Model-Integrated Evidence in ANDA Submissions: Regulatory Expectations, Frequent Pitfalls, and How to Avoid Them

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Advancing Generic Drug Development: Leveraging Model-Integrated Evidence in the Development & Approval of Complex Generic Drugs

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Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Outline

Overview of Model-Integrated Evidence (MIE) in Generic Drugs

- MIE submissions in pre- and post-approval submissions of abbreviated new drug applications (ANDAs)

Regulatory Expectations

- Model development
- Model verification and validation
- Simulation
- Submission documentation

Common Pitfalls, and Strategies to Avoid Them

- Survey of MIE submissions in ANDAs (2021-2025)
- Frequently observed deficiencies and strategies to avoid them

MIE Submissions for Generic Drugs

Pre-Submission (Pre-ANDA)

- **Submission Route**: Pre-ANDA or MIE Industry Meeting Pilot Program
- **Examples**:
  - ✓ Alternative in vivo study design (e.g., crossover study without washout)
  - ✓ Biowaiver request

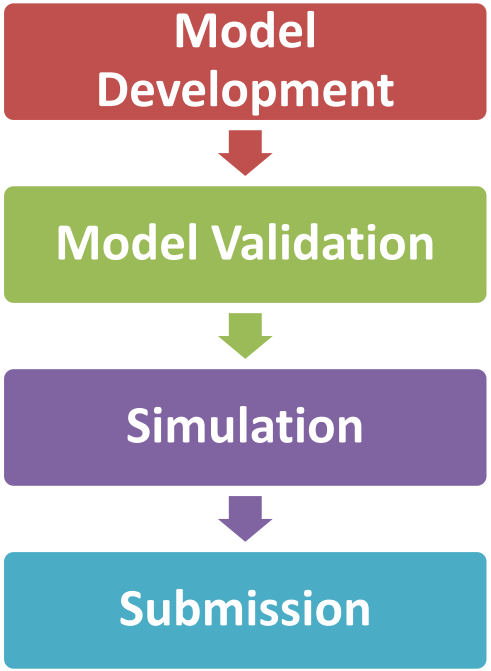
Pre-Approval Phase

- **Submission Route**: ANDA submission or Deficiency letter response
- **Examples**:
  - ✓ Reduced sampling
  - ✓ Shorter study duration
  - ✓ Addressing concerns in enrolled populations

Post-Approval Phase

- **Submission Route**: Supplement submission
- **Examples**:
  - ✓ Post-approval changes in drug products
  - ✓ Reformulation to address nitrosamine impurities

