ASME V&V 40 for Establishing Credibility of CFD Models

Brent Craven, Ph.D.
Research Scientist
Division of Applied Mechanics,
Office of Science and Engineering Laboratories,
Center for Devices and Radiological Health,
U.S. Food and Drug Administration

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Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

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Medical device modeling & simulation

- Consider a transcatheter aortic heart valve

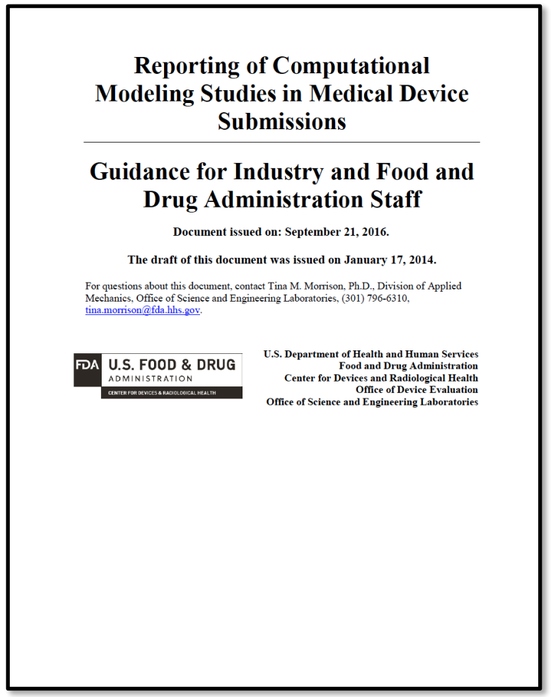
Four Uses of Modeling & Simulation (M&S):

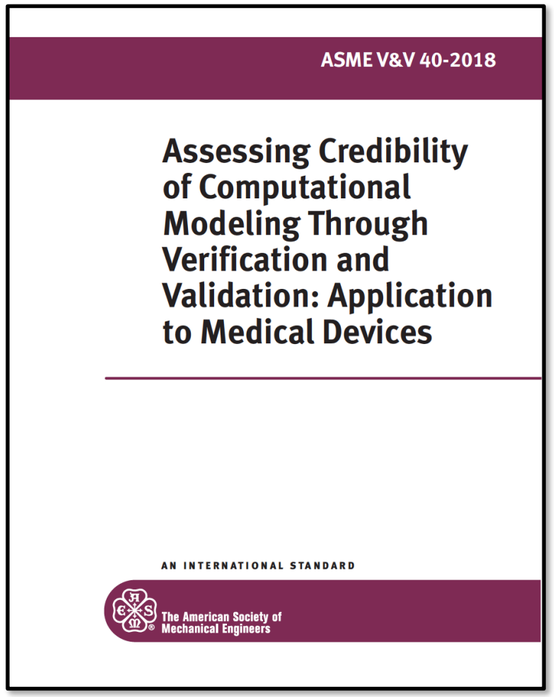
1. **In Silico Pre-Clinical Bench Testing:** M&S to complement traditional benchtop testing of a particular device
2. **In Silico Clinical Trial:** M&S to augment clinical trial of a particular device — e.g., Medical Device Innovation Consortium (MDIC) Virtual Patient Model for pacemaker lead fracture
3. **Software as a Medical Device (SaMD):** Use M&S for "clinical decision support" (e.g., patient-specific device selection, sizing, or placement)
4. **Medical Device Development Tool (MDDT):** M&S platform "qualified" as a "nonclinical assessment model" for predicting a specific device performance metric

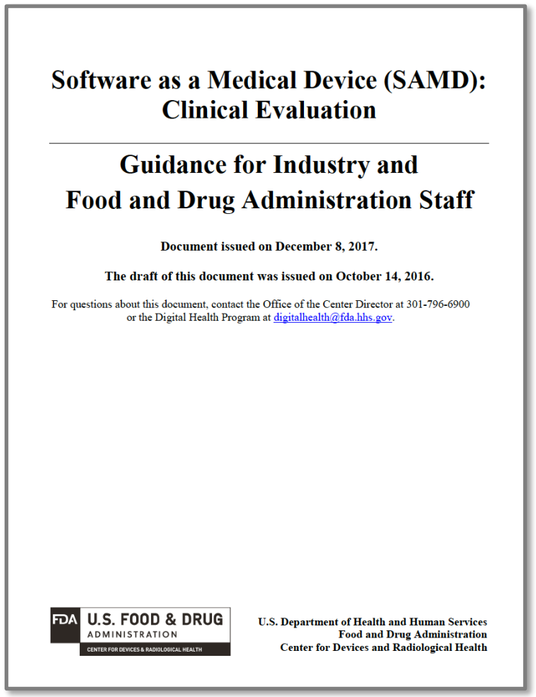
Transcatheter Aortic Heart Valve
(Hellhammer et al. 2018)

