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PBPK Modeling & MIDD: Simcyp vs GastroPlus & FDA NAMs

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Executive Summary

This comprehensive report examines the current and emerging landscape (as of 2026) of physiologically based pharmacokinetic (PBPK) modeling and model-informed drug development (MIDD), with a focus on comparing two leading software platforms (Simcyp™ and GastroPlus®), regulatory acceptance by bodies like the FDA, and the global shift towards **animal-free New Approach Methodologies (NAMs)**. PBPK/PBBM models integrate physiology, formulation, and drug data to predict human pharmacokinetics and support decisions in drug discovery and development (www.sciencedirect.com) (www.mdpi.com). Simcyp and GastroPlus are the predominant commercial PBPK platforms used in industry and submissions (pmc.ncbi.nlm.nih.gov). Published evaluations report broadly comparable predictive accuracy for these platforms, though differences emerge in specific scenarios (e.g. GastroPlus often better predicts absorption for poorly absorbed drugs (suppr.wilddata.cn)). Regulatory agencies are increasingly incorporating PBPK/MIDD into guidance and review: for example, the FDA's final guidance *"M15 General Principles for Model-Informed Drug Development"* (which finalizes the draft issued in December 2024) offers a harmonized framework for model-based evidence (www.fda.gov). Vendor-published case studies describe potential cost and time savings from PBPK-based approaches (e.g. Simulations Plus reports a ~12–45× return on investment for one GastroPlus-based virtual BE study (www.simulations-plus.com); Certara reports an estimated saving of ~$0.5M for a Simcyp model applied to a bioequivalence question (www.certara.com)). These figures are vendor-reported and have not been independently verified.

Concurrently, the FDA and international regulators are spearheading a **paradigm shift** to reduce animal testing in drug development. The 2022 FDA Modernization Act formally removed the requirement that animal studies be the sole route to human trials (www.mdpi.com). The FDA's 2025–2026 roadmap explicitly phases out certain animal tests (starting with biologics) and encourages validated alternatives "including cell-based

assays [and] computational models" (www.mdpi.com). The FDA's NAM program (April 2026) emphasizes replacing animal safety tests with in vitro, organ-on-chip, AI/machine-learning, and PBPK tools, citing that over 90% of drugs safe in animals fail in humans (www.fda.gov). These trends underscore a **synergistic future** where in silico PBPK models (like Simcyp/GastroPlus) and NAMs together drive human-relevant, efficient, and ethical drug development. This report synthesizes historical context, current tools and practices, detailed comparative analyses, case studies, and future implications, all supported by extensive literature and regulatory references.

Introduction and Background

Physiologically Based Pharmacokinetic (PBPK) Modeling and MIDD: PBPK modeling represents the body as interconnected compartments (organs/tissues) with drug-specific and system-specific parameters governing ADME (Absorption, Distribution, Metabolism, Elimination) (www.sciencedirect.com) (pmc.ncbi.nlm.nih.gov). These mechanistic models integrate diverse data (physiology, chemistry, formulation properties, etc.) to simulate drug concentration–time profiles in humans or animal species (www.sciencedirect.com) (pmc.ncbi.nlm.nih.gov). PBPK is a cornerstone of **Model-Informed Drug Development (MIDD)**, a paradigm in which quantitative models (PBPK, population PK, exposure–response, etc.) inform critical decisions across drug discovery and development (www.fda.gov) (pmc.ncbi.nlm.nih.gov). MIDD aims to leverage all available data sources to reduce uncertainty – for example, optimizing first-in-human dose, predicting complex drug–drug interactions (DDIs), guiding pediatric dosing, and supporting biowaivers or formulation changes without de novo trials (www.sciencedirect.com) (www.fda.gov).

For over two decades, PBPK has matured from an academic research tool to an integral part of drug R&D. Its use is now widespread in industry, regulatory agencies, and academia (www.sciencedirect.com) (pmc.ncbi.nlm.nih.gov). Early adopters showed how PBPK could quantitatively link in vitro and animal data to human outcomes. Today, PBPK applications include predicting oral drug absorption (so-called physiologically based biopharmaceutics modeling, PBBM), extrapolating child dosing from adult data, simulating DDIs, and replacing certain clinical or animal tests via **in silico** evidence. Notably, major health authorities "increasingly [accept] PBPK data in drug submissions" (pmc.ncbi.nlm.nih.gov) under various contexts. For example, FDA and EMA guidance recognize PBPK for predicting DDI risk, informing pediatric and special-population dosing, and supporting certain post-approval manufacturing changes (pmc.ncbi.nlm.nih.gov). MIDD has even been codified in legislation: FDA's 2017 reauthorization (part of PDUFA VI) instituted a dedicated MIDD pilot program to explore and standardize model-based approaches (www.fda.gov).

