine
White Oak Campus, Maryland

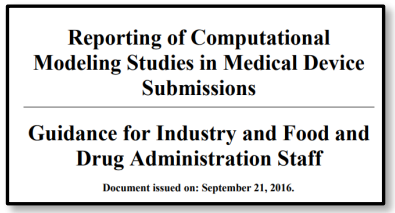
Timeline

2000s — Little formal M&S credibility assessment

~2010 — Growing awareness in devices community (incl. CDRH) of need for better credibility assessment

2013 — ASME V&V40 subcommittee formed

2016 — CDRH M&S Reporting Guidance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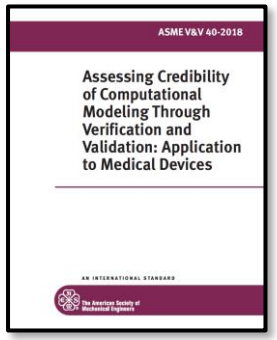
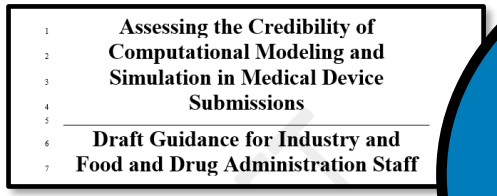
2018 — ASME V&V40 Standard


ASME V&V 40-2018

Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices

2020 — CDRH Draft Guidance on CM&S Credibility Assessment


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

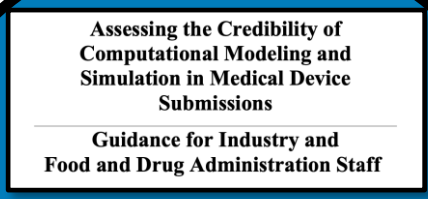
Draft Guidance for Industry and Food and Drug Administration Staff

2020 — OSEL Credibility of Computer M&S Regulatory Science Program Established

U.S. FOOD & DRUG ADMINISTRATION

Credibility of Computational Models Program: Research on Computational Models and Simulation Associated with Medical Devices

2021 — CDRH Final Guidance on CM&S Credibility Assessment


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

Guidance for Industry and Food and Drug Administration Staff

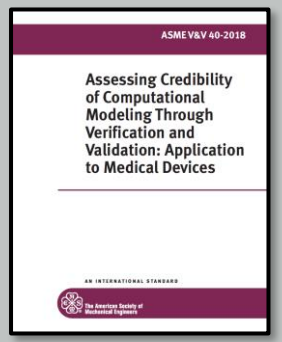
2023

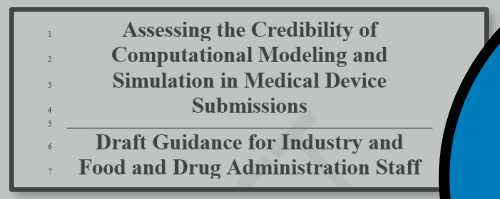
- ASME V&V 40 standard revision
- Good Simulation Practice (GSP)
- Domain/discipline-specific standards & Guidances incorporating credibility assessment

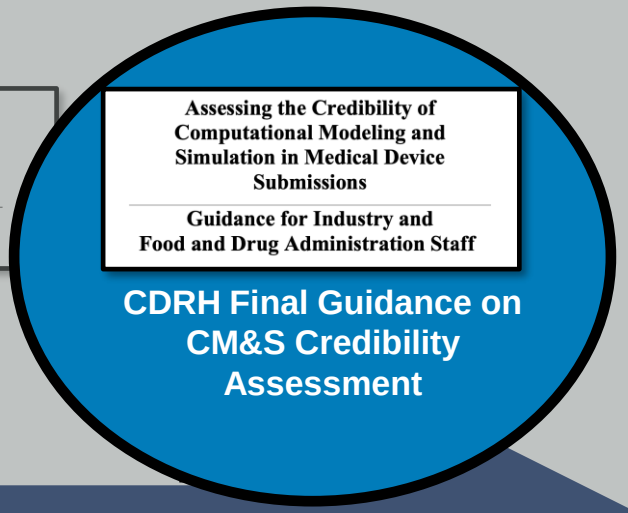
Timeline

Jeff's talk

Pras' talk







Little formal M&S credibility assessment

ASME V&V40 subcommittee formed

ASME V&V40 Standard

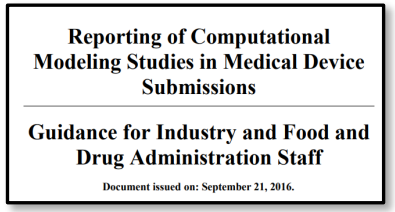
CDRH Draft Guidance on CM&S Credibility Assessment

2000s | ~2010 | 2013 | 2016 | 2018 | 2020 | 2021 | 2023

Growing awareness in devices community (incl. CDRH) of need for better credibility assessment

Now

CDRH M&S Reporting Guidance



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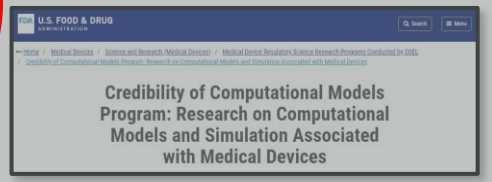

- ASME V&V 40 standard revision
- Good Simulation Practice (GSP)
- Domain/discipline-specific standards & Guidances incorporating credibility assessment

Outline

1. Compare & contrast credibility vs reporting guidance
2. Review reporting guidance body
3. Briefly review subject matter appendices
4. Address frequently asked questions

Two FDA guidance documents address modeling

Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

Introduction ... 1
Scope ... 2
Outline of the CM&S Report ... 2
I. Executive Report Summary ... 3
II. Background/Introduction ... 3
III. Code Verification ... 3
IV. System Configuration ... 4
V. Governing Equations/Constitutive Laws ... 4
VI. System Properties ... 5
VII. System Conditions ... 5
VIII. System Discretization ... 5
IX. Numerical Implementation ... 6
X. Validation ... 6
XI. Results ... 7
XII. Discussion ... 7
XIII. Limitations ... 7
XIV. Conclusions ... 7
XV. References ... 7
Glossary ... 8
Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport ... 10
Subject Matter Appendix II – Computational Solid Mechanics ... 19
Subject Matter Appendix III – Computational Electromagnetics and Optics ... 27
Subject Matter Appendix IV – Computational Ultrasound ... 35
Subject Matter Appendix V – Computational Heat Transfer ... 41

7 pages + 5 subject-matter Appendices (48 pg., total)

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

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

I. Introduction ... 4
II. Background ... 5
III. Scope ... 7
IV. Definitions ... 8
V. Generalized Framework for Assessing Credibility of Computational Modeling in a Regulatory Submission ... 10
VI. Key Concepts for Assessing Credibility of Computational Modeling in a Regulatory Submission ... 15
A. Preliminary steps ... 15
(1) Question of Interest ... 15
(2) Context of use (COU) ... 16
(3) Model risk ... 17
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(1) Code verification results ... 22
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(6) Emergent model behavior ... 29
(7) Model plausibility ... 29
(8) Calculation verification/UQ results using COU simulations ... 30
C. Credibility Factors and Credibility Goals ... 31
D. Adequacy Assessment ... 33
Appendix 1. Considerations for Each Credibility Evidence Category ... 36
Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions ... 40

35 pages + 2 Appendices (42 pg., total)