Regulatory frameworks

- M&S guidance/standards:
  1. **FDA 2016 Guidance:** “Reporting of Computational Modeling Studies in Medical Device Submissions”
  2. **ASME V&V 40-2018:** “Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices”
  3. **FDA 2017 Guidance:** “Software as a Medical Device (SAMD): Clinical Evaluation”

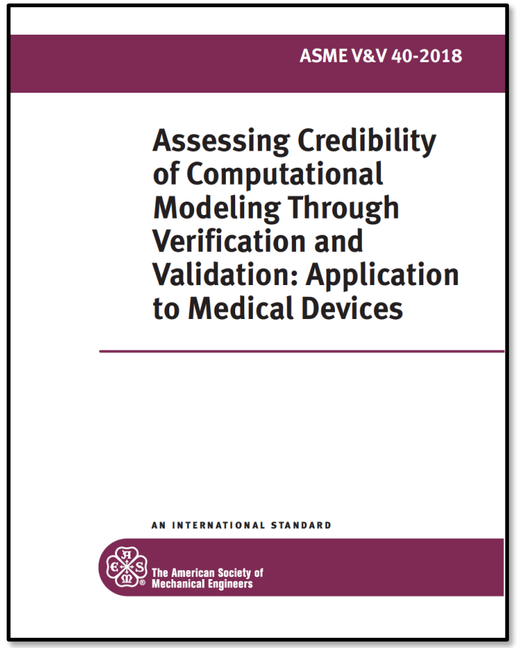






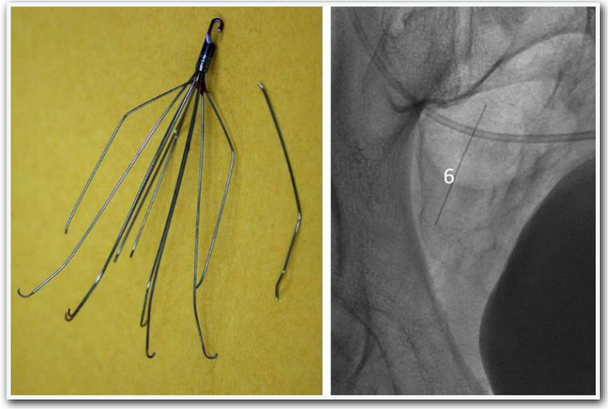
ASME V&V 40 credibility framework

- FDA-recognized standard
- Risk-informed framework for assessing M&S credibility
- Inspired by NASA-STD-7009 (2008), “Standard for Models and Simulation”
- ***Credibility*** - trust in the predictive capability of a computer model for a specific application
- **Foundation of V&V 40:** Level of credibility must be *commensurate with the risk* incurred by using M&S to support a decision



Example: M&S must be highly credible if leveraged as a primary source of evidence in a high-risk decision that has the potential to cause significant patient harm

- Model credibility demonstrated through VVUQ (verification, validation, & uncertainty quantification)