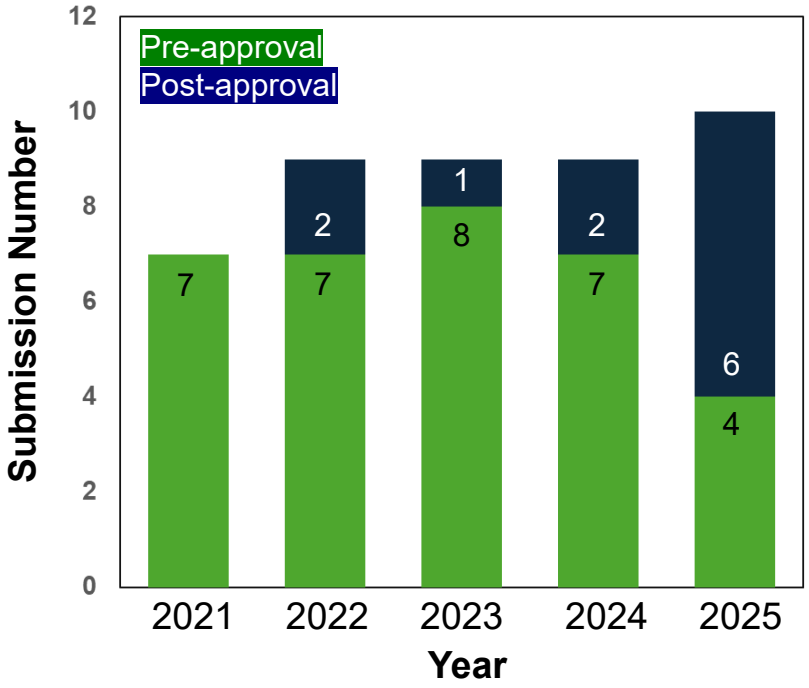
Regulatory Expectations



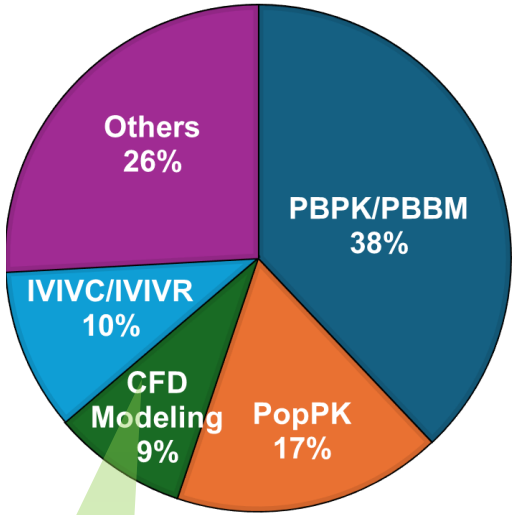
Phase	Regulatory Expectations
• Conceptual modeling • Data collection • Model building	• Model is fit for its intended regulatory **purpose** and is scientifically justified. • **Dataset** for model development is adequate. • All **assumptions** are explicitly stated. • Mechanistic rationale provided for **model inputs**.
• Verification • Validation • Sensitivity analysis	• **Sensitivity analysis** performed for key parameters. • Validation dataset is **independent** from development dataset. • Software version and computational platform are documented and appropriately **qualified**.
• Virtual bioequivalence (BE) testing	• **Uncertainty** is quantified and reported.
• Submission in the ANDA packages	• **Complete documentations** for model development, verification/validation, and simulation are included. • **Model** projects and results are submitted.

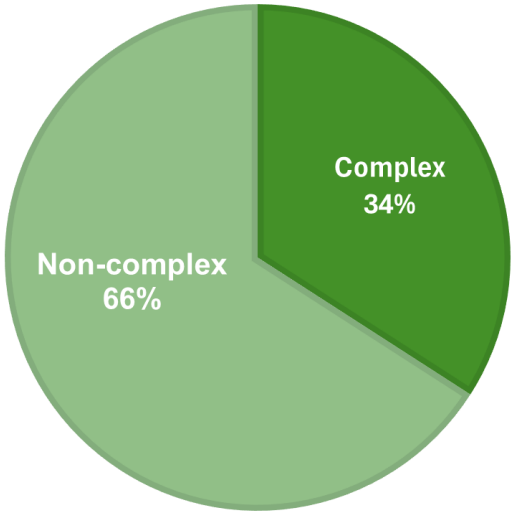
Note: Some regulatory expectations may not be applicable, depending on the model type.

MIE Submission Survey for Generic Drugs



In total 44 pre- and post-approval ANDAs

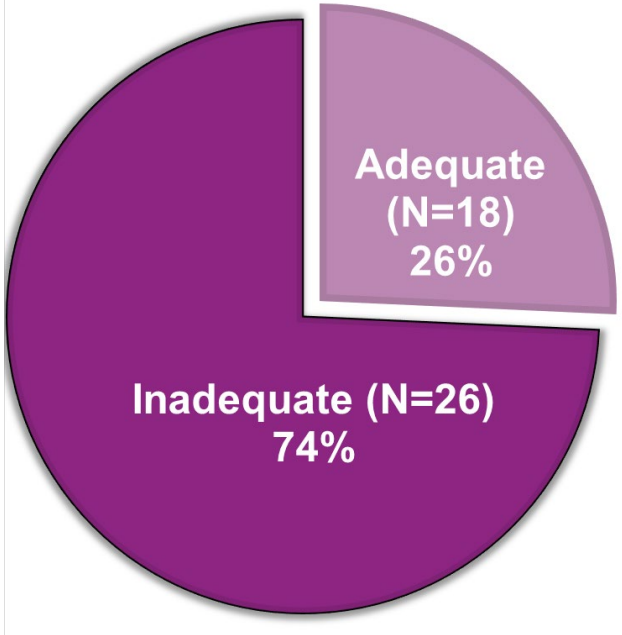




PSG-recommended

IVIVC/R: in vitro-in vivo correlation or relationship
CFD: computational fluid dynamics
PopPK: population pharmacokinetic modeling
PBPK: physiologically based pharmacokinetic modeling
PBBM: physiologically based biopharmaceutics modeling
Others: steady-state simulation and dose-response model