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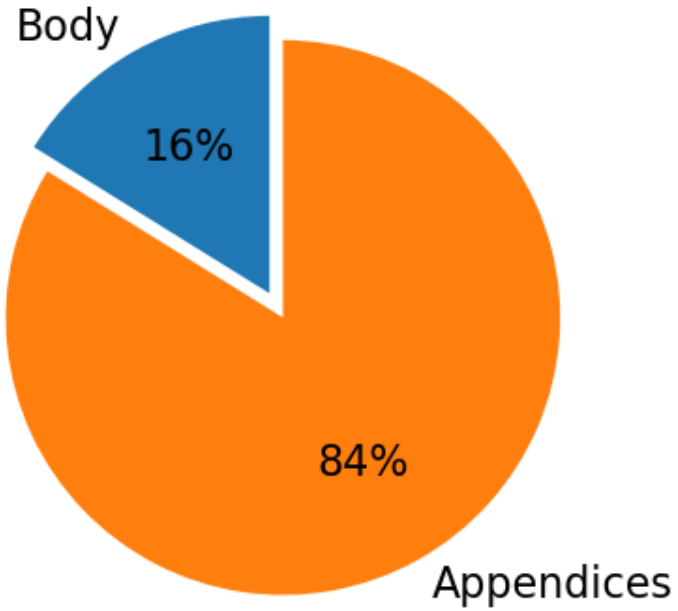

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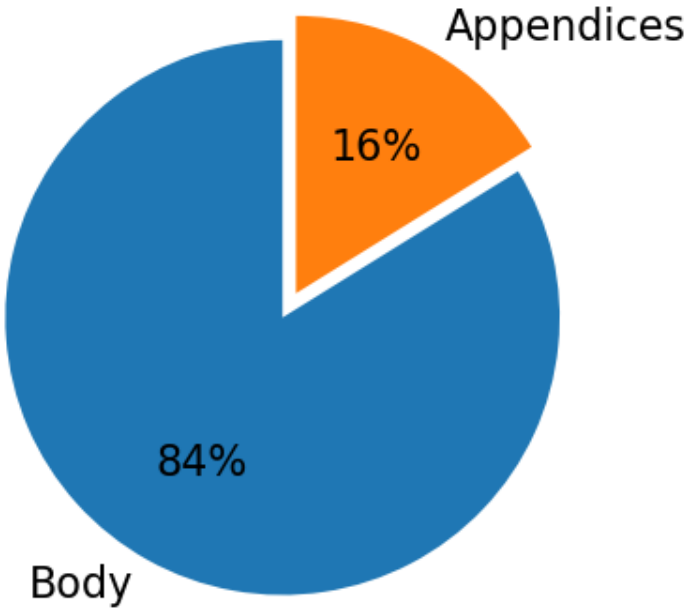

Both guidances comment on reporting

Reporting of Computational Modeling Studies in Medical Device Submissions

Simulation ← Study Report

Guidance for Industry and Food and Drug Administration Staff

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Scope 2
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I. Executive Report Summary 3
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X. Validation 6
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Subject Matter Appendix V – Computational Heat Transfer 41

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

→ Credibility Plan/Report

Guidance for Industry and Food and Drug Administration Staff

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II. Background 5
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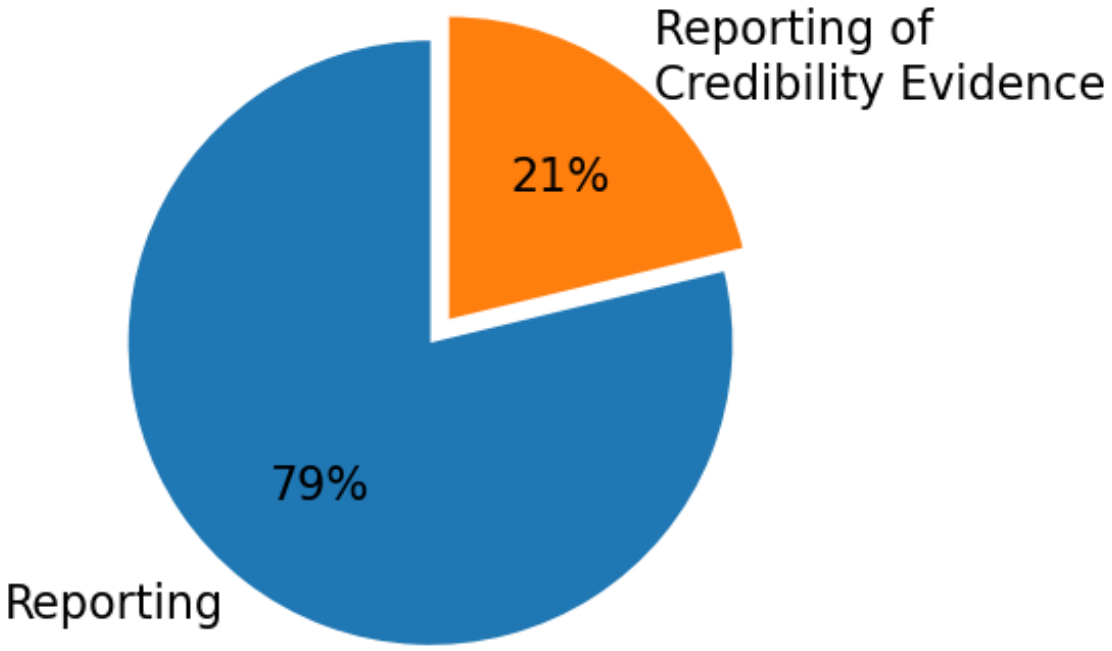

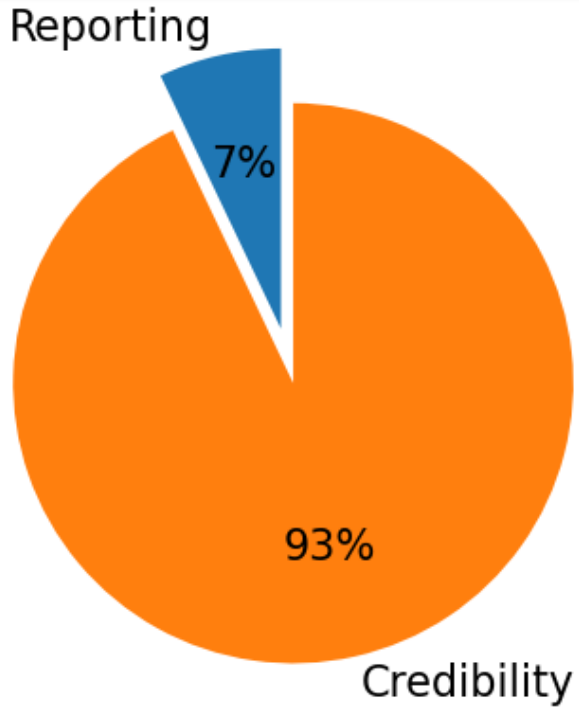

Let's look closer

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Let's look closer

what, how

Reporting of Computational Modeling Studies in Medical Device Submissions

Simulation ← Study Report

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Scope

Computational modeling and simulation studies, together with bench, nonclinical *in vivo*, and clinical studies, can be used to evaluate the safety and effectiveness of medical devices. In order for the CM&S studies to serve as valid scientific evidence in regulatory submissions, specific details need to be included in the report of such studies. In this guidance, the term "CM&S report" refers to the part of a regulatory submission that provides information about a CM&S study; the term does not describe a new submission requirement.