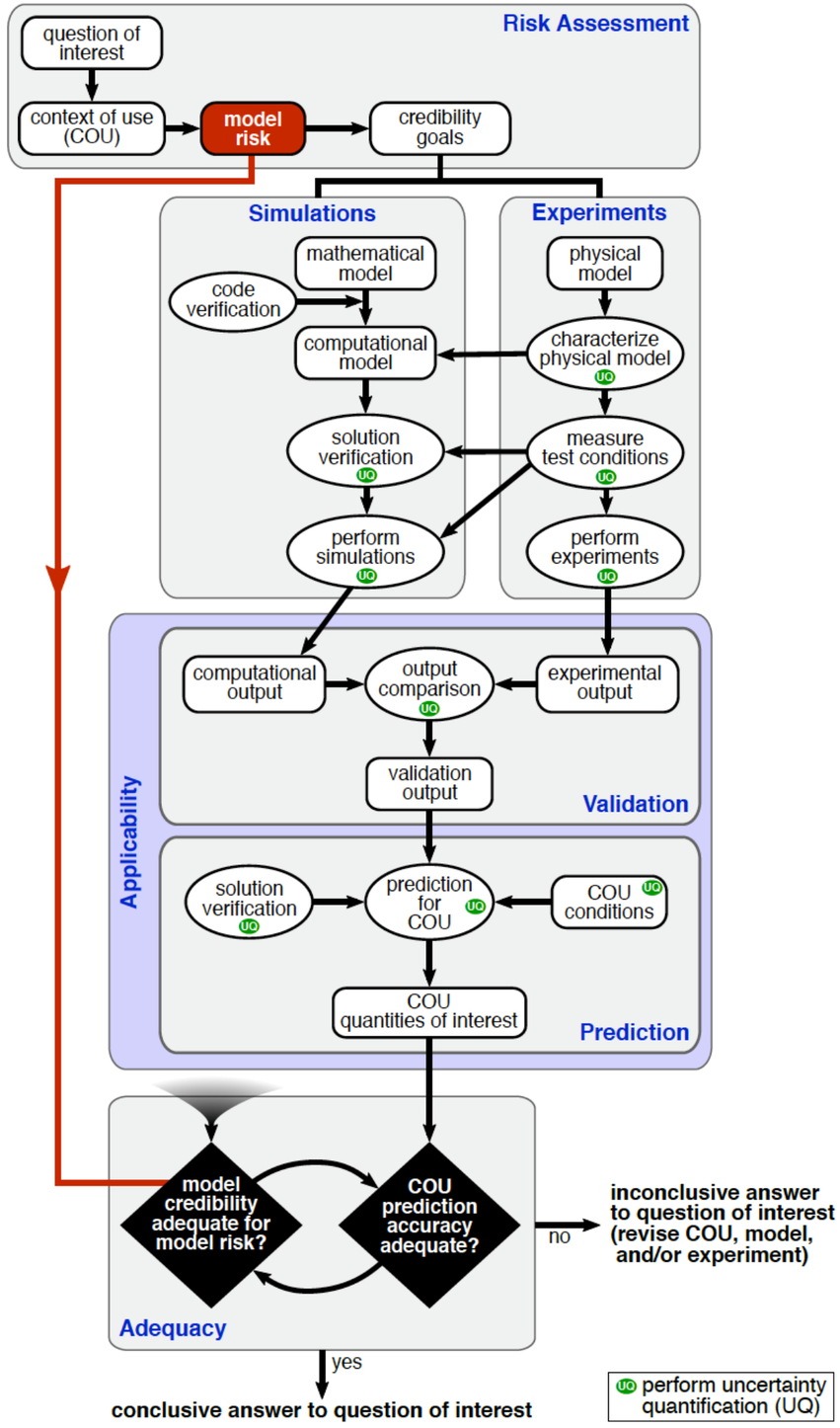


Device Fracture
(Weinberg et al., 2013)

Overview

- Framework combines:
  - Traditional VVUQ activities
  - Risk-based credibility assessment for decision making

- Key steps in the framework:
  - Define ***Question of Interest*** (e.g., overall decision)
  - Define model ***Context of Use (COU)***
  - Assess ***Model Risk***
  - Plan VVUQ activities & set ***credibility goals***
  - Perform VVUQ activities
  - Use model to make ***prediction*** at use conditions
  - Assess model credibility through series of “credibility factors”
  - Assess ***Adequacy*** of model and prediction relative to ***Model Risk***



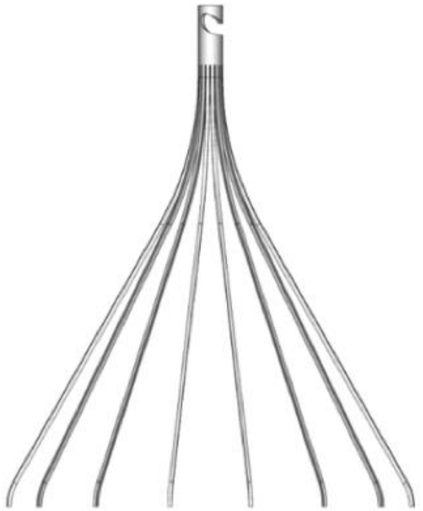
Research Project:
Mock Submission to Initiate a Clinical Trial Using M&S

- **Challenge:** lack of end-to-end examples of using V&V 40 framework
- Collaborative project between FDA, industry, & academia

Objective: End-to-end example of using M&S in a medical device regulatory submission

Aims:

1. Generate M&S evidence & experimental data using generic medical device (IVC blood clot filter)
2. Establish M&S credibility per ASME V&V 40-2018 through rigorous VVUQ
3. Use FDA Guidance to prepare **mock regulatory submission** (IDE) to initiate a clinical trial using M&S as a primary source of evidence
4. Blind & independent FDA review team evaluate mock submission
5. Improve M&S Guidance/standard and regulatory review process
6. Distribute mock submission & software tools



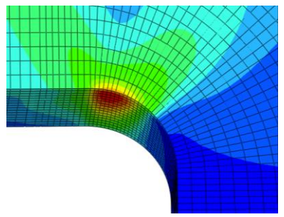
Generic IVC Blood Clot Filter

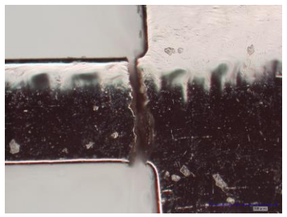
Approach: In Silico Bench Testing

- Use M&S to replicate 2 of the most burdensome bench tests for IVC filters:

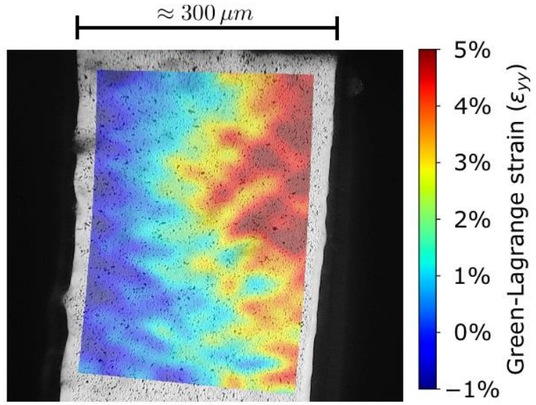
Fatigue Resistance

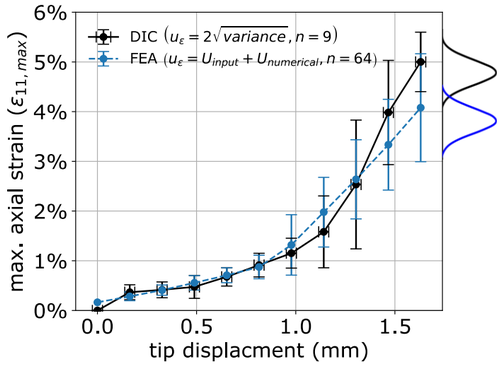
- FEA + device surrogate fatigue experiments: benchtop fatigue safety factor & fracture probability





- Perform VVUQ to demonstrate M&S credibility



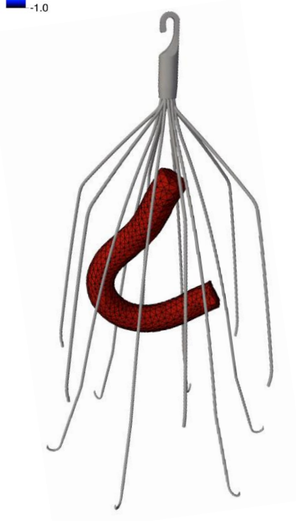


Clot Trapping

- V&V of CFD simulations of flow in a mock vein

- V&V of FSI simulations of GENI IVC filter clot trapping

- Use verified & validated M&S framework to demonstrate substantial equivalence with a predicate IVC filter



Fatigue Question of Interest & COU

Question of Interest

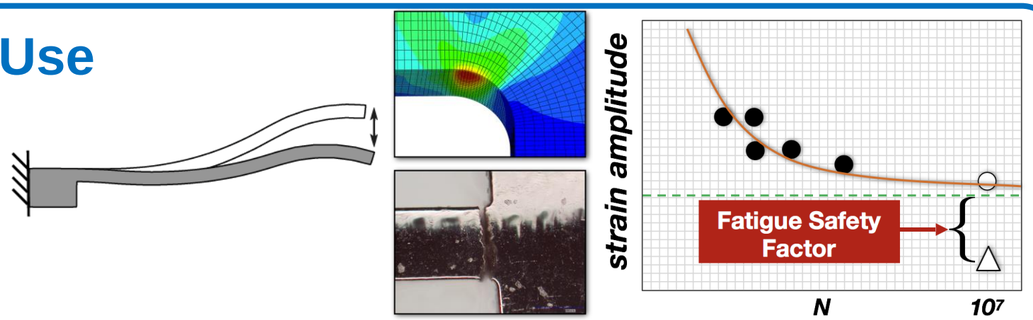
"Is the GENI IVC filter resistant to fatigue fracture under expected worst-case physiological loading conditions"?