NAM (New Approach Methodologies) and the Animal-Free Shift: Alongside PBPK, another transformative trend is the move away from animal-based testing. *New Approach Methodologies (NAMs)* encompass any innovative methods that provide human-relevant data without animal use (www.fda.gov). This includes advanced cell and tissue culture systems (organoids, "organ-on-chip"), omics-based assays, (Q)SAR models, real-world evidence, and computational models like PBPK itself. The 3Rs principle (Replacement, Reduction, Refinement of animal use) has gained powerful momentum – if the predictive power of NAMs is high, they offer a "more humane and human-relevant" drug development pathway (www.fda.gov) (www.mdpi.com). A landmark U.S. law, the **FDA Modernization Act 2.0 (Dec 2022)**, explicitly removed the mandate that new drug applications rely solely on animal studies and encouraged validated alternatives (including "in silico"

approaches) when justified (www.mdpi.com). In 2025 the FDA unveiled a roadmap to phase out certain animal tests (starting with monoclonal antibodies) and to streamline NAM data in IND/NDA submissions (www.mdpi.com). By mid-2026, the FDA had issued draft guidance on NAM use in drug development, and publicly reported significant progress: a Year-1 report claims the agency has launched initiatives replacing animal tests with human-relevant methods, noting that *"over 90% of drugs safe in animals fail in humans"* (www.fda.gov). In summary, both the PBPK/MIDD paradigm and the NAM initiative are parts of a larger evolution toward predictive, mechanism-based, and ethically aligned drug development, which is the focus of this report.

Key Concepts: PBPK, PBBM, and Model-Informed Drug Development

Physiologically Based Pharmacokinetics (PBPK): PBPK models are *bottom-up mechanistic* models built from first principles of physiology and chemistry (www.sciencedirect.com) (pmc.ncbi.nlm.nih.gov). They subdivide the body into compartments (e.g. gut segments, liver, kidneys, tissues) and describe drug exchanges using parameters like tissue volumes, blood flows, permeability, enzyme/transporter kinetics, and formulation-specific attributes. By inputting laboratory (in vitro) and animal data, a PBPK model can **predict** human pharmacokinetic (PK) profiles and exposure under various scenarios (different doses, formulations, populations, co-medications, etc.). Complementary to "bottom-up," PBPK may incorporate "middle-out" refinement by fitting to human data when available (www.sciencedirect.com). In silico, a PBPK/PBBM model outputs predictions of PK metrics (C_max, AUC, t_½), absorption fractions, and even tissue exposures that are otherwise unmeasurable.

Physiologically Based Biopharmaceutics Modeling (PBBM): PBBM is a subset of PBPK focused on oral drug absorption and formulation performance (www.sciencedirect.com) (www.mdpi.com). It explicitly models the gastrointestinal (GI) tract (sometimes divided into dozens of segments) and integrates drug dissolution, solubility, permeability, gut metabolism and transporters. PBBM thus can predict how changes in formulation or GI physiology affect drug bioavailability. Regulatory uses include justifying biowaivers or dissolution specification waivers, supporting post-approval changes, and risk assessments of food effects or pH changes (www.mdpi.com).

Model-Informed Drug Development (MIDD): MIDD is a broad framework encompassing any modeling (PBPK, population PK/PD, exposure–response, quantitative systems pharmacology, etc.) used to inform decisions. The goal is to use *all available quantitative information* to guide drug development strategy and regulatory submissions (www.fda.gov) (pmc.ncbi.nlm.nih.gov). MIDD applications span predicting clinical outcomes, designing efficient clinical trials, dose optimization for special populations, and even refining labeling. For instance, PBPK is often employed within a MIDD strategy to predict the impact of an untested drug interaction or to replace a clinical study on dosing in organ impairment. Notably, the FDA's *"Model-Informed Drug Development Pilot Program"* was a major regulatory initiative to accelerate MIDD adoption. This program (part of FDA Reauthorization/PDUFA commitments) provided companies a venue to interact with FDA on modeling plans (www.fda.gov).

By 2025–2026, MIDD has become mainstream: health authorities explicitly encourage its use, and companies routinely submit PBPK and other model-based analyses in NDAs/ANDAs. For example, a 2025 review of Chinese PBPK research noted that *“major health authorities increasingly [accept] PBPK data in drug submissions”* (pmc.ncbi.nlm.nih.gov). Surveys find PBPK is widely used in industry (especially pharma) and even in regulatory risk assessment for non-drug chemicals (pmc.ncbi.nlm.nih.gov). The increasing regulatory acceptance (discussed below) further reinforces that PBPK and MIDD are no longer experimental novelties but integral tools.

Simcyp vs GastroPlus: Platforms for PBPK/PBBM

Among commercial PBPK platforms, **Simcyp™** (Certara) and **GastroPlus®** (Simulations Plus) are the large incumbents. Both provide extensive built-in human physiology libraries and workflows for simulating ADME, but have different emphases and histories.

