Model Integrated Evidence and Model Master File for Developing Orally Inhaled Drug Products

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Generic Drug Product Approval in the United States

- For generic OIDPs, approval in the United States is dependent in part on establishment of bioequivalence (BE) of the test product to its reference listed drug (RLD) or reference standard (RS) product.
  - As stated by 21 CFR 314.3(b), BE is "the absence of a significant different in the rate and extent which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."
- Establishing BE for locally acting orally inhaled drug products (OIDPs) is especially challenging because there are no studies that can routinely quantify rate and extent of drug delivery to lung tissue.

Current BE Recommendations for OIDPs

- Previously, beginning in 2013, BE recommendations in product-specific guidances (PSGs) for locally acting OIDPs adopted a weight-of-evidence approach that includes demonstration of formulation sameness, device similarity, in vitro BE studies, an in vivo PK study (without a charcoal block), and a comparative clinical endpoint (CCEP) or pharmacodynamics (PD) BE study.
- Recent new and revised PSGs for locally acting OIDPs, beginning in February 2024, have included an option for BE that does not include a CCEP BE or PD BE study. The need for an option without CCEP BE studies was recognized, because these studies are typically insensitive and may require 1,000 or more subjects to properly power the study.[1]

Recommendations in New BE Option Without CCEP/PD BE Study

- Formulation qualitative (Q1) and quantitative (Q2) sameness
- Device similarity
- In vitro studies
  - Single Actuation Content (SAC)
  - Aerodynamic Particle Size Distribution (APSD)
  - For metered dose inhalers (MDIs) only:
    - Priming and Re-priming
    - Plume Geometry
    - Spray Pattern
  - Additional studies – need for each is product-specific
    - Realistic APSD
    - Dissolution
    - Particle Morphology
- In vivo studies
  - Pharmacokinetics (PK)
    - Two-way crossover under fasting conditions in healthy subjects for all product strengths
  - PK with Charcoal Block
- In silico studies (optional)
  - Semi-empirical or computational fluid dynamics (CFD) regional deposition models
  - Physiologically based pharmacokinetic (PBPK) analyses

In Silico Study Recommendations

- Detailed recommendations provided in PSG for formoterol fumarate; glycopyrrolate inhalation metered aerosol (brand name: Bevespi Aerosphere)[1]
  - 16 other PSGs refer to this PSG
- Provide information on:
  - Model purpose
  - Model credibility
  - Statistical comparisons

Model Integrated Evidence (MIE)

- *"Model integrated evidence (MIE) refers to using MIE such as the virtual bioequivalence (VBE) study results not just to plan a pivotal study but to serve as pivotal evidence for the following: (i) product approval or (ii), in combination with relevant in vitro BE testing, support alternatives to otherwise recommended conventional in vivo studies, including but not limited to PK, PD, or comparative clinical end-point studies." – Zhao et al.*[2]
- Features of MIE
  - Integrates all mechanistic and empirical knowledge, including variability
  - Must be "sufficiently supported, validated, and verified by prior data" to be categorized as MIE

MIE to Support Generic OIDP Development and Approval

- Development
  - Understand influence of device changes on aerosolization using CFD
  - Predict outcomes of in vitro and in vivo studies following formulation or device change
- Approval
  - Re-evaluate BE limits for recommended in vitro studies
  - Conduct VBE simulations to provide further support for overall BE approach

Understand Influence of Device Changes on Aerosolization Using CFD

Predict emitted dose and particle size from dry powder inhalers (DPIs) with different designs

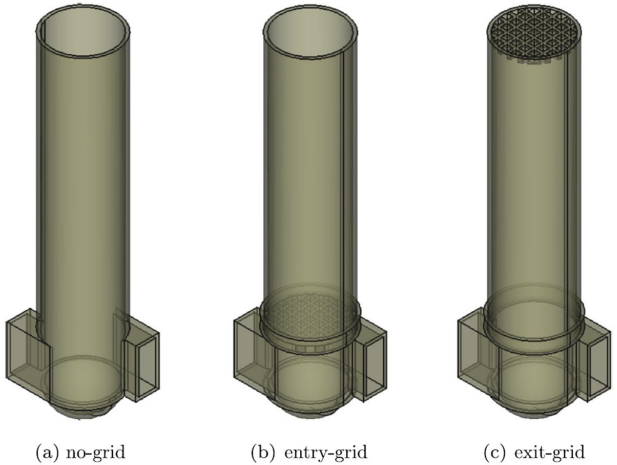


Figure 1 from Fletcher et al.[3] showing three DPI device designs.