The recommended format provided in this document aims to establish uniformity in reporting CM&S studies. FDA recognizes that the level of detail to be reported will vary and will

Report **what** modeling was performed and **how**

trust, credibility

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

→ Credibility Plan/Report

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

III. Scope

The purpose of this guidance document is to provide a general risk-informed framework for assessing CM&S credibility in medical device regulatory submissions that incorporate both traditional validation evidence and/or other types of supporting data. This guidance document is

This guidance document provides recommendations for both planning and reporting model credibility assessment activities. This guidance document does not address methodologies for how to perform modeling studies or technical details for how to gather evidence to support credibility assessment, nor does it provide recommendations concerning the specific level of credibility needed to support regulatory submissions. This guidance is not intended to provide a

Report **why** the model can be **trusted**

Let's look closer

what, how

Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

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Simulation ← Study Report

trust, credibility

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II. Background 5
III. Scope 7
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Let's look closer

what, how, model details

Simulation ← Study Report

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trust, credibility

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→ Credibility Plan/Report

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*"Moreover, for CM&S used in in silico device testing or in silico clinical trials… the **outline does not provide recommendations** for **providing the results** of the simulation study.*

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Let's look closer

what, how, model details, **results**

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→ Credibility Plan/Report

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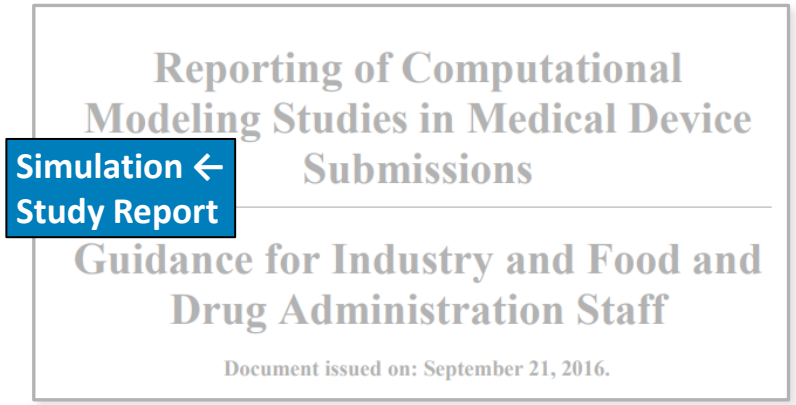

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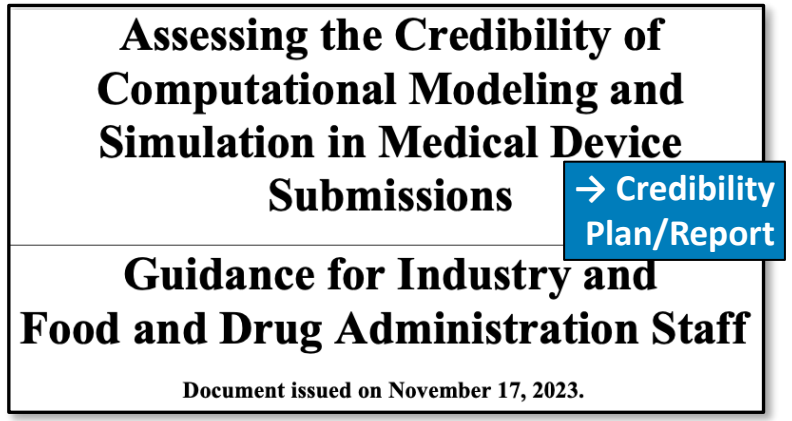

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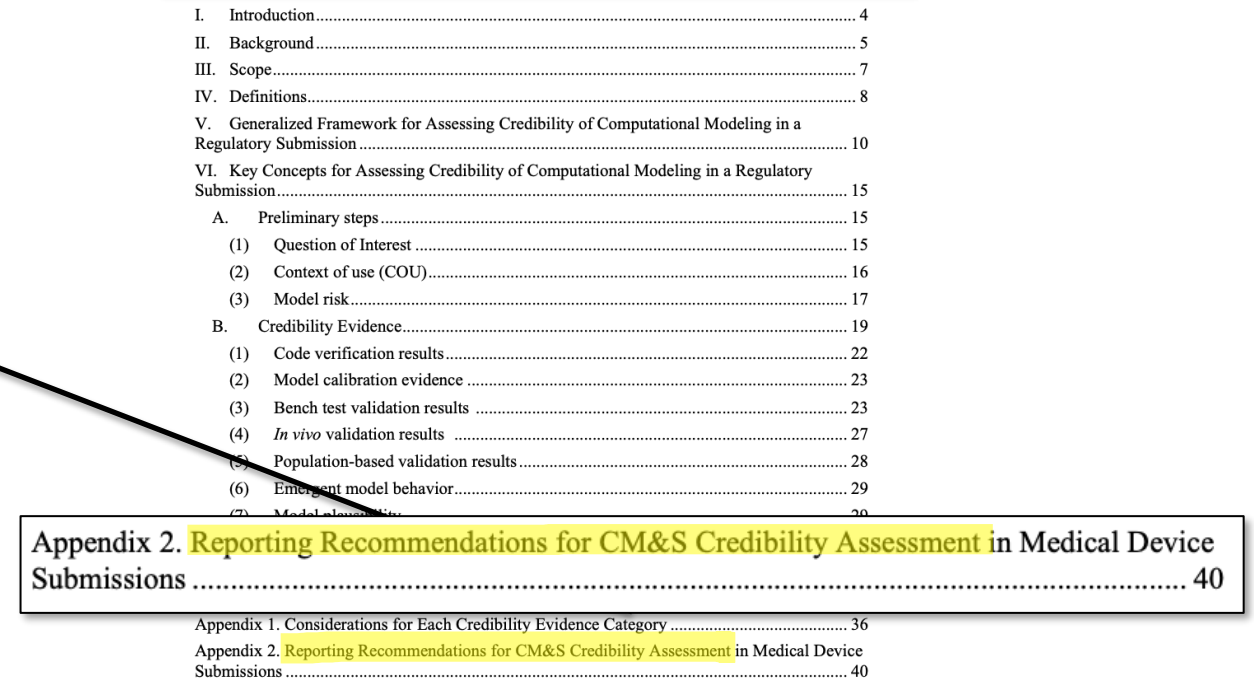
Recommended Content for a Credibility Assessment Report:

1. Executive Summary
2. Background
3. Device Description
4. Proposed Indications for Use
5. Description of Computational Model
6. Model Credibility Assessment
7. Credibility Assessment Limitations
8. Conclusions
9. References
10. Appendices



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(2) Context of use (COU) 16
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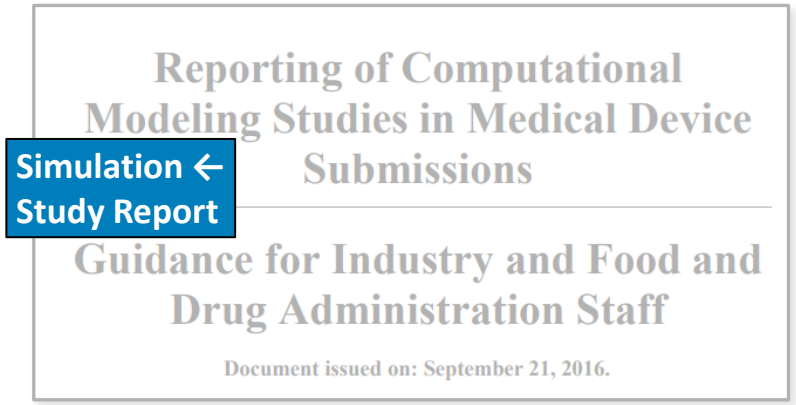
B. Credibility Evidence 19
(1) Code verification results 22
(2) Model calibration evidence 23
(3) Bench test validation results 23
(4) *In vivo* validation results 27
(5) Population-based validation results 28
(6) Emergent model behavior 29
Appendix 1. Considerations for Each Credibility Evidence Category 36
Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

