PBPK Modeling for Oral Drug Products

Regulatory Expectations and Recommendations for Generic Drug Submissions

Arindom Pal, PhD | Pharmacokineticist
Division of Quantitative Methods and Modeling (DQMM) | ORS | OGD | CDER
AGDD Workshop: Leveraging Model-Integrated Evidence (MIE) | August 13, 2026

Disclaimer

The views expressed are those of the presenter and do not necessarily represent the official position of the U.S. Food and Drug Administration.

Outline

- Overview of PBPK for Oral Generic Drug Products
- FDA expectation in model submissions
- Common deficiencies in model submissions
- Case examples
- Key takeaways

Overview: PBPK for Oral Generic Drug Products

- **The Challenge with Traditional Bioequivalence Studies**
  - In vivo PK studies are the gold standard, but can be-
    - Resource-intensive (e.g., studies in patients, parallel design, >2 periods in a crossover design due to NTI or highly variable RLD)
    - Ethically complex (e.g., studies which cannot be conducted in healthy subjects due to safety concern)
    - Challenging for complex formulations (e.g., Polymeric/non-absorbed drugs, locally acting GI drugs)
- **The PBPK Opportunity**
  - Physiologically-based pharmacokinetic (PBPK) modeling and Physiologically-based biopharmaceutics modeling (PBBM) can mechanistically integrate drug properties + GI physiology + formulation inputs (e.g., dissolution) to simulate absorption and systemic exposure
- **Current status**
  - OGD has observed a significant increase in PBPK submissions within ANDAs applications
  - Clear regulatory expectations are essential to ensure submissions are scientifically sound and review-ready

Overview: PBPK for Oral Generic Drug Products

- **Applications of Oral PBPK in ANDA Submissions (Oral Products)**

No.	Applications	Notes (examples)
1	**Bioequivalence Assessment**	Virtual BE simulations
2	**Biowaiver Justification**	BCS-based biowaivers
3	**Dissolution-Related Assessment**	Identify bio-discriminatory/biopredictive dissolution, dissolution safe space determination
4	**Impact of Food on BE**	Support waiver of in vivo fed bioequivalence study
5	**Formulation Changes/Reformulation Justification**	Support BE waiver following excipient modifications (e.g., ascorbic acid addition)
6	**Population Extrapolation**	Male-only to general population, Healthy subjects to patients
7	**Impact of Acid Reducing Agents on BE**	Support waiver of in vivo fasting BE study with Proton Pump Inhibitor (PPI)
8	**Alcohol Dose Dumping Assessment**	Justify the dissimilarity of in vitro dissolution in medium with alcohol
9	**Particle Size Distribution (PSD) Specifications**	Set three-tier PSD acceptance criteria

Ref: Fang Wu et al. Regulatory Experience of Using Totality of Evidence Including PBPK Modelling to Support Alternative BE Approaches. 2026 May FDA-CRCG Generic Oral Product Workshop

Overview: PBPK for Oral Generic Drug Products

- **Key FDA Guidance**
  - PBPK Analyses — Format and Content Guidance for Industry (**August 2018**): Recommended format and content for PBPK submissions in all application types including ANDAs [1]
  - The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls Guidance for Industry (**October 2020**) [2]: Specific guidance for oral biopharmaceutics applications
- **Other Guidance:**
  - ICH M15: International framework for Model-Informed Drug Development (MIDD) evidence — relevant for ANDA sponsors operating globally [3]
  - Relevant Product Specific Guidance (PSG): some now reference PBPK as acceptable supporting evidence (e.g., Olaparib tablet PSG, revised Nov 2024 [4])
- **Important Regulatory Pathways**
  - Model-Integrated Evidence (MIE) Industry Meeting Pilot Between FDA and Generic Drug Applicants (Oct 2023) [5]: provide industry with opportunities for early and focused interactions for science-driven topics using model-integrated evidence approaches for BE establishment
  - Model Master File — MMF Docket (Jan 2025): PBPK models can be submitted separately from ANDAs through the Type V DMF pathway, enabling reuse across submissions

1. https://www.fda.gov/media/101469/download
2. https://www.fda.gov/media/142500/download
3. https://www.fda.gov/media/184747/download
4. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_208558.pdf
5. Model-Integrated Evidence (MIE) Industry Meeting Pilot Between FDA and Generic Drug Applicants | FDA