- **Simcyp PBPK Simulator:** Founded in the U.K. in the early 2000s (later acquired by Certara), Simcyp is a population- and mechanistic-focused PBPK platform. It includes detailed models for human organs and populations (including genetic variability and disease specialities). Simcyp excels at drug–drug interaction (DDI) modeling (extensive CYP and transporter libraries), pediatric and special-population extrapolations (e.g. pregnancy, hepatic/renal impairment), and even preclinical (animal) simulations. The Simcyp platform consists of modular modules: *Simcyp Simulator* for clinical and DDI modeling, *Simcyp Pediatrics* (dose projection for children), and *Simcyp Discovery* (lead optimization and IND planning). It uses multiple best-in-class absorption models (depending on scenario) and has robust enzymatic metabolism models. A recent Certara description touts Simcyp as “the industry leader” with >25 years of iteration and validation (www.certara.com). Simcyp’s outputs include full concentration–time profiles, parameter sensitivities, and virtual population statistics. The software supports scripting and reproducibility, with regular version updates.
- **GastroPlus® (with PBPKPlus™):** GastroPlus, launched in 1998, is a longstanding tool aimed originally at oral drug absorption (hence “Gastro”). It implements the ACAT™ (Advanced Compartmental Absorption and Transit) model, segmenting the GI tract into compartments to simulate disintegration, dissolution, and permeation, with a mechanistic diffusion-layer model for drug absorption. In 2020 Simulations Plus introduced *PBPKPlus*™, integrating full PBPK capability into GastroPlus, building on its absorption core. GastroPlus also includes tools for IV and transdermal administration, and a DDI module that can handle competitive and time-dependent inhibition scenarios (gastroplus.slp-software.com). It has modules for population variation and can run batch (population) simulations (recently called **GPX™** for high-throughput simulations). GastroPlus is widely advertised to support formulation optimization (e.g. particle size, dissolution), formulation bridging, virtual bioequivalence trials, and linking to pharmacodynamics.

In practice, **both platforms are widely used for regulatory submissions**. The ABPI/MHRA review in 2015 noted that industry's main PBPK tools used in clinical pharmacology filings are "GastroPlus, PK-Sim, and Simcyp" (pmc.ncbi.nlm.nih.gov). In China, GastroPlus and Simcyp "remain popular" within the pharmaceutical industry (pmc.ncbi.nlm.nih.gov) (though PK-Sim, an open-source alternative, is growing). Both vendors publish case studies applying their tools to bioequivalence and biopharmaceutics questions: for example, Certara describes a Simcyp PBPK model applied to a manufacturing-site bioequivalence question, with an estimated saving of ~$0.5M (www.certara.com), and Simulations Plus describes GastroPlus-based work on dissolution specifications and virtual BE studies (www.simulations-plus.com). These are vendor-authored accounts; outcomes and savings are vendor-reported and not independently verified.

Nonetheless, the tools do differ in emphasis. **Simcyp** tends to be favored for high-level DDI and systemic population modeling; it has integrated genetic and ethnic variability databases and is renowned for its advanced enzyme/transporter models. **GastroPlus** tends to be favored for detailed GI absorption and formulation work; its ACAT model can incorporate sophisticated dissolution and transporter interplay. In practice, many groups use both: often GastroPlus for especially formulation-driven questions and Simcyp for metabolism/interactions. Table 1 (below) summarizes key comparative features of the two platforms.

Feature	Simcyp® Simulator (Certara)	GastroPlus® (Simulations Plus)
Primary Focus	Whole-body PBPK for drugs/physiology/PD; especially DDI, special populations (pediatric, hepatic/renal impairment, pharmacogenomics).	Mechanistic oral absorption (ACAT) and formulation performance, with whole-body PBPK via PBPKPlus™.
Physiology/Populations	Detailed human physiology database; virtual populations (age, ethnicity, genotype) built-in.	Human physiology with ACAT gut; population simulation via Monte Carlo or variance models (GPX population mode).
Absorption Model	Multiple absorption model options; good for i.v. and oral.	ACAT model segmenting the GI tract into multiple compartments (modified transit & dissolution) (www.sciencedirect.com).
Metabolism/Distribution	Extensive enzyme/transporter libraries; systematic DDI engine; full organ compartments for distribution.	Metabolism (liver, gut) and distribution (two-compartment central+periphery); DDI via CYP induction/inhibition modules.
Administration Routes	i.v., oral, transdermal, subcutaneous; support for inhalation modules.	Oral (primary), i.v., transdermal, other extravascular (IM, etc); PD interactions (ion channels) possible.
Population Simulation	Built-in Monte Carlo; sensitive to parameter variability; user-defined covariates.	GPX Batch Simulation: Monte Carlo across subpopulations; runs scalable virtual trials.
Model Structure Transparency	Executable binary models; extensive system templates; proprietary libraries.	User-adjustable model (e.g. number of GI compartments); results visualization and export.
Software Experience	GUI interface plus advanced scripting (R/Python APIs available); heavy focus on pharma use-cases.	GUI-driven, intuitive menus for formulation input; newer MBMA features and AI-assisted tooling (GastroPlusGPT).
Key Applications	DDI risk assessment; pediatric dosing; organ impairment; bridging; bioequivalence (BE) modeling for generic drugs.	Oral formulation performance; solubility/dissolution impact; bioequivalence waivers; food/pH effects on absorption.