Let's look closer

what, how, model details, results

Simulation ← Study Report



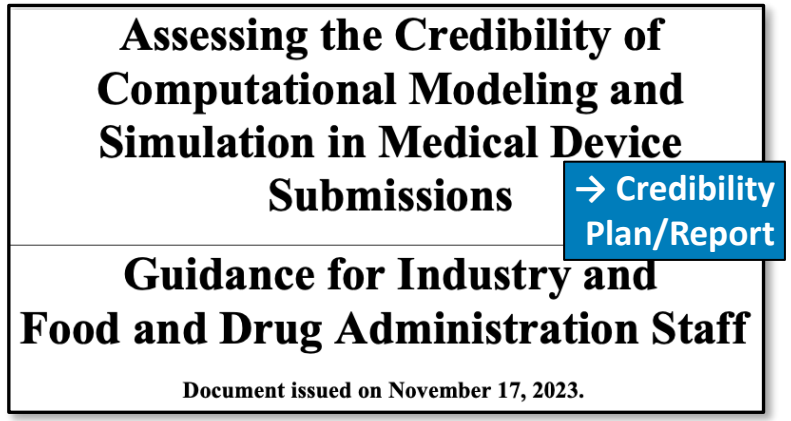
Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

trust, credibility

→ Credibility Plan/Report



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

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

Recommended Content for a Credibility Assessment Report:

1. Executive Summary
2. Background
3. Device Description
4. Proposed Indications for Use
5. **Description of Computational Model** ?
6. Model Credibility Assessment
7. Credibility Assessment Limitations
8. Conclusions
9. References
10. Appendices

I. Introduction 4
II. Background 5
III. Scope 7
IV. Definitions 8
V. Generalized Framework for Assessing Credibility of Computational Modeling in a Regulatory Submission 10
VI. Key Concepts for Assessing Credibility of Computational Modeling in a Regulatory Submission 15
A. Preliminary steps 15
(1) Question of Interest 15
(2) Context of use (COU) 16
(3) Model risk 17
B. Credibility Evidence 19
(1) Code verification results 22
(2) Model calibration evidence 23
(3) Bench test validation results 23
(4) *In vivo* validation results 27
(5) Population-based validation results 28
(6) Emergent model behavior 29
Appendix 1. Considerations for Each Credibility Evidence Category 36
Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

Let's look closer

what, how, model details, results

Simulation ← Study Report

Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

trust, credibility

→ Credibility Plan/Report

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

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

I. Introduction 4
II. Background 5
III. Scope 7
IV. Definitions 8
V. Generalized Framework for Assessing Credibility of Computational Modeling in a Regulatory Submission 10
VI. Key Concepts for Assessing Credibility of Computational Modeling in a Regulatory Submission 15
A. Preliminary steps 15
(1) Question of Interest 15
(2) Context of use (COU) 16
(3) Model risk 17
B. Credibility Evidence 19
(1) Code verification results 22
(2) Model calibration evidence 23
(3) Bench test validation results 23
(4) *In vivo* validation results 27
(5) Population-based validation results 28
(6) Emergent model behavior 29
Appendix 1. Considerations for Each Credibility Evidence Category 36
Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

5. Description of Computational Model: If model details are included elsewhere in the regulatory submission, we ***recommend referencing accordingly…***

Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

Let's look closer

what, how, model details, results

Simulation ← Study Report

Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

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

→ Credibility Plan/Report

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

trust, credibility, **reference model details**

I. Introduction 4
II. Background 5
III. Scope 7
IV. Definitions 8
V. Generalized Framework for Assessing Credibility of Computational Modeling in a Regulatory Submission 10
VI. Key Concepts for Assessing Credibility of Computational Modeling in a Regulatory Submission 15
A. Preliminary steps 15
(1) Question of Interest 15
(2) Context of use (COU) 16
(3) Model risk 17
B. Credibility Evidence 19
(1) Code verification results 22
(2) Model calibration evidence 23
(3) Bench test validation results 23
(4) *In vivo* validation results 27
(5) Population-based validation results 28
(6) Emergent model behavior 29
Appendix 1. Considerations for Each Credibility Evidence Category 36
Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

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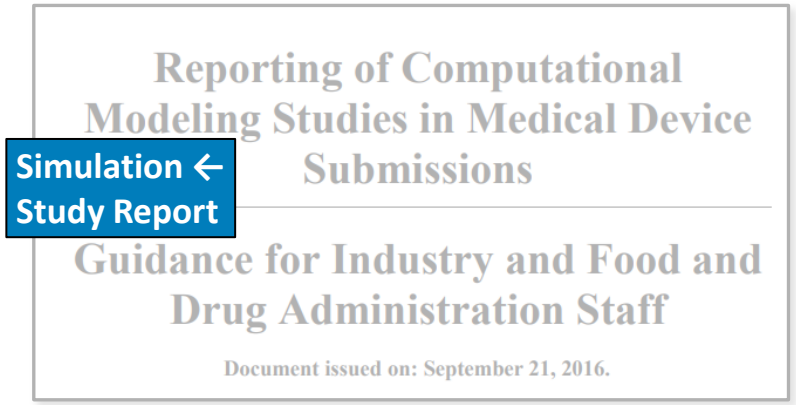
Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

