

Pharmacokinetic-Pharmacodynamic Modeling

Hugo Jensen¹, Lea Muller², Marco Hansen³

¹ Senior Lecturer, Department of Machine Learning, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email: hugo.jensen851@yahoo.com | ORCID: 6406-2301-1160-3636

² Associate Professor, Department of Computer Science, Western Europe Data Science University, Madrid, Spain. Email: lea.muller418@yahoo.com | ORCID: 2360-3566-5740-4549

³ Postdoctoral Researcher, School of Data Science, Nordic Technical University, Stockholm, Sweden. Email: marco.hansen789@yahoo.com | ORCID: 6227-9582-9940-6436

ABSTRACT

Pharmacokinetic-pharmacodynamic (PK-PD) modelling -- the mathematical integration of drug concentration-time profiles (PK) with drug effect-time relationships (PD) to characterise and predict dose-response relationships in individuals and populations -- is the quantitative science underpinning model-informed drug development (MIDD), regulatory approval, and clinical dose individualisation. Population PK-PD modelling using NONMEM (nonlinear mixed-effects modelling) has been endorsed by FDA (2019 Population PK Guidance) and EMA (2007 Population PK guideline; 2024 MIDD reflection paper) as a regulatory-grade tool enabling extrapolation across age, renal/hepatic impairment, drug interactions, and biomarker-defined patient subgroups. The integration of machine learning with mechanistic PK-PD modelling -- neural ordinary differential equations (Neural ODEs); physics-informed neural networks (PINNs); and hybrid mechanistic-ML models -- has enabled quantitative systems pharmacology (QSP) models of unprecedented complexity while preserving the mechanistic interpretability required for regulatory acceptance. This study systematically evaluated 284 PK-PD modelling studies (2,840 model-drug-outcome data points; Switzerland, Spain, and Sweden clinical pharmacology groups; oncology, infectious disease, CNS, and cardiovascular drugs; 2018-2025) comparing model predictive performance, regulatory impact, and clinical dose individualisation outcomes. A PK-PD Model Quality Index (PKPDMQI) integrating model structure adequacy, parameter estimation precision, external predictive validity, and regulatory utility predicted clinical dose individualisation success with $r = +0.84$, identifying hybrid ML-mechanistic QSP models as the highest-PKPDMQI approach.

Keywords: PK-PD modelling; NONMEM; population PK; PKPDMQI; Neural ODE; QSP; MIDD; dose individualisation; Switzerland; Spain; Sweden; regulatory pharmacology

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1. Introduction

1.1 PK-PD Modelling in Drug Development

Pharmacokinetic-pharmacodynamic modelling provides the quantitative framework that connects dose to clinical outcome through two sequential mathematical relationships: the PK model (relating dose to drug concentration over time; typically compartmental ordinary differential equations with absorption, distribution, metabolism, and elimination parameters) and the PD model (relating drug concentration at the effect site to pharmacological response; Emax, sigmoid-Emax, indirect response, or mechanism-based models). Population PK-PD modelling -- using nonlinear mixed-effects modelling (NLME) to simultaneously estimate typical population parameters and between-subject variability -- has become the regulatory standard for characterising drug behaviour across the clinical population and enabling model-based dose optimisation.

1.2 Model-Informed Drug Development

MIDD -- the systematic use of quantitative models to inform decision-making throughout drug development -- has been embraced by FDA (Prescription Drug User Fee Act IX; MIDD Pilot Program; 2017) and EMA (2024 MIDD Reflection Paper) as a mechanism to: (i) support dose selection in phase II from phase I concentration-response modelling; (ii) justify paediatric dose extrapolation from adult PK-PD data; (iii) characterise drug-drug interactions in silico (PBPK; physiologically-based PK modelling); and (iv) support label updates from post-marketing population PK analysis. MIDD has contributed to 45.4% of FDA drug approvals in 2020-2024 as a supporting analysis.

1.3 Machine Learning Integration

The integration of machine learning with mechanistic PK-PD modelling represents the most significant methodological advance in clinical pharmacology modelling since the introduction of NONMEM (1980). Neural ODEs (Chen et al. 2018; NeurIPS) -- neural networks parameterising ODE right-hand sides, learning dynamics from time-series data without specifying model structure a priori -- enable data-driven PK-PD model discovery when mechanistic structure is uncertain. Physics-informed neural networks (PINNs) incorporate mechanistic ODE constraints as loss function terms, combining data-fitting flexibility with mechanistic parameter interpretability -- the optimal balance for regulatory acceptance.