Feature	Simcyp® Simulator (Certara)	GastroPlus® (Simulations Plus)
Regulatory Milestones	Vendor case study of a Simcyp PBPK model applied to a BE question; estimated saving ~$500K (vendor-reported) (www.certara.com).	Vendor case study of GastroPlus modeling used to support wider dissolution specifications; estimated saving ~$7.5M (vendor-reported) (www.simulations-plus.com).
Example Case Study	Manufacturing-site change BE question modeled with Simcyp (vendor case study) (www.certara.com).	Cladribine tablets virtual BE modeling with GastroPlus; vendor reports ~4 months and ~$0.115M saved (vendor-reported) (www.simulations-plus.com).

Table 1: Comparative features of Simcyp® vs GastroPlus® PBPK/PBBM platforms.

The evidence suggests that **both platforms are very capable**, and choice often depends on the question. For standard bioequivalence and dissolution concerns, GastroPlus's formulations tools and published use-cases have made it highly trusted in that space (www.simulations-plus.com). For DDI and special population (including biologics and pediatric), Simcyp has been historically strong, and Certara notes that Simcyp had recently completed a grant for FDA's Office of Generics focused on enhancing PBPK models for orally dosed drug products (www.certara.com). Notably, in a large blinded comparison using the IMI OrBiTo database, average PK predictive performance was *similar* between Simcyp and GastroPlus when using harmonized inputs (www.sciencedirect.com). Thus, scientifically, neither dominates universally; success often depends on accurate input data and expert model building.

Comparative Performance: Literature Analyses and Studies

Academic studies have directly compared Simcyp and GastroPlus predictive performance under controlled conditions. In general, these indicate that **average accuracy is broadly comparable**, but neither is perfect and each may excel in different scenarios.

In one well-known study (OrBiTo Project, OrBiTo Task 4.20 (www.sciencedirect.com)), 58 drugs were modeled using Simcyp (v15) and GastroPlus (v9) with standardized expert-guaranteed input datasets. The **average fold error (AFE)** for key PK parameters (AUC, C_max, t_½) ranged roughly from 1.1–2.0 across softwares (www.sciencedirect.com). For example, mean AUC was predicted within 2-fold on average by both platforms (AFE 1.11–1.97) (www.sciencedirect.com). Overall, roughly half of predictions were within 2-fold error and ~90% were within 10-fold (www.sciencedirect.com) – indicating good but not perfect accuracy. Crucially, the OrBiTo analysis found *no clear difference* in average performance between Simcyp and GastroPlus (www.sciencedirect.com). The report concluded that while "average predictive performance did not clearly differ" between platforms, individual compounds could vary, and accuracy was limited by input data quality and compound complexities (www.sciencedirect.com) (suppr.wilddata.cn).

In a contrasting, smaller study focused on **incomplete (poor) oral absorption**, GI-Sim and GastroPlus showed better performance than Simcyp. Sjögren et al. (2016) modeled 12 low-absorption drugs a priori using Simcyp 13.1, GastroPlus 8.0 and GI-Sim 4.1 (suppr.wilddata.cn). They reported *absolute average fold error (AAFE)* for AUC of 2.2 for Simcyp but only 1.6 for GastroPlus (and 1.3 for GI-Sim) (suppr.wilddata.cn). Similarly, for C_max the AAFE was 2.2 (Simcyp) vs 1.6 (GastroPlus) (suppr.wilddata.cn). The authors noted

that Simcyp tended to **underpredict** AUC and C_max (especially as absorbable fraction decreased) (suppr.wilddata.cn), whereas GastroPlus also showed a tendency for underprediction, but with no correlation with predicted fabs. They concluded *"GI-Sim and GastroPlus perform better than Simcyp in predicting the intestinal absorption"* of incompletely absorbed drugs (suppr.wilddata.cn). This suggests that for very poorly soluble/permeable compounds, GastroPlus's models (and/or its ability to fine-tune GI physiology) may give an edge.

Case reports add practical context, though the two below are vendor-authored and their figures are vendor-reported estimates. In one example, Simulations Plus describes a mid-size pharmaceutical company that used GastroPlus® PBBM to support wider tablet dissolution specifications after regulators asked for stronger justification, reporting an estimated ~$7.5M in avoided clinical study costs (www.simulations-plus.com). In another, Certara describes Simcyp® modeling, including its particle population balance approach, applied to a manufacturing-site bioequivalence question, with an estimated saving of ~$0.5M (www.certara.com). Biologics can be modeled too: while published comparisons of PBPK platforms for monoclonal antibodies are limited, one recent conference abstract reported diversity among Simcyp, PK-Sim and GastroPlus outputs in tissue distribution (with plasma predictions similar) (biblio.ugent.be), hinting at the complexity of modeling large molecules.

In summary, the literature indicates: (a) Both Simcyp and GastroPlus can produce reasonable PK predictions when well-informed; (b) On average their performance is comparable (www.sciencedirect.com), but (c) for specific challenges (e.g. very low absorption or complex formulations) one tool may outperform the other (suppr.wilddata.cn). Modelers often validate and adapt both tools (and sometimes others like PK-Sim) for maximum confidence. A prudent approach is "question-driven": choose and validate the model that best fits the scientific question, rather than assuming one software is universally superior (www.mdpi.com) (suppr.wilddata.cn).

FDA and International Regulatory Acceptance

Regulators worldwide have increasingly embraced PBPK/MIDD and NAM. The U.S. FDA, in particular, has allocated significant effort and policy changes to support these approaches.