Let's look closer

what, how, model details, results

Simulation ← Study Report

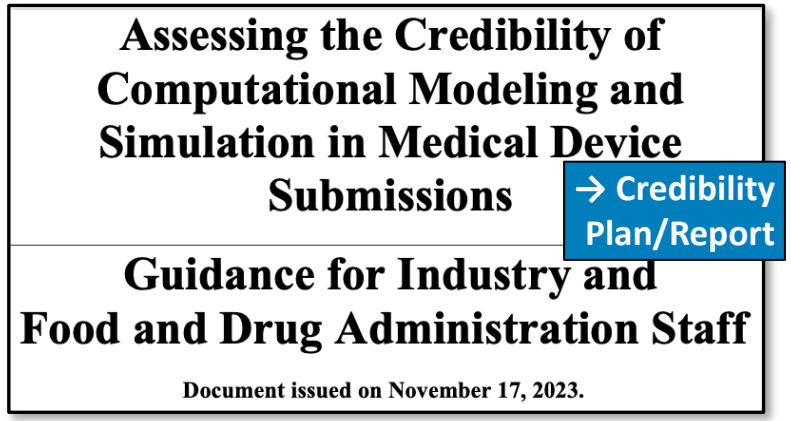


Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

→ Credibility Plan/Report

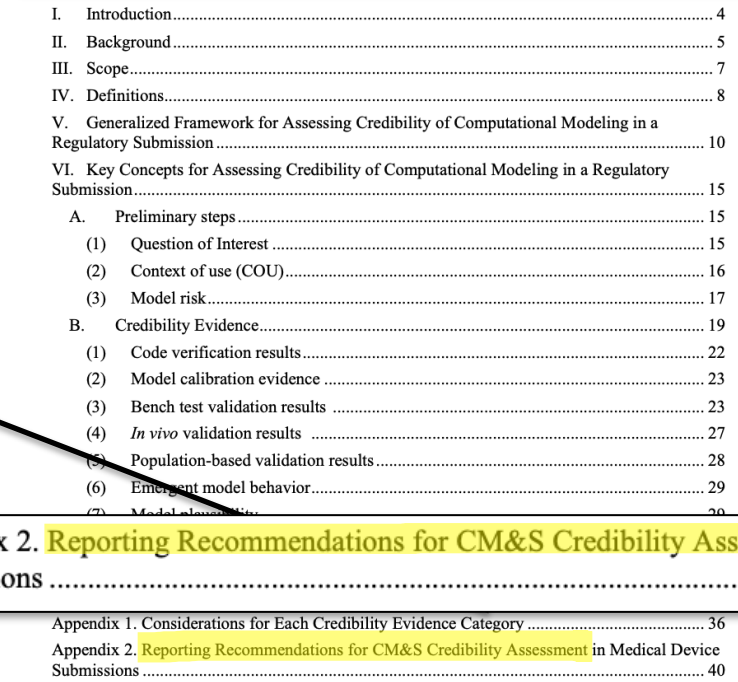


Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

trust, credibility, reference model details



I. Introduction 4
II. Background 5
III. Scope 7
IV. Definitions 8
V. Generalized Framework for Assessing Credibility of Computational Modeling in a Regulatory Submission 10
VI. Key Concepts for Assessing Credibility of Computational Modeling in a Regulatory Submission 15
A. Preliminary steps 15
(1) Question of Interest 15
(2) Context of use (COU) 16
(3) Model risk 17
B. Credibility Evidence 19
(1) Code verification results 22
(2) Model calibration evidence 23
(3) Bench test validation results 23
(4) *In vivo* validation results 27
(5) Population-based validation results 28
(6) Emergent model behavior 29
Appendix 1. Considerations for Each Credibility Evidence Category 36
Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

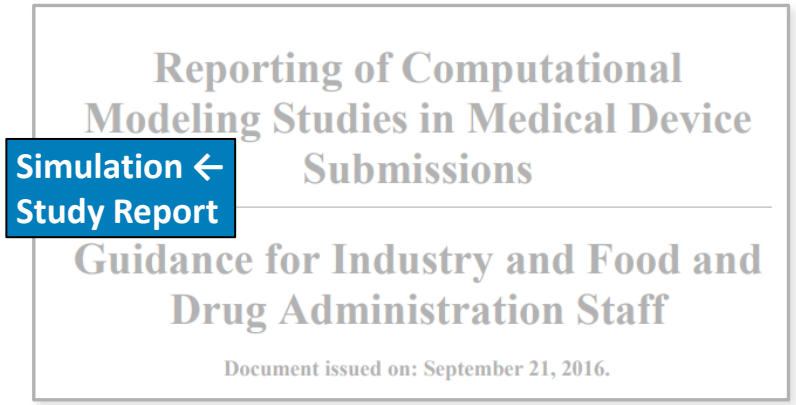
*[W]e recommend that you provide **two reports**... In the **first report**, we recommend you **reference your Credibility Assessment Report** as appropriate...*

*...(i.e., Section III: **Code Verification**, Section VIII: **System Discretization—Calculation Verification**, and Section X: **Validation**).*

Let's look closer

what, how, model details, results, **reference credibility evidence**

Simulation ← Study Report

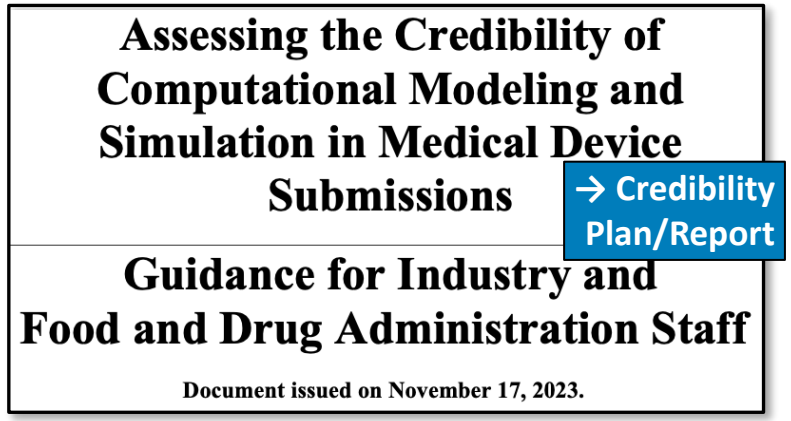


Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

→ Credibility Plan/Report



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

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

trust, credibility, reference model details

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I. Introduction 4
II. Background 5
III. Scope 7
IV. Definitions 8
V. Generalized Framework for Assessing Credibility of Computational Modeling in a Regulatory Submission 10
VI. Key Concepts for Assessing Credibility of Computational Modeling in a Regulatory Submission 15
A. Preliminary steps 15
(1) Question of Interest 15
(2) Context of use (COU) 16
(3) Model risk 17
B. Credibility Evidence 19
(1) Code verification results 22
(2) Model calibration evidence 23
(3) Bench test validation results 23
(4) *In vivo* validation results 27
(5) Population-based validation results 28
(6) Emergent model behavior 29
Appendix 1. Considerations for Each Credibility Evidence Category 36
Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions 40

Let's look closer

what, how, model details, results, **reference credibility evidence**

Reporting of Computational Modeling Studies in Medical Device Submissions

Simulation ← Study Report

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8
Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport 10
Subject Matter Appendix II – Computational Solid Mechanics 19
Subject Matter Appendix III – Computational Electromagnetics and Optics 27
Subject Matter Appendix IV – Computational Ultrasound 35
Subject Matter Appendix V – Computational Heat Transfer 41

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

→ Credibility Plan/Report

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

trust, credibility, reference model details

Let's look closer

Outline of the CM&S Report 2

I. Executive Report Summary 3

II. Background/Introduction 3

III. Code Verification .....

IV. System Configuration ..

what, how, model details

V. Governing Equations/C

VI. System Properties.....

VII. System Conditions .....

VIII. System Discretization ..

IX. Numerical Implementati

X. Validation..... 6

results XI. Results..... 7

XII. Discussion 7

XIII. Limitations 7

XIV. Conclusions..... 7

XV. References..... 7

Credibility guidance recommends cross-referencing from Model Report to Credibility Assessment Report

Let's look closer

what, how, model details, results, **reference credibility evidence**

Reporting of Computational Modeling Studies in Medical Device Submissions

Simulation ← Study Report

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8
Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport 10
Subject Matter Appendix II – Computational Solid Mechanics 19
Subject Matter Appendix III – Computational Electromagnetics and Optics 27
Subject Matter Appendix IV – Computational Ultrasound 35
Subject Matter Appendix V – Computational Heat Transfer 41

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

→ Credibility Plan/Report

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

trust, credibility, reference model details, **evidence categories (VVUQ++)**

Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7

what, how, model details

results

Let's look closer

what, how, model details, results, reference credibility evidence

Simulation ← Study Report

Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

Introduction ... 1
Scope ... 2
Outline of the CM&S Report ... 2
I. Executive Report Summary ... 3
II. Background/Introduction ... 3
III. Code Verification ... 3
IV. System Configuration ... 4
V. Governing Equations/Constitutive Laws ... 4
VI. System Properties ... 5
VII. System Conditions ... 5
VIII. System Discretization ... 5
IX. Numerical Implementation ... 6
X. Validation ... 6
XI. Results ... 7
XII. Discussion ... 7
XIII. Limitations ... 7
XIV. Conclusions ... 7
XV. References ... 7
Glossary ... 8
Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport ... 10
Subject Matter Appendix II – Computational Solid Mechanics ... 19
Subject Matter Appendix III – Computational Electromagnetics and Optics ... 27
Subject Matter Appendix IV – Computational Ultrasound ... 35
Subject Matter Appendix V – Computational Heat Transfer ... 41