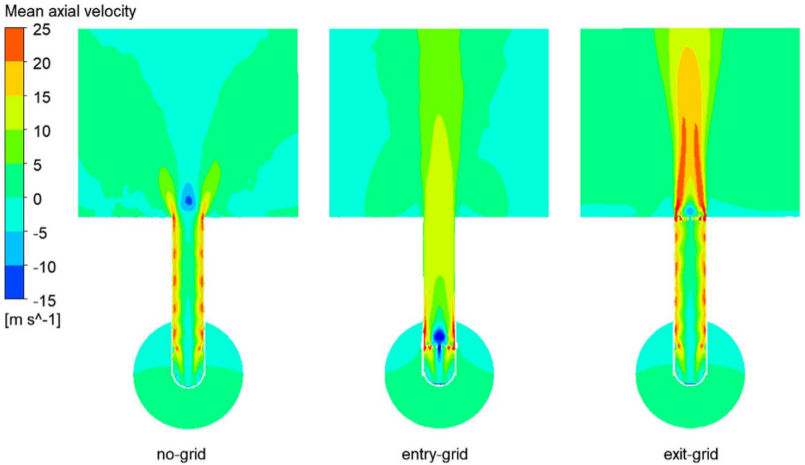


Figure 5a from Fletcher et al.[3] showing CFD predictions of mean axial velocity with three DPI device designs.

Predict Outcomes of In Vitro and In Vivo Studies Following Formulation or Device Change

Predict PK for test and reference products of an OIDP, perhaps supported by an in vivo pilot PK study.

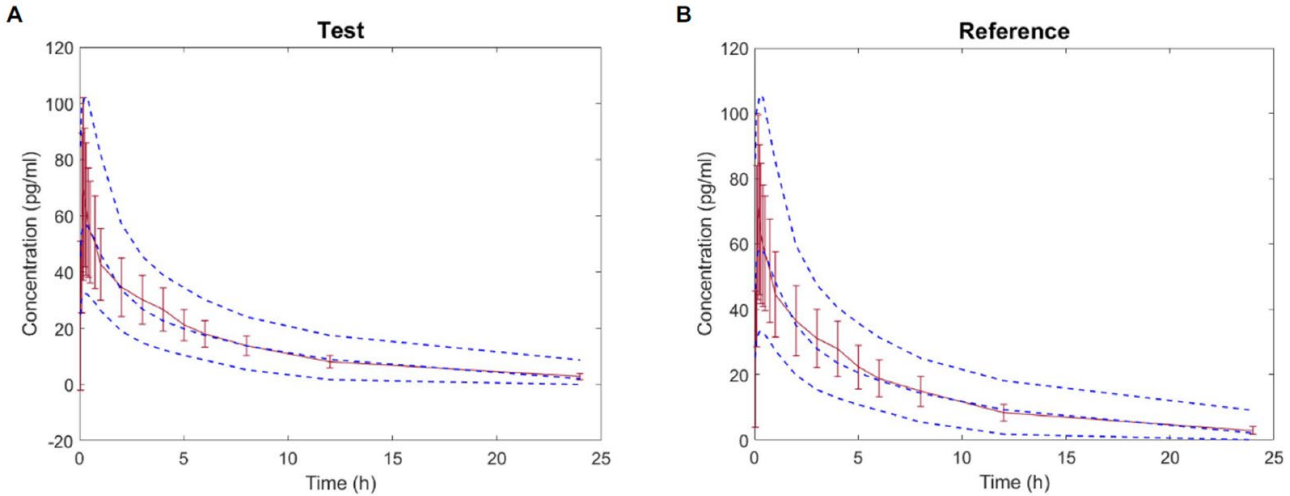


Figure 3 from Zhang et al.[4] showing plasma concentration predictions (blue dotted line) and observed mean data ± standard deviation (n = 38) (red line) for test and reference products following administration of 80 µg of ipratropium bromide inhalation metered aerosol.