FDA's MIDD and PBPK Guidance: The FDA's attention to MIDD began well over a decade ago, but accelerated in the 2010s. Under the 21st Century Cures Act and PDUFA VI, FDA launched a Model-Informed Drug Development Pilot Program. This created an avenue for sponsors to discuss and gain feedback on PBPK/PK/PD plans (www.fda.gov). FDA issued the draft ICH M15 guidance on *"General Principles for Model-Informed Drug Development"* on December 30, 2024, and has since issued the final guidance, which outlines multidisciplinary MIDD best practices (including planning, evaluation, documentation) and a harmonized framework for assessing model-based evidence (www.fda.gov). The final guidance reflects global consensus toward formalizing MIDD standards.

FDA's stance on PBPK is also codified in internal guidance documents. In September 2020 the FDA released a Draft Guidance specifically on **PBPK for biopharmaceutics** (oral drug development, manufacturing changes, and controls) (www.fda.gov). This draft outlines how to use PBPK to support oral drug submissions, including recommendations on model justification, validation and documentation (though it remains in draft and not formally implemented). The EMA similarly issued a finalized "Guideline on Reporting of PBPK Modelling and Simulation" (EMA/CHMP/458101/2016) to standardize content of PBPK submissions (www.ema.europa.eu). These regulatory guidances signal that agencies not only accept PBPK/PBBM analyses but provide structured expectations for them.

Regulatory Use-Cases and Outcomes: Both FDA and EMA have seen multiple PBPK-based approvals or labels. Analyses have shown numerous FDA product labels citing PBPK (e.g. for DDI predictions) (pmc.ncbi.nlm.nih.gov). A survey of PBPK applications found that submissions for biowaivers, formulation bridging, and DDI have increased significantly (www.mdpi.com) (pmc.ncbi.nlm.nih.gov). For example, Health Canada reported doubling of PBBM submission reviews in 2021–2023, and the FDA disclosed nearly *50 submissions* using PBBM for post-approval changes (with ~48% accepted) (www.mdpi.com). These numbers illustrate growing regulatory engagement; at the same time, the FDA cautions that certain submissions fail due to insufficient validation or documentation (www.mdpi.com), underscoring the need for robust model credibility.

FDA also maintains continued focus on DDI and special populations via PBPK. The *"Focus Areas: Model-Informed Product Development"* webpage (2024 update) explicitly highlights MIDD as a key agency priority, describing its use (including PBPK) for dose finding, trial design, and assessment of interactions/failure states (www.fda.gov). It states that FDA is working to transform computational modeling "from a valuable scientific tool to a valuable medical device regulatory tool" (www.fda.gov). In summary, **PBPK/MIDD is no longer fringe**: the FDA formally encourages its use (e.g. in Pediatrics waivers, Generic drug reviews, and first-in-human dosing) (www.fda.gov), provided models are well-justified.

NAMs and Animal Testing: Beyond PBPK, the FDA has launched a concerted program to reduce animal use via NAMs. In 2025, the FDA released an agency-wide *"Roadmap to Reducing Animal Testing"* which begins eliminating certain animal test requirements (initially for biologic mAbs) (www.mdpi.com) (www.fda.gov). In April 2026, FDA declared that after one year of implementation it has initiated key actions: e.g. issuing a report on progress, adding public resources, and encouraging NAMs (computational models, organ-on-chip) in submissions (www.fda.gov) (www.mdpi.com). Key points: *NAMs are defined broadly to include in vitro human-based systems and in silico models* (www.fda.gov); FDA resources list contexts where NAMs or reduced animal studies are acceptable (www.fda.gov). For example, CDER's "Streamlined Nonclinical Studies" references illustrate that in vitro assays and computational models can replace certain cardio- and neuro-toxicology assessments (www.fda.gov). Importantly, MAct 2.0 (Dec 2022) now explicitly allows "cell-based assays [and] computational models" instead of animal reference tests when justified (www.mdpi.com). This legal shift paved the way for recent policy: an FDA announcement (Apr 2025) confirmed a plan to *phase out animal testing requirements* for mAbs and encourages NAM data in INDs (www.mdpi.com).

Collectively, these efforts demonstrate that by 2026 **US regulatory policy strongly supports in silico and other non-animal models** as credible evidence. The FDA emphasizes that NAMs "may offer ways to achieve safety goals more effectively" than animal tests (www.fda.gov). In practice, this means companies can propose

PBPK/PBBM models in lieu of some animal studies, particularly if models are validated and fit-for-purpose. The emerging guidance landscape (FDA's final M15 guidance and NAM guidance (www.fda.gov), EMA's PBPK guideline (www.ema.europa.eu), etc.) reflects a harmonizing international MIDD environment.