→ Credibility Plan/Report

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

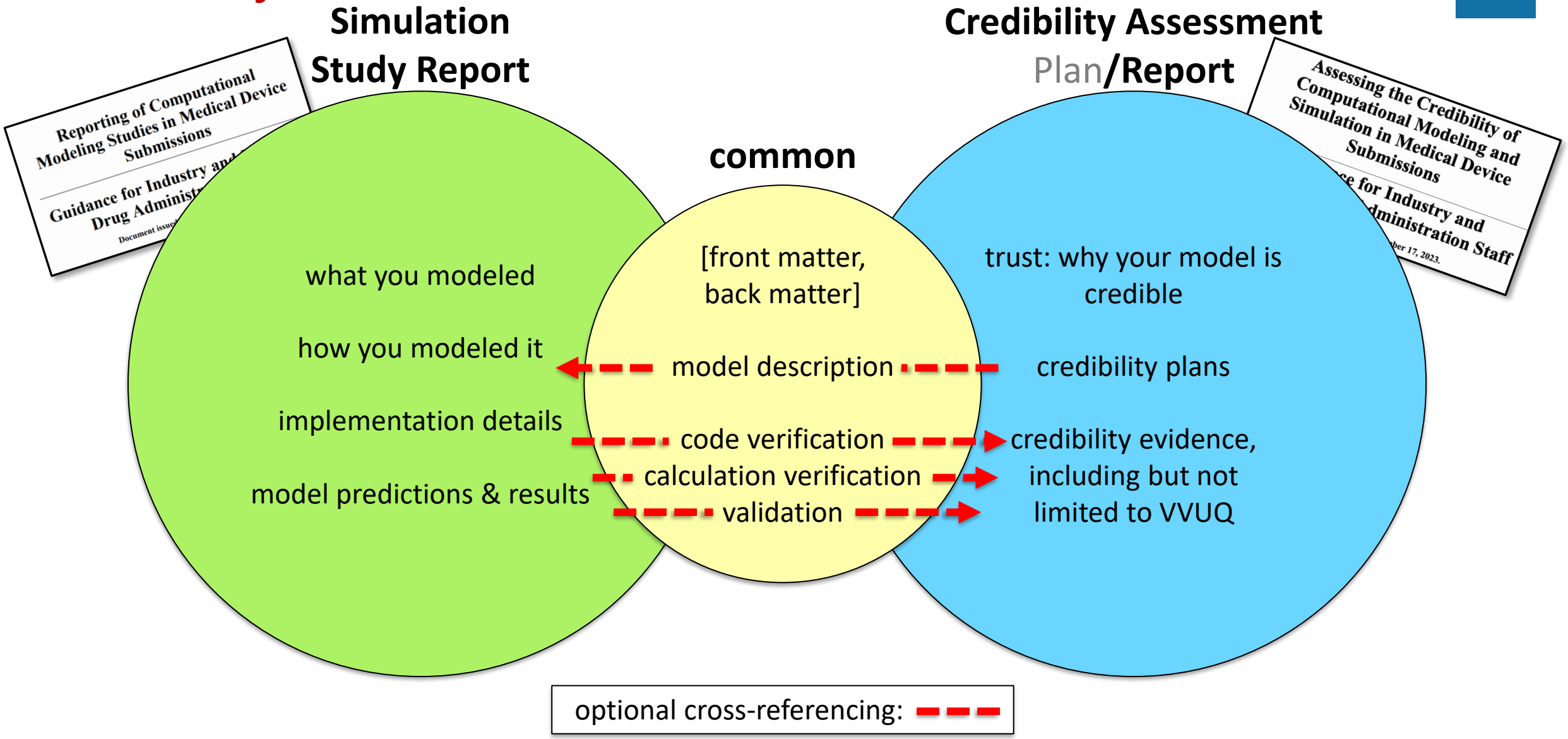
Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

I. Introduction ... 4
II. Background ... 5
III. Scope ... 7
IV. Definitions ... 8
V. General Framework for Assessing Credibility of Computational Modeling in a Regulatory Submission ... 10
VI. Key Concepts for Assessing Credibility of Computational Modeling in a Regulatory Submission ... 15
A. Preliminary steps ... 15
(1) Question of Interest ... 15
(2) Context of use (COU) ... 16
(3) Model risk ... 17
B. Credibility Evidence ... 19
(1) Code verification results ... 22
(2) Model calibration evidence ... 23
(3) Bench test validation results ... 23
(4) *In vivo* validation results ... 27
(5) Population-based validation results ... 28
(6) Emergent model behavior ... 29
(7) Model plausibility ... 29
(8) Calculation verification/UQ results using COU simulations ... 30
C. Credibility Factors and Credibility Goals ... 31
D. Adequacy Assessment ... 33
Appendix 1. Considerations for Each Credibility Evidence Category ... 36
Appendix 2. Reporting Recommendations for CM&S Credibility Assessment in Medical Device Submissions ... 40

trust, credibility, reference model details, evidence categories (VVUQ++)

Summary


Simulation Study Report
Credibility Assessment Plan/Report
Reporting of Computational Modeling Studies in Medical Device Submissions
Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions
common
what you modeled
how you modeled it
implementation details
model predictions & results
[front matter, back matter]
model description
code verification
calculation verification
validation
trust: why your model is credible
credibility plans
credibility evidence, including but not limited to VVUQ
optional cross-referencing:

Outline

1. Compare & contrast credibility vs reporting guidance
2. **Review reporting guidance body**
3. Briefly review subject matter appendices
4. Address frequently asked questions

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

Introduction

For many years, computational modeling and simulation (CM&S) studies have been used by sponsors to support device design/development and have been reported in medical device submissions. These studies have traditionally been used in the areas of fluid dynamics (e.g., calculate shear stress in ventricular assist devices), solid mechanics (e.g., determine maximum stress locations in a hip implant), electromagnetics and optics (e.g., radiofrequency safety in magnetic resonance imaging, fluorescence for fiber optic spectroscopy devices), ultrasound propagation (e.g., absorbed energy distribution for therapeutic ultrasound), and thermal propagation (e.g., temperature rises with radiofrequency and laser ablation devices). The purpose of this guidance document is to provide recommendations to industry on the formatting, organization, and content of reports of CM&S studies that are used to support medical device submissions. Moreover, this guidance is also for FDA Staff, to improve the consistency and predictability of the review of CM&S studies and to better facilitate full interpretation and complete review of those studies.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

Scope

Computational modeling and simulation studies, together with bench, nonclinical *in vivo*, and clinical studies, can be used to evaluate the safety and effectiveness of medical devices. In order for the CM&S studies to serve as valid scientific evidence in regulatory submissions, specific details need to be included in the report of such studies. In this guidance, the term "CM&S report" refers to the part of a regulatory submission that provides information about a CM&S study; the term does not describe a new submission requirement.

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

Outline of the CM&S Report

In the following section, we provide the recommended headings and details for a CM&S report contained within a regulatory submission.

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

I. Executive Report Summary

We recommend that you provide a concise and complete overview of the report of the computational modeling and/or simulation study, that includes the following:

- Context of use of the CM&S study including a clear identification of the quantity(s) of interest (QOI) (e.g., to determine the maximum stress value(s) and location(s))
- Scope of the analysis (e.g., for a device that has multiple sizes and/or configurations, specify which sizes and/or configurations were modeled, and how the computational model relates to the intended patient population)
- Type of analysis (e.g., fluid dynamics and mass transport, solid mechanics, electromagnetics and optics, ultrasound, heat transfer)
- Conclusions with respect to the context of use
- Keywords: we recommend that you provide up to five keywords or key phrases that describe the modeling modality, the device product code, any relevant materials of the device, analysis type, and if applicable, location in the body. For more information on the device product code, refer to the FDA guidance entitled "Medical Device Classification Product Codes" issued on April 11, 2013. The following are examples of keywords that outline this information:
  - e.g., finite element analysis, MIH, nitinol, fatigue, aorta
  - e.g., radiofrequency dosimetry, OQG, cobalt chromium, magnetic resonance safety, hip

  This information will be used for semantic text mining of CM&S reports to better understand the impact of this guidance on CM&S studies used in regulatory submissions.