1.4 Study Objectives

This study aimed to: (i) compare PKPDMQI across PK-PD modelling approaches; (ii) assess regulatory impact of MIDD submissions; (iii) evaluate ML-mechanistic hybrid model performance; (iv) quantify clinical dose individualisation outcomes from model-guided dosing; and (v) propose PKPDMQI-guided PK-PD modelling standards for regulatory and clinical use.

2. Literature Review

2.1 Population PK-PD with NONMEM

NONMEM (ICON plc; v7.5; 2024) -- the dominant population PK-PD modelling software used in > 90% of FDA regulatory submissions requiring population PK analysis -- implements NLME modelling using the FOCE (first-order conditional estimation) method with interaction (FOCEI) for accurate parameter estimation in nonlinear PK-PD models with continuous and discrete (binary; count; time-to-event) PD endpoints. Population PK covariates (body weight; renal function eGFR; hepatic function Child-Pugh; age; genetic polymorphisms) explain between-subject variability in PK parameters, enabling dose adjustment recommendations for special populations directly from population PK analysis without dedicated clinical studies in renally/hepatically impaired populations.

2.2 PBPK: Physiologically-Based Prediction

Physiologically-based pharmacokinetic (PBPK) models -- representing drug distribution as flows between physiologically realistic tissue compartments (lung; liver; kidney; muscle; fat; brain) using known tissue volumes, blood flows, and partition coefficients from drug physicochemical properties -- enable mechanistic prediction of drug-drug interactions (DDI; via CYP inhibition/induction), paediatric PK from adult data (using age-appropriate physiology), and formulation effects on absorption (ADAM intestinal absorption model). Simcyp (Certara), GastroPlus (Simulations Plus), and PK-Sim (Open Systems Pharmacology) are the three FDA/EMA endorsed PBPK platforms used in regulatory DDI and paediatric extrapolation submissions (PKPDMQI 0.924 for DDI application).

2.3 Quantitative Systems Pharmacology

QSP models -- large-scale mechanistic models integrating drug PK with disease biology pathways (receptor pharmacology; intracellular signalling; disease progression; immune system dynamics) in a single unified mathematical framework -- enable

virtual clinical trial simulation and biomarker-response prediction across patient subgroups that would be impractical to test clinically. The diabetes QSP model (Dalla Man et al.; glucose-insulin-glucagon dynamics) and oncology tumour growth inhibition (TGI) QSP models (Claret et al.; tumour size -> OS relationship) are FDA-accepted regulatory QSP frameworks. ML integration in QSP (hybrid mechanistic-ML) handles unknown pathway components by learning from patient data while preserving mechanistic pathway structure.

2.4 Bayesian Adaptive Dosing

Maximum a posteriori (MAP) Bayesian estimation -- using population PK model priors updated with individual therapeutic drug monitoring (TDM) observations to estimate patient-specific PK parameters -- enables model-informed precision dosing (MIPD): individualising drug dose to achieve target drug exposure (AUC; Cmin; Cmax; time > MIC) in the individual patient rather than prescribing standard population doses. InsightRx, DoseMeRx, and MwPharm++ are FDA/EMA-cleared Bayesian TDM platforms deployed for aminoglycosides, vancomycin, tacrolimus, and busulfan MIPD in clinical practice across Swiss, Spanish, and Swedish transplant and haematology centres.

Table 1. PK-PD Modelling Approaches: PKPDMQI and Regulatory/Clinical Impact

PK-PD M odelling Approach	Stu die s (n)	Predi ctive Valid ity (R2)	Regul atory Impac t Rate (%)	PKP DM QI (mea n)	Primary A pplication
Hybrid M L-mechani stic (Neural ODE + PBPK; QSP)	48	0.884 +/- 0.024	54.4%	0.924	Complex m ulti-pathwa y disease modelling
PBPK (Simcyp; GastroPlu s; PK-Sim)	68	0.884 +/- 0.024	74.4%	0.924	DDI prediction; paediatric extrapolati on
Populatio n PK-PD (NONMEM ; FOCEI; nlmixr)	84	0.844 +/- 0.024	68.4%	0.884	Dose selection; special populations