Re-Evaluate BE Limits for Recommended In Vitro Studies

Use end-to-end model that uses input in vitro data to predict lung deposition, PK, and PD metrics, to re-evaluate in vitro BE limits

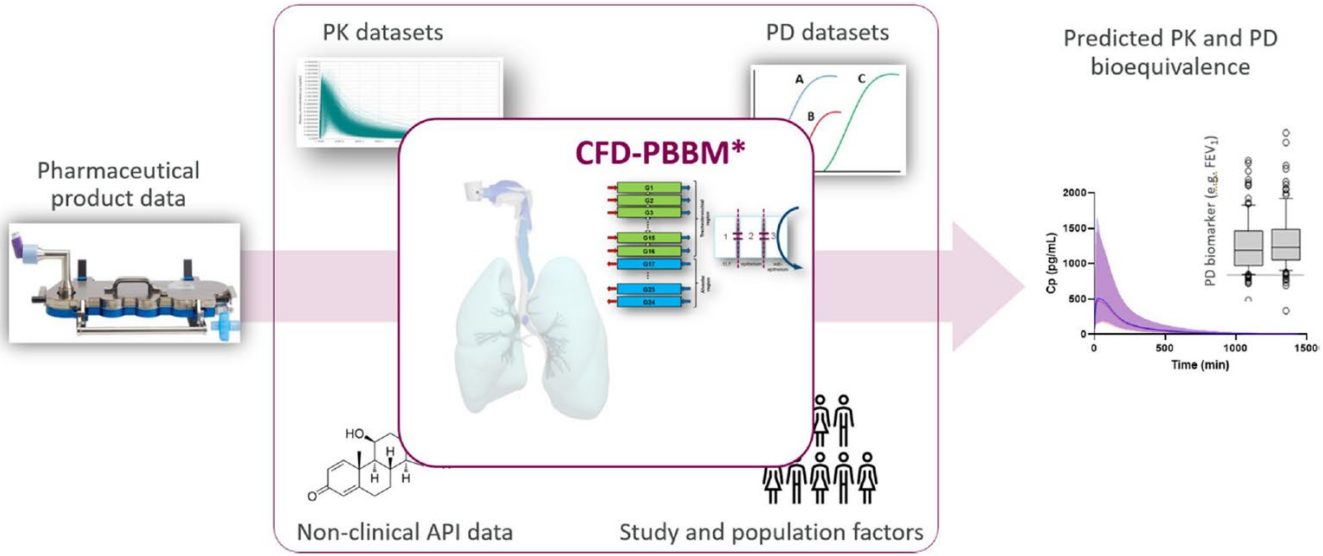
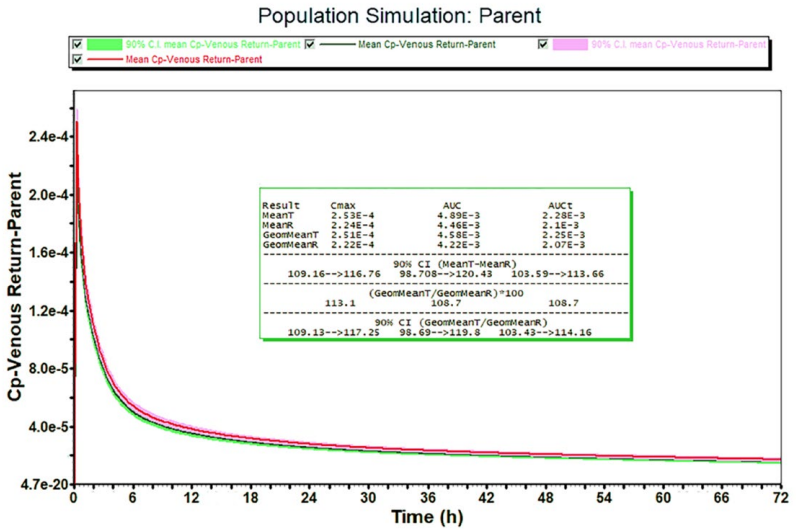


Figure 3 from Fridén[5] showing modeling workflow that integrates in vitro and in vivo data with CFD-physiologically based biopharmaceutics model (PBBM) to predict PK and PD metrics.