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

II. Background/Introduction

We recommend that you provide a brief description of the device system and intended use environment. Discuss the context of use of the analysis, as this will dictate the relevant details necessary for review.

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

Pattern:

[#]. Topic

A. Details

B. Assumptions, simplifications and rationale:

"You should describe and provide rationale for the assumptions and simplifications used…"

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

III. Code Verification

We recommend that you provide a brief description of the software quality assurance (SQA) and numerical code verification (NCV) that you performed. Code verification establishes the correctness of the code used as software tools for CM&S and establishes the correctness and fidelity of the numerical algorithms; this is accomplished through SQA and NCV. Software tools include off-the-shelf, modified-off-the-shelf, or user-developed. Code verification is important, regardless of the software type.

Credibility guidance recommends cross-referencing from Simulation Study Report to Credibility Assessment Report

B. Assumptions, simplifications and rationale

You should describe and provide rationale for the applicability of the verified code to your computational domain. If applicable, describe and rationale for differences between the code used for verification and the code used for the context of use. Moreover, provide rationale to support the selection of the numerical settings, regardless if the settings are default or modified.

Note that the details regarding calculation verification, the other component to the

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

IV. System Configuration

We recommend that you provide information regarding the system configuration (e.g., the geometry of the device, the computational domain, the structure of a physiological control system, the *in vitro* test that is modeled).

A. Details

You should describe the components of the system (e.g., device, *in vivo* and/or *in vitro* environment), including appropriately scaled/dimensioned images and/or diagrams.

You should describe the methods (e.g., image reconstruction and resolution, computer aided design (CAD)) used to generate the system configuration, including format, and discuss how the configuration was appropriately captured for the intended analysis.

You should describe the software used to generate the system configuration (e.g., CAD software, image segmentation software, control-system simulation software). Describe the imaging modality if image reconstruction was used to generate geometry.

B. Assumptions, simplifications, and rationale

You should describe and provide rationale for the assumptions and simplifications used to generate the system configuration as compared to the actual device and environment. If appropriate, provide a clinical rationale for the *in vivo*/*in vitro* models (e.g., size, disease state, mathematical convenience versus clinical relevance)

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

V. Governing Equations/Constitutive Laws

We recommend that you provide information regarding the governing equations and/or constitutive laws used to perform the computational analysis.

A. Details

You should provide a description of the governing equations/constitutive laws for the system. Provide the actual equations, if appropriate.

B. Assumptions, simplifications, and rationale

You should describe and provide rationale for the assumptions and simplifications of the governing equations/constitutive laws chosen to represent the system.

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

VI. System Properties

We recommend that you provide information regarding the biological, chemical, physical and physiological properties of the system, as appropriate.

A. Details

You should describe and quantify all system properties used in the analysis. These might include biological material properties (e.g., cells, tissues, organs) and/or processes (e.g., cell signals), and/or states (e.g., diseased, healthy), chemical properties, physiological properties and physical properties that define the materials and/or process characteristics. Please also discuss the variability (e.g., temporal, spatial, across individuals/samples) of system properties, if applicable.

B. Assumptions, simplifications, and rationale

You should describe and provide rationale for the assumptions and simplifications used to determine the system properties. Identify the source and provide the reference for the properties (e.g., literature, *in vivo*, *ex vivo*, *in vitro* testing).

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

VII. System Conditions

We recommend that you provide information regarding the conditions that were imposed on the system. These might include, but are not limited to, the boundary and loading conditions, initial conditions, and other constraints that control the system.

A. Details

You should describe the system conditions imposed on the model and their variability, if applicable. If appropriate, provide a graphical representation of the conditions, depicting how they are applied to the system.

B. Assumptions, simplifications, and rationale

You should describe and provide rationale for the assumptions and simplifications used to determine the conditions applied on the system. Provide appropriate documentation (e.g., literature, test reports, clinical data, medical imaging data)

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

VIII. System Discretization

We recommend that you provide information regarding the discretization and refinement techniq

Credibility guidance recommends cross-referencing from Simulation Study Report to Credibility Assessment Report

criteria used to determine that the solution was sufficiently resolved.

B. Assumptions, simplifications, and rationale

You should describe and provide rationale for the assumptions and simplifications used to discretize the computational domain. Report the criteria used to determine that the discretization was sufficient to resolve the QOI(s).

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

IX. Numerical Implementation

We recommend that you provide information regarding the numerical implementation used to solve the governing equations.

A. Details

You should describe the numerical implementation methodology and/or numerical method used to solve the governing equations. State the solver parameters (e.g., tolerance, relaxation) and convergence criteria.

B, Assumptions, simplifications, and rationale

You should describe and provide rationale for the assumptions and simplifications used to determine the solver and associated parameters. Note that rationale should be provided for the solver settings, whether they are adjusted from the default settings or not.

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

X. Validation

We recommend that you provide information regarding the method(s) employed to validate the computational model for the context of use.

Credibility guidance recommends cross-referencing from Simulation Study Report to Credibility Assessment Report

B. Assumptions, simplifications, and rationale

You should describe and provide the rationale for the assumptions and simplifications of the method (e.g., *in vivo*, *ex vivo* or *in vitro* test) used to validate the computational model. You should discuss why the method of comparison and the degree of agreement between QOI(s) from the comparator and computational model are appropriate for using the computational model in the context of use.

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

XI. Results

We recommend that you present the quantitative results, the QOI(s), from the CM&S study. You should provide the results with sufficient level of detail, including labels and legends. The results may be presented in more than one format (e.g., table, graph).

XII. Discussion

We recommend that you discuss how the results from the CM&S study relate to the context of use. If appropriate, discuss the regulatory and/or clinical relevance of the results.

XIII. Limitations

We recommend that you provide details regarding how the assumptions, simplifications, sensitivity and uncertainty analyses described in the previous sections might affect the output of the computational model, the interpretation of the results, and the relevance to the context of use.

XIV. Conclusions

We recommend that you state the overall conclusions of the CM&S study and if the regulatory objective(s) have been met.

XV. References

We recommend that you provide a list of the appropriate references used to support the CM&S study.

Let's look closer

Introduction 1
Scope 2
Outline of the CM&S Report 2
I. Executive Report Summary 3
II. Background/Introduction 3
III. Code Verification 3
IV. System Configuration 4
V. Governing Equations/Constitutive Laws 4
VI. System Properties 5
VII. System Conditions 5
VIII. System Discretization 5
IX. Numerical Implementation 6
X. Validation 6
XI. Results 7
XII. Discussion 7
XIII. Limitations 7
XIV. Conclusions 7
XV. References 7
Glossary 8

Glossary

For purposes of this guidance, the following terms are defined.

Accuracy: the difference between a parameter, variable or derived quantity (or a set of parameters or variables) within a model, simulation, or experiment and the true value or the assumed true value.

Analysis: any post-processing or interpretation of the individual values, arrays, files of data, or suites of executions resulting from a simulation.

Calculation Verification: the process of determining the solution accuracy of a particular calculation.

Code Verification: the process of determining that the numerical algorithms are correctly implemented in the computer code and identifying errors in the software.

