SimulationsPlus

Why Mechanistic Modeling Has Become the Preferred Framework for Modern Generic Development

When the question is mechanism, deconvolution estimates. **PBBM explains.**

Classical deconvolution methods (including Wagner-Nelson, Loo-Riegelman, and numerical deconvolution) were developed for simple products, such as immediate-release formulations with linear pharmacokinetics and high permeability.

For modern generic development involving BCS II–IV compounds PBBM provides the regulatory accepted, mechanistic framework needed to understand, predict, and justify product performance.

This includes:

- Modified-release formulations
- Fed-state effects
- pH-dependent solubility
- Nonlinear PK, oncology products
- Nitrosamine reformulations
- Discontinued reference products

WHY THIS MATTERS

PBBM supports biowaivers, formulation bridging, dissolution safe-space development, virtual bioequivalence assessments, manufacturing change justification, and risk reduction strategies that are difficult or sometimes impossible to support using classical deconvolution alone.

SCIENTIFIC PROOF POINTS

- Linear PK is a core deconvolution assumption, often violated in practice.
- Wagner-Nelson performance is highly sensitive to absorption rate.
- Dissolution and absorption cannot be independently separated using traditional deconvolution.
- First-pass metabolism sometimes requires mechanistic representation.
- Regulatory utilization of PBPK/PBBM continues to grow.
- ICH M13A explicitly recognizes PBPK/PBBM in specific scenarios.
- FDA links conventional deconvolution's limitations to low IVIVC success rates. (Article)

	Classical Deconvolution (WN/LR/Numerical)	PBBM
PK linearity	Assumes linear PK — "often violated" in practice.	Mechanistic; no linearity assumption required.
Dissolution vs. absorption	Typically can't separate them — only the combined process is estimated.	Resolves release, dissolution, and permeation as distinct steps.
First-pass metabolism	Lumps gut wall/hepatic metabolism into the same combined signal — can misattribute a metabolism effect to a dissolution/absorption effect.	Models gut-wall permeability, gut wall metabolism, and hepatic clearance separately.
Low-permeability drugs	Wagner-Nelson systematically underperforms (measures fraction absorbed, not fraction dissolved).	Handles low-permeability, complex-absorption drugs natively.
Track record	Literature success is largely selection bias — 27 surveyed IVIVC papers were almost all high-permeability BCS I/II, exactly where WN's weaknesses don't show.	Validated across BCS classes, fed/fasted states, and special populations (pediatric, complex generics).
Regulatory trajectory	No dedicated FDA guidance; treated as legacy/default method.	Dedicated FDA draft guidance (2020); named in ICH M13A; 6 global regulators aligned (FDA, EMA, MHRA, Health Canada, ANVISA, PMDA).
Submission outcomes	Only ~40% of IVIVC submissions reviewed by FDA (2008-2015) were accepted. (Article)	PBPK-supported SUPAC submissions up from 5% → 36% since the 2020 FDA's draft guidance published.
Use-case ceiling	Biowaivers, bridging, and dissolution safe-space arguments structurally out of reach.	Explicitly supports biowaivers, formulation bridging, fed BE waivers, dissolution safe space.

SUMMARY

For simple products, classical deconvolution may be sufficient. For complex generics and modern regulatory flexibility pathways, mechanistic PBBM provides a more informative and decision-relevant framework.

Full References

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2. ICH M13A Guideline (2024).
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4. Current State and New Horizons in PBBM, Mol. Pharm. PMC11707736
5. AAPS J industry perspective on PBPK absorption modeling: DOI: 10.1208/s12248-019-0292-3
6. Deconvolution and IVIVC: Rate-Limiting Conditions: PMC4779109
7. Physiologically Relevant IVIVC for Sildenafil: PMC6631943
8. Jones CR et al. Gut Wall Metabolism. AAPS J. 2016;18(3):589-604. PMC5256607
9. From In Vivo Predictive Dissolution to Virtual Bioequivalence: A GastroPlus-Driven Framework for Generic Candesartan Cilexetil Tablets. Pharmaceutics. 2025;18(4):562
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