Conduct VBE Simulations to Provide Further Support for Overall BE Approach

Predict PK for test and reference products of an OIDP and perform statistical BE comparison to support overall BE approach, especially when recommended studies are not conducted.

Figure 8 from Tang et al.[6] showing results of virtual BE simulations following administration of 150 µg of indacaterol with a DPI for reference formulation with median particle size of 5 µm as compared with test formulation with median particle size of 6.5 µm.



Parameter	$T_{6.5}$ µm/ $R_{5µm}$(%)	90% confidence interval (%)	$T_{3.5}$ µm/ $R_{5µm}$(%)	90% confidence interval (%)
AUC_{0-t}	108.7	103.43 – 114.16	107.4	102.17–112.99
$AUC_{0-\infty}$	108.7	98.69–119.80	107.5	97.27–118.81
C_{max}	113.1	109.13–117.25	111.2	107.67–114.83

Table 6 from Tang et al.[6] showing results of virtual BE comparisons for reference product with test formulations with median particle sizes of 3.5 µm and 6.5 µm.

MIE Industry Meeting Pilot Program

- Generic OIDP applicants may meet with FDA before submitting an abbreviated new drug application (ANDA) to discuss scientific issues via a pre-ANDA Product Development (PDEV) Meeting.[7]
- Alternative BE approaches may be addressed via the pre-ANDA PDEV Meeting process, but questions that are specific to technical aspects of modeling may be addressed via the MIE Industry Meeting Pilot Program.[8]
  - "The primary goal of the MIE Pilot Program is to foster early and focused interactions between industry and FDA on science-driven topics related to MIE approaches for establishing BE in generic drug development."[8]

Model Master File (MMF)

- *"an "MMF" or "MMF submission" refers to a set of information and data on an in silico quantitative model or modeling platform supported by sufficient V&V." – Federal register notice*[9]
  - V&V – Verification and Validation
- MMFs can be submitted as Type V Drug Master Files (DMF).[9]

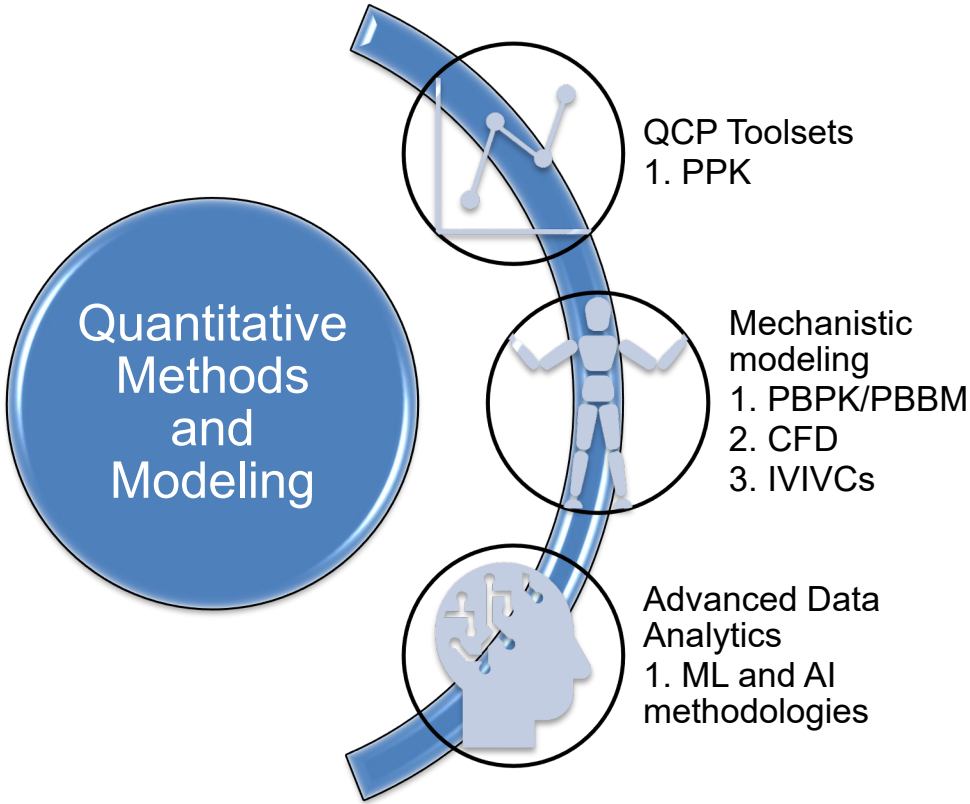
What is an MMF?