Comparator: the experimental methodology that is used to perform validation. The comparator data can be taken from a laboratory bench-test, an animal study, an imaging study, or a clinical study. The selection of the comparator should be based on the context of use.

Computational domain: the spatial and/or temporal domain for which the analysis was conducted. See also System Discretization.

Computational model: the numerical implementation of the mathematical model performed by means of a computer.

Constitutive law: an expression which describes the relationship between biological, chemical or physical quantities for a specific material or substance and an external stimuli (e.g., Hooke's Law).

Context of use: the purpose or intent of the computational model and/or simulation study, specifically the role of the CM&S study in the regulatory submission.

Convergence analysis: the process of ensuring the solution resolves the physics of interest and the variation of the solution remains within a pre-specified range as the discretization is refined.

Governing equation: the mathematical relationship that describes the phenomena of interest.

Mathematical model: the mathematical equations, boundary values, initial conditions, and modeling data needed to describe the conceptual model.

Model: a description or representation of a system, entity, phenomena, or process (adapted from Banks, J., ed. (1998). Handbook of Simulation. New York: John Wiley & Sons). Any data that go into a model are considered part of the model. Models may be mathematical, physical, or logical representations of a system, entity, phenomenon, or process. Models can be used by simulation to predict a future state, if so desired.

Quantity of Interest: the desired output from the computational model. For a particular context of use, there can be multiple quantities of interest.

Sensitivity: the degree to which the output is affected by a particular input.

Simulation: the imitation of the characteristics of a system, entity, phenomena, or process using a computational model; a specific "run" of the model with one set of parameters that results in the quantity of interest or multiple quantities of interest.

Subject matter: a particular technical discipline, system, or process regarding computational modeling methodologies.

System discretization: the division of the computational domain of the system into discrete parts for numerical implementation.

Uncertainty: the estimated amount or percentage by which an observed or calculated value may differ from the true value (The American Heritage Dictionary of the English Language, 4th ed.).

Validation: The process of determining the degree to which a model or a simulation is an accurate representation of the real world from the perspective of the intended uses of the model or the simulation (American Society of Mechanical Engineering Verification &Validation Guide – ASME V&V 10-1-2012).

Verification: The process of determining that a computational model accurately represents the underlying mathematical model and its solution from the perspective of the intended uses of modeling and simulation (American Society of Mechanical Engineering Verification &Validation Standard – ASME V&V 20-2009). See also Code Verification and Calculation Verification.

*See also glossaries in FDA credibility guidance, ASME VV40-2018, & ASME VVUQ1-2022

Outline

1. Compare & contrast credibility vs reporting guidance
2. Review reporting guidance body
3. **Briefly review subject matter appendices**
4. Address frequently asked questions

Reporting guidance includes 5 subject matter appendices

Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport..... 10
Subject Matter Appendix II – Computational Solid Mechanics..... 19
Subject Matter Appendix III – Computational Electromagnetics and Optics 27
Subject Matter Appendix IV – Computational Ultrasound 35
Subject Matter Appendix V – Computational Heat Transfer 41

Each revisits report outline recommended in body

Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport..... 10
Subject Matter Appendix II – Computational Solid Mechanics.....
Subject Matter Appendix III – Computational Electromagnetics and Optics .....
Subject Matter Appendix IV – Computational Ultrasound .....
Subject Matter Appendix V – Computational Heat Transfer .....

I.	Executive Report Summary.....
II.	Background/Introduction.....
III.	Code Verification.....
IV.	System Configuration.....
V.	Governing Equations/Constitutive Laws
VI.	System Properties.....
VII.	System Conditions.....
VIII.	System Discretization.....
IX.	Numerical Implementation.....
X.	Validation.....
XI.	Results.....
XII.	Discussion.....
XIII.	Limitations.....
XIV.	Conclusions.....
XV.	References.....

Reporting guidance includes 5 subject matter appendices

Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport..... 10
Subject Matter Appendix II – Computational Solid Mechanics..... 19
Subject Matter Appendix III – Computational Electromagnetics and Optics 27
Subject Matter Appendix IV – Computational Ultrasound 35
Subject Matter Appendix V – Computational Heat Transfer 41

Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport

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[1] ASME V&V20-2009, Standard for Verification and Validation in Computational Fluid Dynamics and Heat Transfer **FDA recognized 2022**

[2] Oberkampf, W.L., Trucano, T.G., and Hirsch, C., 2004 "Verification, validation, and predictive capability in computational engineering and physics," Applied Mechanics Reviews, 57, pp. 345–384.

[3] Oberkampf W.L. and Barone M.F., 2006 "Measures of agreement between computation and experiment: Validation metrics," Journal of Computational Physics, 217, pp. 5-36.

Reporting guidance includes 5 subject matter appendices

Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport..... 10
Subject Matter Appendix II – Computational Solid Mechanics..... 19
Subject Matter Appendix III – Computational Electromagnetics and Optics 27
Subject Matter Appendix IV – Computational Ultrasound 35
Subject Matter Appendix V – Computational Heat Transfer 41

Subject Matter Appendix II – Computational Solid Mechanics

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Reporting guidance includes 5 subject matter appendices

Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport..... 10
Subject Matter Appendix II – Computational Solid Mechanics..... 19
Subject Matter Appendix III – Computational Electromagnetics and Optics..... 27
Subject Matter Appendix IV – Computational Ultrasound..... 35
Subject Matter Appendix V – Computational Heat Transfer..... 41

Subject Matter Appendix III – Computational Electromagnetics and Optics

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[1] IEEE 1597.1-2008 - IEEE Standard for Validation of Computational Electromagnetics Computer Modeling and Simulations

Reporting guidance includes 5 subject matter appendices

Subject Matter Appendix I – Computational Fluid Dynamics and Mass Transport..... 10
Subject Matter Appendix II – Computational Solid Mechanics..... 19
Subject Matter Appendix III – Computational Electromagnetics and Optics 27
Subject Matter Appendix IV – Computational Ultrasound..... 35
Subject Matter Appendix V – Computational Heat Transfer 41

Subject Matter Appendix IV – Computational Ultrasound

Subject Matter Appendix V – Computational Heat Transfer

Outline

1. Compare & contrast credibility vs reporting guidance
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4. **Address frequently asked questions**

Frequently Asked Questions

1) I want to submit a Credibility Assessment Plan to FDA for feedback as part of a presubmission.
   I do not yet have model results.
   Do I need to submit a separate Simulation Study Report following the reporting guidance?
   - *(may include model details in credibility plan itself; see Credibility guidance, Appendix 2)*

2) I am developing a device that relies on physics-based simulation as part of its intended used.
   There are no singular "study results", as new simulations are performed for each clinical use.
   Which guidance documents are relevant?
   - *(reporting guidance not directly applicable, but you may wish to use it for reporting model details; credibility guidance provides some specific recommendations for software embedded within a device; IMDRF software guidance also relevant)*

3) I am using an advanced constitutive model in a commercial code for which some details are proprietary.
   What should I report if the precise governing equations are unknown?
   - *(report details that are available; consider providing feedback to software vendor)*

4) My submission relies on results produced using a hybrid of physics-based and AI/ML models.
   How should I report model details for hybrid models?
   - *(recommend a Qsub; reporting & credibility guidances address models that are primarily physics-based)*

Thank you

- Credibility of Computational Modeling Program Members

Kenneth Aycock
CDRH/OSEL

Brent Craven
CDRH/OSEL

Pras Pathmanathan
CDRH/OSEL

- Many others

contact: kenneth.aycock@fda.hhs.gov