UTILIZING COMPUTATIONAL MODELING AND SIMULATION FOR DRUG DELIVERY DEVICE DEVELOPMENT AND STEPS TO ASSESS MODEL CREDIBILITY FOR REGULATORY EVIDENCE GENERATION

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INTRODUCTION

Developing drug delivery devices requires balancing patient usability, manufacturing variation, and regulatory expectations. Traditionally, these challenges have been addressed through repeated cycles of physical prototyping and testing, which can be costly, impact schedule, and sometimes not address all known risks of the device.

Computational modeling and simulation (CM&S) now provide an opportunity to evaluate essential drug delivery outputs (EDDOs) virtually during the prototyping stage and carries that into regulatory evidence generation.

Physics based numerical methods such as finite element analysis (FEA) and computational fluid dynamics (CFD) can predict performance measures like delivery time, drag force, dose accuracy, holdup volume, etc. These models can evaluate a variety of user, environmental, and manufacturing conditions that will be expected along the life of the device. When these models have the appropriate credibility attached to them, following frameworks such as ASME V&V40:2018 and recent CDRH FDA guidance, they can serve as evidence in regulatory submissions.

This poster demonstrates how CM&S can be applied to an example drug delivery device to assess EDDOs, reduce reliance on repeated physical testing, and accelerate development timelines.

OBJECTIVES

- This poster aims to identify a path for generation of regulatory evidence to support traditional regulatory evidence generation like clinical studies, benchtop testing, etc. It is not intended to present this solution as a standalone replacement for evidence generation.
- Demonstrate how computational modeling and simulation (CM&S) can be applied to drug delivery device development to evaluate essential drug delivery outputs (EDDOs).
- Show how physics-based models can predict performance measures such as drug delivery time, squeeze/drag force, dose accuracy, and others under variable user, environmental, and manufacturing conditions.
- Illustrate how credibility assessment frameworks (ASME V&V40:2018 and FDA CDRH guidance) can be applied to establish model credibility for regulatory evidence generation for combination products.
- Highlight the advantages of integrating CM&S into development workflows, including reduced reliance on repeated prototyping, improved risk assessment, and accelerated timelines.

MATERIALS & METHODS

A dual-chamber drug delivery prototype was selected as the example device to demonstrate computational modeling and simulation (CM&S) approaches.

EDDOs for this device consisted of drug delivery time, user squeeze force, delivered volume, hold up volume, etc. Drug delivery time was selected as an EDDO for this device to showcase how CM&S can be utilized to generate regulatory evidence.

Physics-based numerical methods were employed to evaluate these outputs under representative user, environmental, and manufacturing conditions. Finite element analysis (FEA) was used to assess structural performance and user-applied forces, while computational fluid dynamics (CFD) was used to model drug flow rates and pressure profiles.

Additional parametric analyses were performed to evaluate the influence of device tolerances, material properties, environmental conditions, and user input on drug delivery time.

Credibility of the computational models was established following the ASME V&V40:2018 framework and recent FDA CDRH guidance. Verification activities included mesh and numerical convergence studies, while validation compared simulation outputs against empirical bench test data while varying key model inputs.

THE MODEL INPUTS EVALUATED IN THIS STUDY WERE:

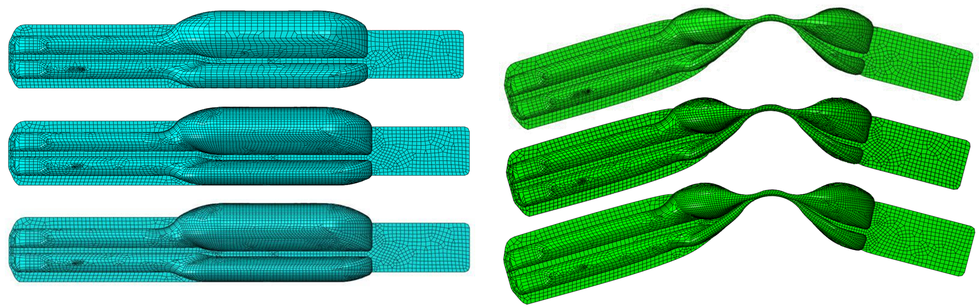
- Needle Diameter
- Container Dimensions
- User Finger Position
- Device and drug temperature

Risk-based considerations guided the level of rigor applied to each credibility assessment activity. The overall workflow integrated modeling, empirical testing, and credibility assessment into a repeatable process designed to generate regulatory-grade evidence while reducing reliance on repeated physical prototyping.