Evidence-Based Analyses and Case Studies

Predictive Performance and Validation

Published meta-analyses and reviews provide data on PBPK model accuracy. For example, a recent MDPI review notes that PBPK/PBBM outcomes often have **inherent variability**. In the OrBiTo software comparison, PK parameters (AUC, C_max, t_½) were predicted with average fold errors (AFE) between 1.11 and 1.97, and oral bioavailability (F_oral) predictions for the 19 APIs with i.v. data showed an AFE of 1.37 and an AAFE of 1.75 (www.sciencedirect.com), indicating considerable variability in prediction accuracy. However, half of all simulations in OrBiTo were still *outside* 2-fold error (www.sciencedirect.com), underscoring model limitations. The same review reports that the FDA had received nearly 50 submissions using PBBM for post-approval changes, of which 48% were deemed acceptable (www.mdpi.com). Common shortcomings include inadequate documentation and model validation steps (e.g. lack of independent test data) (www.mdpi.com).

Thus the **credibility of PBPK models is dependent on best practices**. Regulatory guidance and expert workshops stress transparent justification: specifying software/platform, software versions, source of system parameters and in vitro data, sensitivity analyses, and qualified prediction. Each platform similarly requires qualification for specific uses. An ABPI/MHRA report noted that each software vendor has "internal systems to evaluate and track reliability" of their models (pmc.ncbi.nlm.nih.gov), and that open-source or independent validation datasets are needed for transparency. The FDA's NAM guidance draft also stresses "validation, context of use, human relevance" as criteria for NAM (and by extension PBPK) data (www.mdpi.com). Fundamentally, regulators seek PBPK modeling to answer a *specific regulatory question* (e.g. "Is it safe to widen dissolution limits?") rather than blind predictions.

Case Study: Formulation Bridging and Dissolution

Simulations Plus describes a case in which global regulatory agencies pushed back on a sponsor's proposed dissolution specification (Q80% at 45 minutes) and asked for stronger justification. Instead of new clinical trials, the company used GastroPlus to simulate many "virtual biorelevant" dissolution scenarios. The PBPK/PBBM model, validated against existing human PK data, predicted that wider dissolution ranges would not impact systemic exposure. The vendor reports that the modeling supported wider dissolution specifications than the sponsor's proposed Q80% at 45 minutes, eliminating the need for clinical studies estimated at $7M plus $0.5M in manufacturing costs (www.simulations-plus.com). This GastroPlus-based strategy achieved a 12–45× ROI (www.simulations-plus.com), depending on the alternate route chosen (vendor-reported); the regulatory outcome is not independently documented here.

Case Study: Generic Bioequivalence (BCS Biowaiver)

Simulations Plus describes a case in which a global pharmaceutical company developing a generic cladribine (BCS Class III) tablet used a GastroPlus absorption/PBPK model to examine the drug's sensitivity to gastric pH, solubility and degradation and to support virtual bioequivalence analysis. The vendor reports savings of about 4 months and an estimated $115K in study costs, an ~85% return on expenditure (www.simulations-plus.com). These figures and any associated regulatory outcome are vendor-reported and not independently documented here; this account is not a template for regulatory strategy, and any use of PBPK modeling to support bioequivalence or biowaiver requests should be agreed with the relevant regulator.

Case Study: Manufacturing Site Change and Bioequivalence

Certara describes a case in which a sponsor's top-selling product moved to a different manufacturing site, potentially altering its particle characteristics, and FDA asked for a bioequivalence comparison. Simcyp scientists used the Simcyp PBPK platform (including a particle population balance approach) to model the drug's dissolution changes and its complex PK (multiple peaks, enterohepatic recirculation, etc.), verifying the model against the original BE clinical data. Certara reports an estimated saving of ~$0.5M and several months (www.certara.com); this is a vendor-authored account and the regulatory outcome is not independently documented here.

These vendor-reported examples illustrate how **model-informed strategies** can be applied to bioequivalence and dissolution questions. By integrating mechanistic understanding with virtual trials, sponsors may be able to reduce reliance on costly in vivo studies, subject to regulatory agreement in each case.

The Animal-Free NAM Shift in PBPK/MIDD

A pivotal element of the 2026 landscape is the wholesale embrace of NAMs to replace animal testing. **PBPK modeling itself is considered a NAM** – it is an in silico approach grounded in human biology. But NAMs extend far beyond PBPK: they include any scientifically validated, non-animal method. Key points in this shift:

- **Regulatory Milestones:** The 2022 FDA Modernization Act (Dec 29, 2022) explicitly removes the legal mandate that animal studies be the only route to first-in-human trials. This legislative change means that validated **NAMs** (including human cell-based assays, computational models, etc.) can be used to support Investigational New Drug (IND) applications (www.mdpi.com). In 2025, FDA released a roadmap announcing it will *"phase out certain animal testing requirements"*, starting with monoclonal antibodies and select drugs, and urging sponsors to include NAM data in submissions (www.mdpi.com). By April 2026, the FDA proclaimed achieving its Year-1 goals of reducing animal tests, and highlighted that NAMs are accelerating drug development while "sparing thousands of laboratory animals annually" (www.fda.gov).
- **NAM Guidance and Definitions:** The FDA's NAM portal defines NAMs as in vitro human-based systems, in silico modeling, and advanced data analytics that can improve predictive relevance over animal tests (www.fda.gov). FDA's NAM page lists a 2026 CDER draft guidance, "General Considerations for the Use of New Approach Methodologies in Drug Development," described as

providing a validation framework and regulatory expectations for using non-animal methods (www.fda.gov). For nonclinical safety, CDER's "Streamlined Nonclinical Studies" outlines contexts where NAMs or reduced animal protocols are acceptable (www.fda.gov). For example, CDER's streamlined nonclinical studies page describes human iPSC-derived cardiomyocytes (hiPSC-CMs) as a new approach methodology in the context of cardiovascular safety pharmacology (www.fda.gov). CDER leadership states that integrating NAMs (and other alternative methods) can *"achieve [safety and efficacy] goals more effectively and efficiently than traditional animal testing"* (www.fda.gov).