Model submission: FDA Expectations and submission checklist

- ✅ **Clearly defined scientific question and regulatory purpose**
- ✅ **Drug & Formulation Inputs**
  - Physicochemical data
  - Multi-pH/biorelevant/biopredictive dissolution data for both generic and RLD as formulation inputs
  - For poorly soluble drugs: particle size distribution, supersaturation data (amorphous solid dispersions)
- ✅ **Model Selection**
  - Justify absorption model selection
  - Validate systemic model with IV/oral solution PK data from RLD before incorporating formulation-specific inputs
- ✅ **Verification & Validation**
  - Verification and validation depends on the context of use (e.g., PBPK modeling to replace pivotal PK BE study would have higher expectation standards)
  - Validate model using independent datasets (which are not used in parameter optimization)
  - Predict RLD PK profiles (AUC, Cmax, Tmax) using observed data across multiple conditions (fasting/fed, strengths, populations)
  - Acceptance criterion: predicted vs. observed within ±20% prediction error
  - Demonstrate bio-discriminatory capability: model can identify non-BE formulation or batch

Model submission: FDA Expectations and submission checklist

- ✅ **Sensitivity & Uncertainty Analysis**
  - Identify parameters driving predictions (local/global sensitivity); quantify uncertainty bounds on simulated PK endpoints
  - Population matching: align virtual population age, weight, BMI, sex to the actual BE study demographics
- ✅ **Submit all model files (not only results) for FDA independent verification**
- ✅ **All assumptions, parameter sources, software version, and deviations documented transparently**

General Regulatory Considerations for Model Submission

- **Clearly state the Question of Interest** — explicitly define what the model is intended to answer
- **Define the Context of Use** — provide a concise description of the model, its role and scope, the data used to build it, and any additional supporting evidence.
- **Rate and justify Model Influence** — assess whether model outcomes are the sole or partial basis for the decision (low/medium/high), and justify the rating.
- **Rate and justify Consequence of Wrong Decision** — consider both severity and likelihood of a wrong decision impacting patient safety or efficacy.
- **Derive and justify Model Risk** — combine model influence and consequence of wrong decision into an overall risk rating (low/medium/high) that drives the level of model evaluation.
- **Rate and justify Model Impact** — justify how much the proposed strategy deviates from existing regulatory standards or expectations.

Common Deficiencies in PBPK Submissions: What to Avoid

- ❌ Insufficient Model Validation: Model validated only to training data; no independent validation dataset used — FDA cannot assess predictive performance
- ❌ Missing Sensitivity/Uncertainty Analysis: No identification of which parameters most influence predictions; no quantification of uncertainty bounds on simulated PK
- ❌ Poor Dissolution Characterization: Single-pH dissolution only; no biorelevant data; no comparative RLD vs. generic dissolution profiles provided
- ❌ Unjustified Model Choices: No rationale for the selection of absorption model type, or parameter values
- ❌ Overpromising the Model: Claiming PBPK results replace a BE study without the support of totality of the evidence
- ❌ Incomplete Reporting: Missing software version, parameter provenance, simulation settings — results are not reproducible
- ❌ Failure to Submit Model Files: FDA expects actual model files (not just results tables) for independent verification and reproducibility

Common Deficiencies in PBPK Submissions: FDA Findings (2012–2026)