*Note: Put in terms of the overall decision to be made, outside of the scope of the model

Model Context of Use

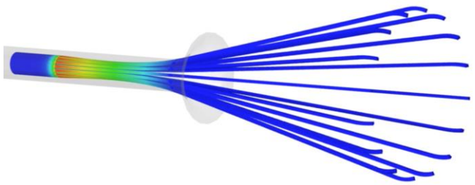
1. Device Surrogates (Single Strut of Full Device):

- FEA → peak strain amplitude ± uncertainty under conditions spanning *hyperphysiological* in simulations replicating ISO 25539-3:2011 flat-plate fatigue test
- FEA + fatigue test outcomes → device-specific strain-life diagram



2. Full Device:

- FEA → peak strain amplitude ± uncertainty under worst-case *physiological* conditions in simulations replicating ISO 25539-3:2011 flat-plate fatigue test



*Note: Be as specific as possible

Fatigue Prediction

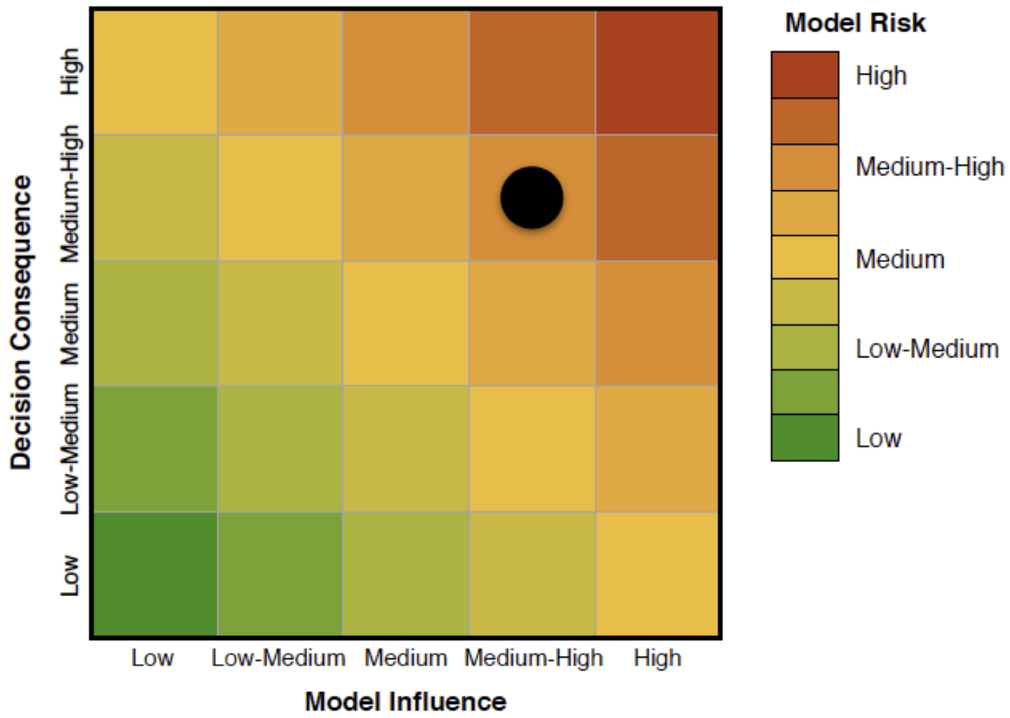
1. Benchtop fatigue safety factor with uncertainty: **FS ± Uncertainty**
2. Probability of benchtop fatigue fracture (p_{frac})

Model Risk Assessment

- ***Model Risk*** considers:
  1. ***Model Influence:*** Influence of model relative to other sources of data
  2. ***Decision Consequence:*** Potential outcome of an incorrect overall decision

- ***Model Influence:***
  - M&S outputs have significant influence
  - Not the only source of evidence → experimental fatigue data also used
  - **Model Influence: Medium-High**

- ***Decision Consequence:***
  - Potential outcome of an incorrect overall decision:
    "Is the GENI IVC filter resistant to fatigue fracture under expected worst-case physiological loading conditions?"
  - Rigorous assessment using risk management framework of ISO 14971:2019 and ISO/TR 24971:2020 considering:
    1. Potential ***severity*** of patient harm
    2. ***Probability of occurrence*** of harm
  - Based on extensive review of adverse events in clinical literature
  - Identify possible ***hazardous situations*** and the resultant patient ***harm*** for the ***hazard*** of fatigue fracture
  - Conservatively estimate severity and worst-case probability of occurrence based on reported adverse events
  - **Overall Decision Consequence: Medium-High**