MMFs support

- MIE approaches

Types of MMFs

- Drug product specific models
- In silico framework for products following the same route of administration
- Modeling methodology or framework for a particular context of use



MMF Webinar[10]

QCP: quantitative clinical pharmacology, PBBM: physiological biopharmaceutics modeling, IVIVC: in vitro in vivo correlation, ML: machine learning, AI: artificial intelligence

MMF Facts

- Only assessed by FDA when referenced in a regulatory application.
- An MMF is reassessed with every application that references it according to its context of use.
- There is no requirement to file an MMF when including a model with an application.
- The owner may update the MMF at any time.
- There may be multiple MMFs for the same regulatory purpose.

Slide adapted from MMF Webinar,[10] Fang et al.,[11] and Zhao et al.[12]

Why Submit an MMF?

- Public listing of submitted MMFs (titles) promotes awareness within the industry
- Assist smaller firms with obtaining benefits of modeling
- Promote model standardization and acceptance
- Facilitate model re-use
- Accelerate regulatory assessment time and consistency
- Support further model advancements

Slide adapted from Zhao et al.[12]

Two Potential MMF Applications for OIDPs

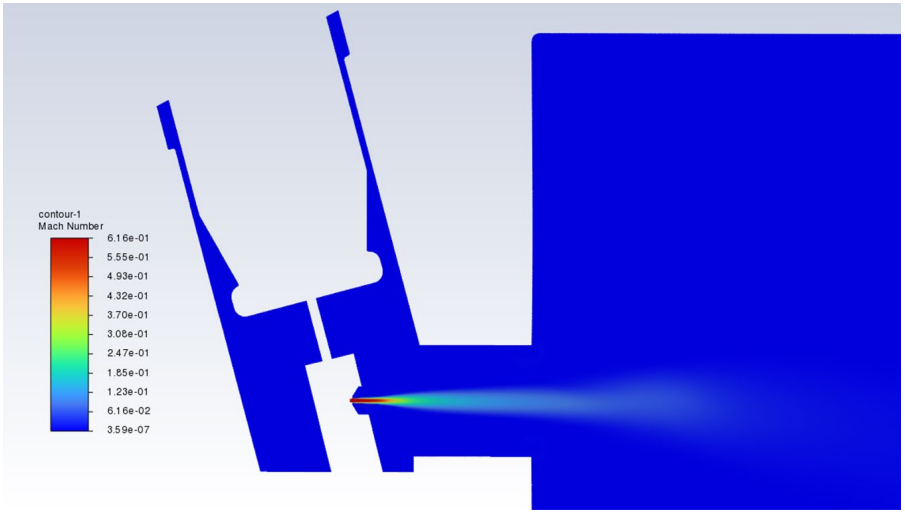
1. Regional deposition CFD or semi-empirical model for a given device type (i.e., MDI, DPI, or inhalation metered spray) may be re-used for other drug products without need for extensive work to establish model credibility.
2. Inhalation PBPK model for a given active ingredient may be re-used for development of OIDP PBPK model for other drug products that include the same active ingredient.

Example 1: CFD Model for MDIs

- Model purpose: Assess impact of observed differences in realistic APSD data on predicted regional lung deposition.
- Physical models consider thermal energy, species transport, turbulence, transient effects, and compressibility effects.
- Model inputs include realistic APSD and plume geometry in vitro data.
- Mesh and time step sensitivity is established.
- Model validated using in vivo nuclear imaging data for multiple drug products.