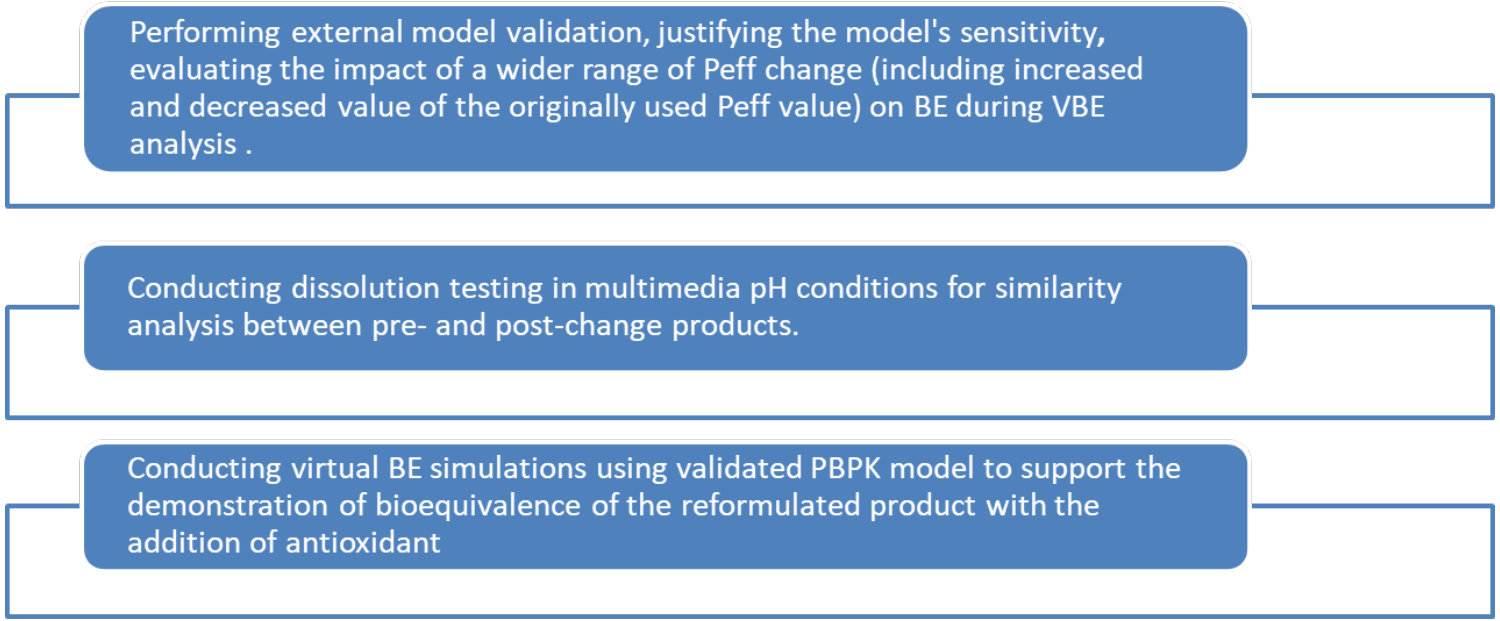
- **Overall: 52% Adequate | 48% Inadequate — Based on review of regulatory cases from 2012-2026**
  - Inadequate models resulted in Complete Response Letters or Rejection
- **Deficiency 1 — Inadequate Model Validation (40% of cases)**
  - Same dataset used for both model building AND 'validation' — no independent test of predictive performance
  - No testing with non-BE batches/formulations → model cannot distinguish BE from non-BE (false confidence)
- **Deficiency 2 — Non-Biopredictive Dissolution Inputs (30% of cases)**
  - Quality Control (QC) media (e.g., pH 6.8 phosphate buffer) dissoltuion used as sole model input — may not be physiologically representative
  - Fed-state predictions made using fasting-state dissolution data | Fasting acid-labile drugs require FaSSGF (pH 1.6)
- **Deficiency 3 — Model Insensitivity to Formulation Differences (20% of cases)**
  - Z-factor (dissolution scalar) in plateau region — changes in dissolution cause <5% change in predicted PK
  - IVIVC built on formulations with similar dissolution rates; extrapolation outside validated range
- **Deficiency 4 — Population Mismatch in Virtual Simulations (10% of cases)**
  - Wrong demographics (age, weight, BMI) used vs. actual BE study population — predictions off by >20%
  - Patient population PK data used with healthy-subject physiology model without justification or acknowledgment

Case Example 1: Use of PBPK to justify reformulation for Nitrosamine Control

- **RLD: Cymbalta (Duloxetine) DR Capsules 20/30/60 mg | SUPAC-MR Level 3 Change**
- **The Challenge**
  - Duloxetine HCl has acid instability and hence formulated as enteric-coated DR capsule. It has BCS Class III properties (high solubility, low-to-moderate permeability)
  - Addition of antioxidant as stabilizer to control nitrosoduloxetine impurity — constitutes a post-approval formulation change
  - Applicant proposed PBPK + VBE as alternative to conducting a new in vivo fasting BE study for the reformulated product

Case Example 1: Use of PBPK to justify reformulation for Nitrosamine Control

- **Key Findings and totality of evidence recommendation**
  - FDA reviewed the applicant's modeling and simulations, found several deficiencies on model development, validation and the sensitivity of the model for detecting non-BE scenarios, and provided recommendations shown below.



Case Example 1: Use of PBPK to justify reformulation for Nitrosamine Control

- **Totality of evidence provided by the applicant (in response to FDA's recommendation):**
  - Biopharmaceutic Classification System (BCS) information of drug substance and release mechanism of the product
  - Applicant conducted multi-pH dissolution testing that demonstrated similarity between pre- and post-change products
  - Applicant performed external model validation using additional formulation data. Conducted sensitivity analyses over a wider range of permeability values and demonstrated model sensitivity to detect theoretical non-bioequivalent scenarios.
  - Virtual bioequivalence simulations using validated PBPK showed BE of reformulated product compared to RLD for higher strength.