- **Integration with PBPK and MIDD:** The NAM movement complements PBPK-based MIDD. For instance, high-quality in vitro data (intestinal permeability, hepatic clearance, transporter kinetics) from human-derived systems feed directly into PBPK models to improve predictions. Advanced organ-on-chip devices can generate dynamic absorption or metabolism data that are incorporated into GastroPlus or Simcyp simulations. Machine learning (ML) and AI are also being leveraged to predict ADME properties and to help parameterize PBPK models in silico (www.mdpi.com). An editorial note emphasizes *"mechanism-rich, human-centric"* development enabled by NAMs integrated into PBPK/PBBM (www.mdpi.com). In other words, as NAMs provide more human-relevant inputs, PBPK models become fitter for replacing animal studies. For example, replacing an animal oral PK study with in vitro dissolution data plus a validated PBPK model is a direct manifestation of this shift.
- **Practical Outcomes:** Evidence from regulatory filings shows NAM impact. The U.S. FDA reports encouraging data: in the first year of its roadmap, agencies are seeing NAM inclusion in submissions and are ready to accept qualified alternatives (www.fda.gov) (www.mdpi.com). Regulators note that in specific cases, NAMs have already *replaced* certain animal tests without compromising decision quality. One example is the FDA roadmap's starting point with monoclonal antibodies, where the aim is to reduce animal testing through NAMs.
- **Industry Implications:** For pharmaceutical companies, this means a growing imperative to adopt NAM/PBPK strategies. Budget-wise, NAM studies often cost less than animal studies and can be faster. Companies that embrace this trend find competitive advantage: shorter development cycles, ethical branding, and earlier risk identification. The ROI from earlier case studies (see the case studies above) suggests that replacing a clinical or animal trial with modeling is not just ethically commendable but economically compelling. Many in industry foresee (and regulators encourage) a future where in silico models and human cell data form the default path for absorption, distribution and safety assessments, as opposed to animal surrogates.

Overall, the NAM agenda is transforming drug R&D norms. By 2026, it is not a fringe concept but a central regulatory expectation. PBPK modeling (Simcyp or GastroPlus) is a key tool within this transformation, bridging in vitro human data and clinical outcomes.

Data Synthesis and Discussion

Several quantitative findings emerge from the above evidence:

- **Predictive Accuracy**: The OrBiTo study reported that roughly half of PBPK predictions fell within 2-fold of observed human PK (e.g. AUC, C_max) (www.sciencedirect.com). GastroPlus tended to underpredict C_max less than Simcyp in poorly absorbed drugs (suppr.wilddata.cn), as evidenced by lower AAFE. In the generic BE case, GastroPlus modeling provided vendor-reported supportive virtual bioequivalence results (85% ROI) (www.simulations-plus.com). Variability persists: regulators note many PBPK submissions fail due to uncertainties in input parameters or new conditions (pathological states) not covered by models (www.mdpi.com).
- **Regulatory Adoption Rates**: The FDA's disclosure that 48% of PBBM submissions were accepted signals both progress and caution (www.mdpi.com). Indeed, about half of PBBM proposals required further justification, indicating real but not total acceptance. However, Health Canada's doubling of PBBM reviews shows enthusiastic take-up. The existence of multiple guidance documents (FDA draft PBPK, NAM draft, EMA PBPK, etc.) suggests that by 2026, PBPK/PBBM is at least *expected* to be part of the toolkit – with NIH/FDA convening workshops on credibility of computational models (www.fda.gov).
- **Case Outcomes**: The documented cost/time savings (e.g. >$7M in one GastroPlus case (www.simulations-plus.com), $0.5M in the Simcyp BE case (www.certara.com), months of development time) demonstrate that the models yield substantial economic benefit. ROI of 12×–45× in one example (www.simulations-plus.com) highlights how even a modest modeling investment can dwarf the expense of trials. These data serve as compelling evidence for industry to continue adopting MIDD.
- **NAM Impact Metrics**: While still emerging, NAM initiatives report promising early results: the FDA's Year 1 Progress report (2026) claims thousands of animal uses are being averted (www.fda.gov), and new test guidelines (e.g. replacing rabbit pyrogen tests with human cell assays) are already taking effect (www.fda.gov). The full transition will take years, but progress is quantifiable.

In summary, evidence indicates **accelerating momentum**: more PBPK-based submissions (US/EU/Canada), more NAM-based regulatory acceptances, and documented benefits when models are used. At the same time, known limitations (model uncertainty, data gaps) remain active areas for research and standardization, as highlighted in industry surveys (www.mdpi.com). Future efforts will focus on building confidence: establishing "fit-for-purpose" validation of models, expanding human-relevant data for gating, and harmonizing global guidelines (e.g. implementation of the now-final ICH M15 guideline).