MIE Submission Survey for Generic Drugs



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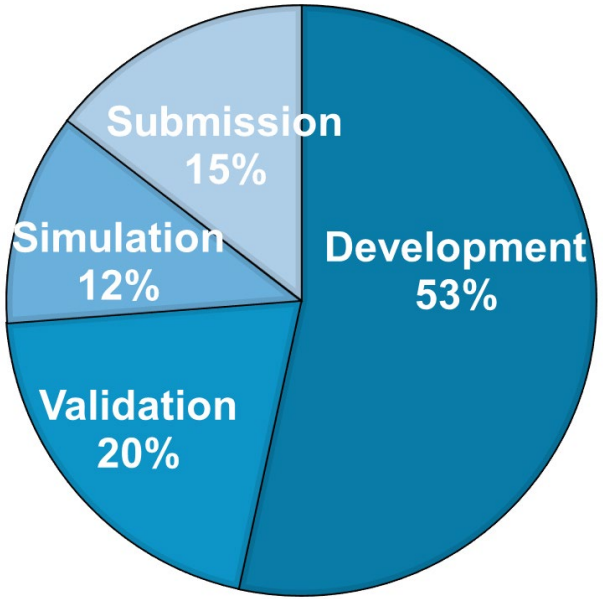
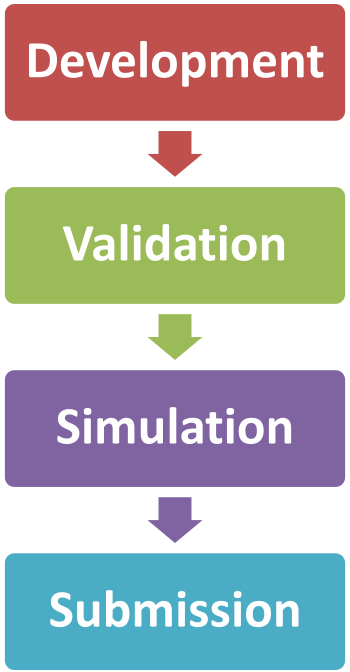


In total 88 Deficiencies

Observed Submission Gaps



Common Mistakes

- **Model scope** is vague or not linked to specific regulatory question.
- **Dataset** for model development is insufficient or inadequately justified.
- **Assumptions** are implicit or embedded only in the model code.
- **Model inputs** are selected without justification or sourced from non-comparable populations.

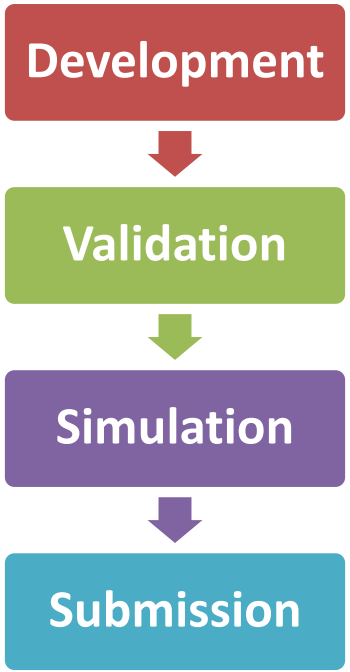
- **Sensitivity analysis** omitted or limited to single-parameter perturbations.
- Same dataset used for both building and validating the model.
- Validation dataset is not **independent** of the development dataset.
- Software validation documentation **absent** or outdated.

- Only nominal (**best-case**) predictions reported.

- Only a portion of the required **reports** for model development/validation/ simulation are submitted.
- Model files and results are **omitted,** or partial model files are submitted.

Note: The common mistakes outlined above are compiled from those observed across multiple types of modeling.

Common Pitfalls and Strategies to Avoid Them



Specific Examples	How to Avoid Them
1. Model built without **verifying** compound-specific input parameters. 2. **Model inputs** are from non-physiologically relevant studies.	1. Define the regulatory **purpose** first. 2. Do not rely solely on default software parameters without scientific justification. 3. **Justify** every parameter individually. 4. Document the **source** of each input parameter.
1. Incomplete model validation. 2. Internal validation only. 3. No **pre-defined** acceptance criteria.	1. Always use **independent external** datasets for validation. 2. Pre-specify all acceptance criteria as per the relevant regulatory **guidances**.
1. Incomplete uncertainty report.	1. Characterize and report **uncertainty** associated with key model parameters and simulation outcomes.
1. **Model code** or structure not provided. 2. Only outputs submitted.	1. **Submit executable model files**, annotated code where applicable, and parameter tables, and sufficient documentation to reproduce the analyses.

Note: The examples outlined above are compiled from those observed across multiple types of modeling.

Summary

- **Regulatory expectations**: Models must be appropriately verified and validated for the intended context of use and submitted with complete documentation.
- **Survey findings**: MIE submissions over the past 5 years revealed frequently identified deficiencies across all stages.
- **Common gaps**: Key deficiencies include vague model scope, unjustified inputs, internal-only validation, and incomplete submission packages.
- **Early interaction with FDA** can facilitate discussion of the proposed modeling strategy and help reduce avoidable review deficiencies.

Resources

- ICH M15 General Principles for Model-Informed Drug Development (**Jun 2026**)
- Population Pharmacokinetics (**Feb 2022**)
- Physiologically Based Pharmacokinetic Analyses-Format and Content (**Sep 2018**)
- The Use of Physiologically Based Pharmacokinetic Analyses-Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls (**Sep 2020**)
- Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (**Sep 1997**)

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