Case Example 1: Use of PBPK to justify reformulation for Nitrosamine Control

- **Regulatory Outcome & Lessons Learned**
  - Modeling data support the assessment that the added antioxidant presents "low risk for non-bioequivalence" based on virtual bioequivalence simulations for higher strength and totality of evidence.
  - The totality of evidence, including analysis of BCS information of drug substance, release mechanism of drug product, dissolution comparative data, and PBPK modeling and virtual BE simulations, support not conducting/waive the in vivo BE study for the reformulated duloxetine HCl delayed release capsules.
  - First-ever PBPK-based regulatory approval of a nitrosamine reformulation case

Case Example 2: PBPK absorption model in Assessing the Impact of Particle Size Distribution (PSD) on BE

RLD: Absorica (Isotretinoin) Capsule, 10, 20, 30 mg

Background

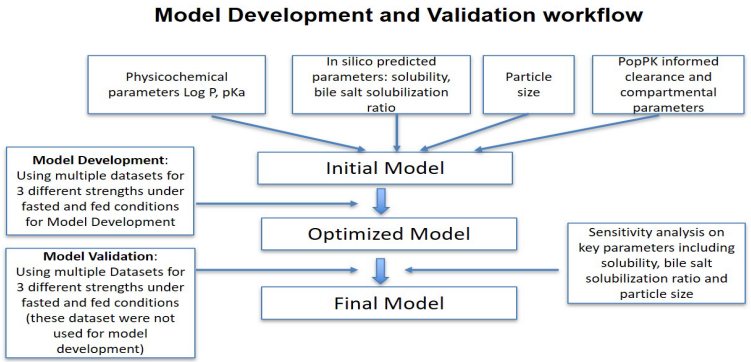
- For a capsule product, PK parameters, e.g., Cmax and AUC were found to be sensitive to changes in mean particle size of the drug Isotretinoin under fasting condition.
- In the initial submission , FDA identified inconsistency in PK parameters between the pilot and pivotal studies for the reference listed drug (RLD), which may be due to the difference in subject populations of the two studies.
- It was also identified that different batches being used in the pivotal and pilot studies under fasting conditions, which may also lead to the inconsistency in PK parameters due to the batch-to-batch variations, e.g., difference in PSD.

Recommendation from FDA

- FDA recommended the applicant to include PSD data from available batches (both pilot and pivotal) using relevant in vivo PK data for PSD model building, and to support 3 tier PSD specification setting.
- A more mechanistic model to link particle size distribution with in vivo PK data was recommended.

Case Example 2: PBPK absorption model in Assessing the Impact of Particle Size Distribution (PSD) on BE

- **Applicant's response to FDA recommendations**
  - The Applicant submitted a mechanistic absorption model to link PSD with in vivo PK data.
  - Model application: Simulation using PBPK model with fixed D50 and changed D10 and D90



Formulation	D10	D50	D90	Test/Reference Ratios			BE
				Cmax	AUCt	AUC inf	
Reference	X10	X50	X90				
Test 1	X10--	X50	X90--	107	105	106	Pass
Test 2	X10-	X50	X90-	100	98.3	98.2	Pass
Test 3	X10+	X50	X90+	81.2	81.5	81.3	Pass
Test 4	X10++	X50	X90++	80.3	79.8	80.3	Fail

Case Example 2: PBPK absorption model in Assessing the Impact of Particle Size Distribution (PSD) on BE

- **Regulatory Outcome & Lessons Learned**
  - PBPK modeling and simulation suggested that the test vs reference PK metrics showed a low risk of non-BE when D90 changed over a wide range with a certain fixed value of D50 for all strengths.
  - The modeling results support a satisfactory BE assessment of this generic product and setting a clinically relevant 3 tier PSD specification.

The Path Forward & Key Takeaways

- **Building Successful PBPK Submissions**
  - ✅ Duloxetine: PBPK + VBE supported nitrosamine reformulation waiver — avoiding unnecessary in vivo study
  - ✅ Isotretinoin: The mechanistic PBPK modeling with PSD input supported a satisfactory BE assessment, and setting a clinically relevant 3 tier PSD specification.
- **OGD's Commitment to Industry**
  - FDA supports scientifically rigorous, MIE-based approaches to generic drug development
  - PSGs are being updated to incorporate PBPK supportive evidence options
  - Pre-ANDA/MIE Pilot Program offers direct dialogue before ANDA submission
- **Top Recommendations for Applicants**
  - Engage early via pre-ANDA or MIE Pilot Program meeting — align on strategy before full model development
  - Build model rigorously: independent validation, biopredictive dissolution inputs, non-BE batch testing, population matching
  - Submit completely: model files + datasets + VBE design + PSA — not just results tables
  - A well-validated model may support multiple ANDAs via the Model Master File (MMF) pathway

Acknowledgments

FDA/CDER/OGD/ORS/Division of Quantitative Methods and Modeling

Dr. Fang Wu, Dr. Yi-Hsien Cheng, Dr. Raqeeb Jamil (previous ORISE fellow), Dr. Nitin Charbe

Dr. Andrew Babiskin, Dr. Lanyan Fang

FDA/CDER/OGD/ORS Leadership

Dr. Robert Lionberger and Dr. Lei K. Zhang

AGDD, SBIA organizing committee