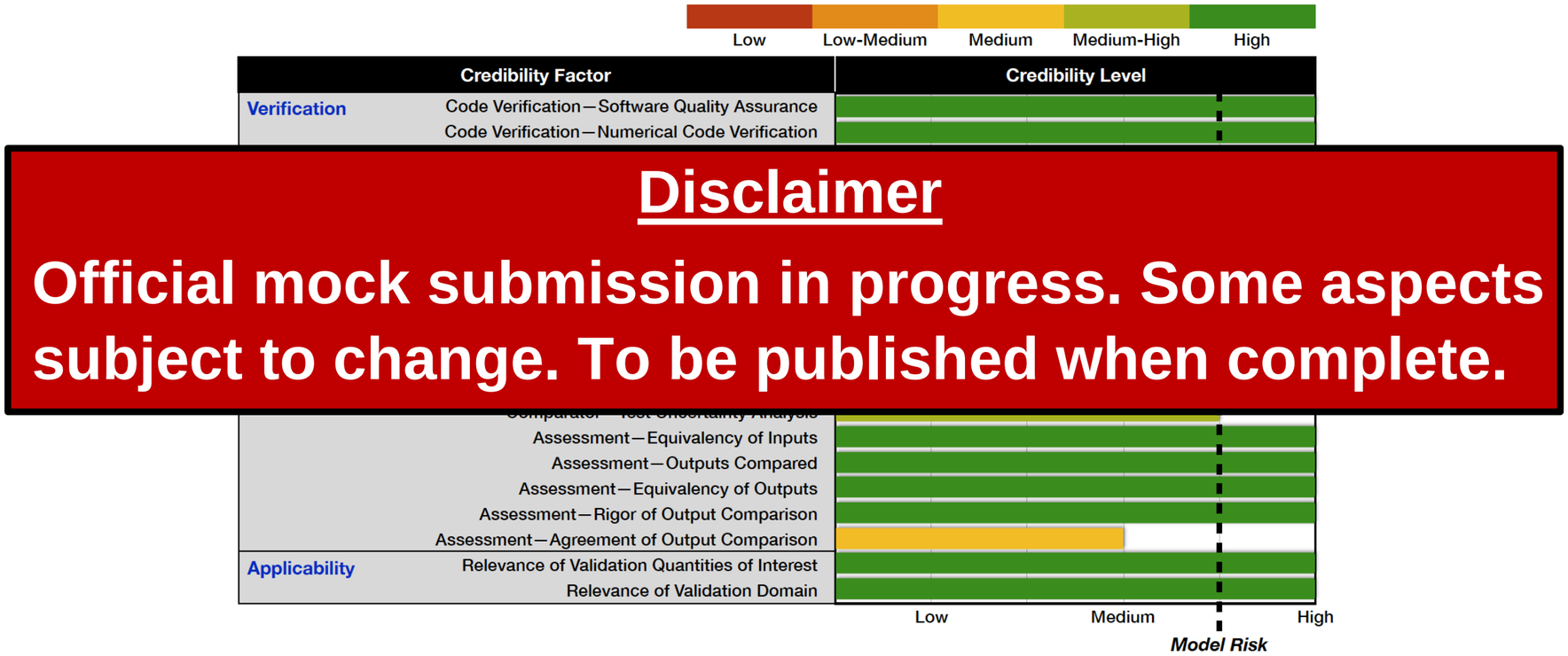


Model Risk

Medium-High

Adequacy Assessment

- Can be highly subjective
- Performed semi-quantitative ***adequacy assessment*** considering totality of evidence
- Factors for which **Credibility ≥ Model Risk**: Assume adequate (no justification)
- Factors for which **Credibility < Model Risk**: Detailed justification for how it affects overall credibility to support decision
- Final post-hoc adequacy assessment will also consider predicted durability from COU simulations
  - How close to fatigue safety factor of 1 and how frequently is fracture anticipated?
  - **For example:**
    FS = 10 ± 2 … Likely adequate ☑
    FS = 2 ± 1 … More evidence needed to reduce uncertainty or device is not fatigue resistant?



Disclaimer

Official mock submission in progress. Some aspects subject to change. To be published when complete.

Questions or Comments?

Brent.Craven@fda.hhs.gov