Future Directions and Implications

Looking ahead beyond 2026, several trends and challenges are clear:

- **Convergence of Digital Tools and NAM:** The synthesis of mechanistic modeling with AI/ML and high-throughput in vitro systems will intensify. For instance, GastroPlusGPT™ exemplifies using AI to assist model building. Network-enabled "digital twin" models of patients may emerge, combining PBPK with quantitative systems pharmacology (QSP) to predict efficacy and safety in virtual trials. FDA and NIH are investing in computational methods (e.g. in silico clinical trials frameworks). This convergence will further justify regulatory reliance on models.

- **Regulatory Harmonization:** With the final ICH M15 guidance (draft issued December 2024), there will be more internationally consistent expectations for model evaluation. Parallel regulatory efforts on NAMs and model-informed development indicate agencies striving to speak the same language. Future formal adoption of these guidelines will likely lower the threshold for accepting simulations in lieu of experiments, provided quality standards are met.
- **Expanding NAM Validation:** As FDA has noted, key will be rigorous *qualifications* of NAMs and models. For example, a PBPK model intended to waive a human study must be validated against external data of similar drugs. Standardized reporting formats and independently curated datasets are being discussed by consortia. Private–public partnerships (e.g. IMI OrBiTo, EFPIA) continue to collect well-characterized PK data to enable cross-platform benchmarking. In essence, the field will move towards treating validated in silico models almost like “in silico clinical trials” – with known confidence intervals.
- **Applications in Rare Diseases and Biologics:** MIDD/NAM approaches are especially valuable for areas where trials are difficult or animal models poor predictors (e.g., pediatrics, rare disease, neuropharmacology). We expect more of this – possibly regulatory acceptance of PBPK-based dose selection for first trials in rare diseases, and replacing juvenile animal toxicology with organ-on-chip plus PBPK. Given the FDA’s interest in reducing animal chronics for biologics, likely monoclonal antibody dosing and safety in humans will increasingly rely on humanized PK models rather than primate studies.
- **Educational and Cultural Change:** Broadly, both regulators and industry scientists will need to think in modeling terms. The field may develop requirements for MIDD plans (similar to statistical analysis plans) in INDs. Pharmaceutical curricula and regulatory training will emphasize computational and in vitro methods. Over time, we may see regulatory safety review divisions that include computational modeling experts, much as imaging or statistics.

In conclusion, by 2026 and beyond, PBPK modeling (via tools like Simcyp, GastroPlus, PK-Sim, etc.) and NAMs are reshaping drug development. They promise faster, cheaper, and more human-relevant decisions. The evidence – from published studies, case successes, and regulatory plans – points to a future where model-informed strategies are standard, not exceptional. The data and trends reviewed here provide a guide for stakeholders: to adopt best practices in modeling, to stay aligned with evolving regulatory expectations (M15, NAM guidance), and to invest in technologies that replace less-efficient animal tests.

Conclusion

Physiologically based modeling and MIDD have moved from niche to mainstream in the biopharmaceutical enterprise. By 2026, PBPK modeling (including commercial platforms such as Simcyp and GastroPlus) is widely used to address questions from bioequivalence to special-population dosing and, where agreed with regulators, can in some cases reduce the need for new clinical or animal studies. The comparative analyses indicate that no single PBPK platform is universally superior; rather, experts judiciously select or combine tools based on each modeling context (www.sciencedirect.com) (suppr.wilddata.cn). Regulatory agencies have

issued guidance on PBPK modeling and model-informed drug development, and the vendors publish case studies of model-based submissions (www.simulations-plus.com) (www.certara.com), although their outcomes and savings are vendor-reported.

Simultaneously, a cultural and regulatory shift toward **animal-free** methods is firmly underway. The FDA and peers have declared that validated *in vitro* and *in silico* methods are not merely supplements but viable *alternatives* to traditional animal tests (www.fda.gov) (www.mdpi.com). NAMs – including organoids, microphysiology, and importantly computational PBPK/PBBM – are now critical components of the drug evaluation toolbox. The convergence of NAMs with PBPK is particularly synergistic: as more human-relevant data flow into models, the more confidence regulators place in model-based predictions.

This report has provided an in-depth, evidence-rich exploration of these themes. Many figures cited here, particularly cost savings and ROI from vendor case studies, are vendor-reported and have not been independently verified. From historical background to current case studies and future outlook, we have strived for completeness. As the field progresses, continued accumulation of data on model performance, broader regulatory harmonization, and ongoing technological innovation will be key. For stakeholders in drug development, the message is clear: embrace PBPK/MIDD and NAMs now, as they represent not only the cutting edge of science but also the path to more efficient, patient-centric, and ethical drug development.

Sources: Sources are cited inline throughout this article; for example, the OrBiTo software comparison (www.sciencedirect.com).

Source links

Links cited in this article, in order of first appearance. Full addresses are provided for readers using extracted text.

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