RESULTS

A risk-based credibility assessment was performed to establish the required level of model credibility. The model was designated medium risk—reflecting a high consequence of decision error but low model influence—indicating that a moderate level of verification and validation rigor was appropriate.

Verification activities included mesh sensitivity analysis, CFD time-step convergence testing, and subject matter expert (SME) checks for model setup. The mesh convergence study demonstrated that the predicted drug delivery time changed by less than 1% between successive mesh refinements, confirming numerical stability. Time-step convergence similarly showed negligible variation in predicted delivery time across decreasing time-step sizes.



Validation activities focused on assessing model input sensitivity and comparing results with expected physical testing. This physical testing indicated no greater than an 8% error in predicted delivery time over a range of Needle Diameters (Figure 1). Model input analysis identified needle dimensions as the dominant factor affecting drug delivery time, while drug temperature, container dimensions, and user input variability showed significantly lower sensitivity (Figure 2). These results confirmed that the model accurately captured the primary physical drivers of performance without undue sensitivity to secondary inputs.

Figure 1

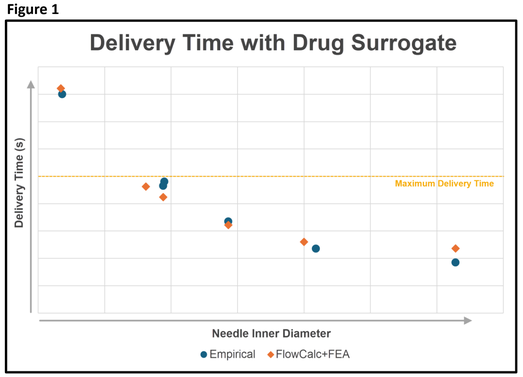
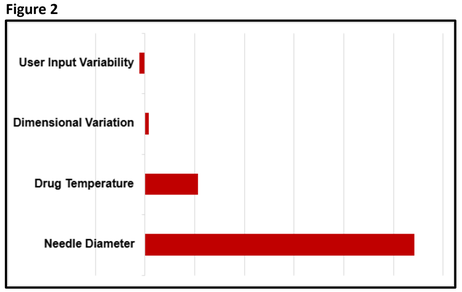
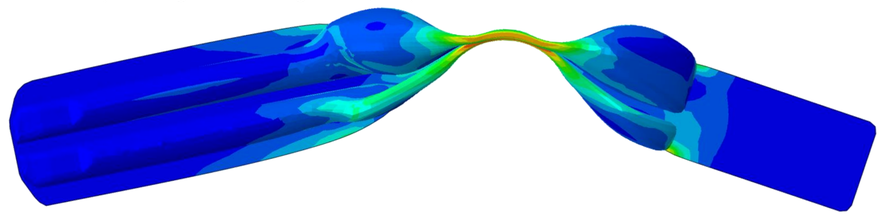


Figure 2



Overall, the combination of verification and validation activities provided quantitative evidence that the computational model was numerically stable, appropriately sensitive to key design parameters, and credible for its intended use in predicting essential drug delivery outputs.



CONCLUSIONS AND DISCUSSIONS

The integrated verification and validation activities demonstrate that the computational model is both numerically robust and physically representative of the drug delivery system. The close agreement with experimental data and appropriate parameter sensitivity confirm that the model provides reliable predictive capability for design evaluation and optimization. These findings establish sufficient credibility for regulatory submission, supporting the model's use in reducing the need for extensive physical testing while maintaining confidence in predicted performance outcomes.

This presents an example of how CM&S can be utilized to showcase how evidence can be generated to verify EDDO. This is meant to be a representative and prompt the use of these approaches for additional EDDOs on devices as well as other uses for regulatory evidence generation with models. Examples of alternative areas are: on market material changes, limiting testing on platform dosages, and assessing reliability with high reliability targets

REFERENCES

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