Computer aided design model of fluticasone propionate inhalation metered aerosol and mouth-throat model – internal FDA model.

Example 1: CFD Model for MDIs (cont'd)



Cross section of continuous phase prediction of Mach number for HFA-134a jet during MDI actuation.

- Single human airway geometry (including extrathoracic and lung regions) or set of human airway geometries remains constant across multiple drug product models.
- Considering that model verification and model validation would already be established, only software quality assurance exercises may be needed to support model credibility.
- To be used for another drug product, there would need to be no significant formulation differences such as solution-based vs. suspension-based MDIs or single active ingredient vs. multiple active ingredients.

Example 2: Inhalation PBPK Model

- Model purpose: Describe systemic disposition of the active ingredient following inhalation administration.
- Reusability: May be applicable to any OIDP that includes the same active ingredient.
- Includes PK data or sources from where PK data are acquired, as well as the model files and modeling analysis plan and report.
- Model parameters determined based on PBPK model are included in MMF.

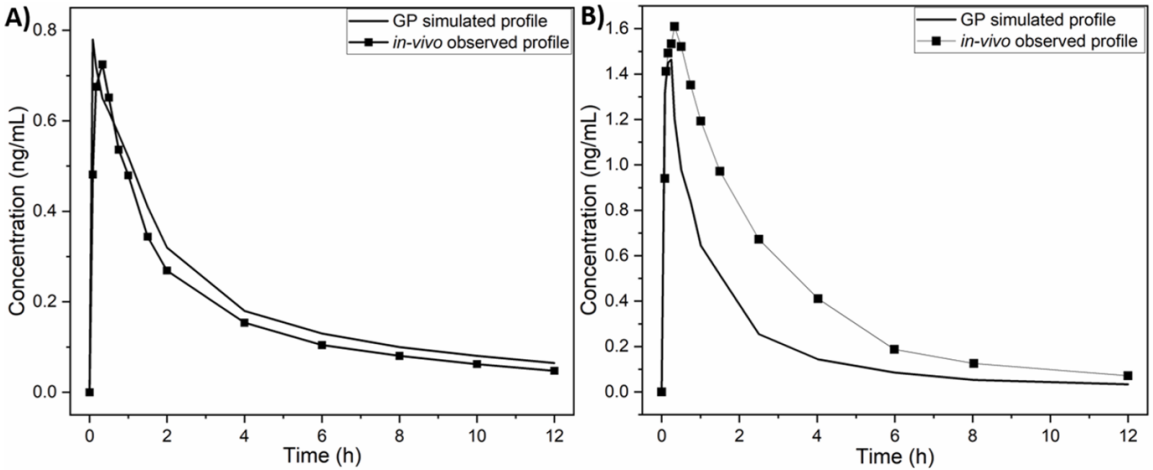


Figure 5 from Radivojev et al.[13] showing predicted (using GastroPlus [GP]) and observed plasma concentration data for a) albuterol sulfate and b) budesonide.

Additional MMF Resources

- Public workshops co-organized by Center for Research on Complex Generics (CRCG) and FDA[14,15]
  - *Best Practices for Utilizing Modeling Approaches to Support Generic Product Development* – October 27-28, 2022
  - *Considerations and Potential Regulatory Applications for a Model Master File* – May 2-3, 2024
- Theme issue in Pharmaceutical Research: FDA Modeling Master File[16]
- March 13, 2025 Webinar: Model Master Files: Advancing Modeling and Simulation in Generic Drug Development and Regulatory Submissions: Slides from Webinar[10]

Conclusions

1. Development and approval of generic OIDPs may be supported by MIE approaches, which include modeling along with all available information.

2. The use of MMFs is expected to further promote the use of modeling, improve access to the benefits of modeling, and facilitate model re-use, among other benefits.

3. Several case studies relevant to OIDPs were presented to illustrate potential MIE approaches as well as introduce candidates for MMF submission.

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We Are OGD

Ask me why...

"I make sure that the **generic** drug and the **brand** drug work **the same**."

"The first time I was able to buy my son's inhaler as a generic and realized that my out of pocket dropped, I cried and was able to breathe a sigh of relief."

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