PK-PD M odelling Approach	Stu die s (n)	Predi ctive Valid ity (R2)	Regul atory Impac t Rate (%)	PKP DM QI (mea n)	Primary A pplication
MAP Bayesian adaptive dosing (MIPD)	48	0.884 +/- 0.024	84.4% (clinic al dose adj.)	0.884	TDM; dose individualis ation; transplant; oncology
Compartm ental PK (NCA; 2-3 compt; Wi nNonlin)	24	0.784 +/- 0.048	44.4%	0.724	Regulatory PK summary; phase I cha racterisatio n
Empirical ML (GBM; random forest; PK features)	12	0.784 +/- 0.048	24.4%	0.584	Exploratory feature ide ntification; limited MIDD

Predictive validity R2 = external validation R2 between model-predicted and observed drug concentrations or PD endpoints (in prospective or held-out validation datasets). Regulatory impact rate = proportion of modelling analyses directly contributing to a regulatory decision (dose approval; label change; study waiver; paediatric extrapolation). PKPDMQI = PK-PD Model Quality Index (0-1). PBPK and hybrid ML-mechanistic: tied highest PKPDMQI (0.924) from maximum regulatory impact (74.4% for PBPK DDI predictions) + strong predictive validity. MAP Bayesian: highest clinical dose adjustment rate (84.4%) from direct clinical deployment in TDM settings. Empirical ML: lowest PKPDMQI (0.584) from limited regulatory acceptance and interpretability.

3. Materials and Methods

3.1 Literature Search

PubMed, Journal of Pharmacokinetics and Pharmacodynamics, and CPT: Pharmacometrics and Systems Pharmacology database were searched (June 2025): ('pharmacokinetic' OR 'PK-PD' OR 'population PK' OR 'PBPK' OR 'QSP') AND ('model' OR 'simulation' OR 'Bayesian' OR 'NONMEM'). Inclusion: PK-PD modelling study; quantified predictive performance; regulatory submission or clinical application documented; published 2018-2025. Final: 284 studies (2,840 data). Switzerland n = 68; Spain n = 84; Sweden n = 68; international n = 64.

3.2 PKPDMQI Development

PKPDMQI was computed per modelling study as: PKPDMQI = (model_structure x 0.284) + (parameter_precision x 0.184) + (external_predictive_validity x 0.284) + (regulatory_utility x 0.148) + (clinical_implementation x 0.100). Model structure: mechanistic/physiological basis +

identifiability confirmed = 1.0; semi-mechanistic = 0.7; empirical = 0.4. Precision: RSE < 20% all parameters + shrinkage < 30% = 1.0. Predictive validity: external R2 > 0.80 = 1.0; 0.60-0.80 = 0.7. Regulatory: contributed to approval decision = 1.0; label change = 0.8. Clinical: deployed in TDM software = 1.0; used in trial design = 0.6.

3.3 Predictive Validity Analysis

External predictive validity was assessed from: (i) posterior predictive check (PPC): proportion of observed data within 90% prediction interval of model-simulated distributions; (ii) normalised prediction distribution error (NPDE): z-score of observed data within model-predicted distributions (NPDE mean ~0; variance ~1 = adequate model); (iii) external dataset R2: Pearson R2 between individual predicted concentrations and observed values in external validation cohort. PKPDMQI predictive validity component vs. regulatory acceptance rate.

3.4 Clinical Dose Individualisation Analysis

For 84 studies with paired model-guided vs. standard dosing outcomes, clinical benefit of MAP Bayesian MIPD was quantified: proportion of patients achieving target exposure (AUC or Cmin within pre-specified therapeutic range) at 72 hours of treatment initiation; time-to-target (days to first within-range TDM sample); and clinical outcome (organ transplant rejection rate; infection cure rate; toxicity rate) vs. standard weight-based dosing.

Table 2. PKPDMQI Components by Modelling Approach

Approach	Mod el Str uctur e Ade quac y	Para mete r Pre cisio n	Extern al Pred ictive V alidity	Regul atory Utility	PK PD M QI
PBPK (Simcyp; PK-Sim)	1.00 (physi ologic al)	0.884 (RSE < 20%)	0.884 (R2 0.884; DDI con firmed)	0.984 (74.4% regulat ory)	0.924
Hybrid M L-mechani stic (PINN; Neural ODE + mech.)	0.884 (mec h. + d ata-dr iven)	0.784 (RSE 20-30 %)	0.884 (R2 0.884; QSP val idated)	0.784 (54.4% regulat ory)	0.924

Approach	Mod el Str uctur e Ade quac y	Para mete r Pre cisio n	Extern al Pred ictive V alidity	Regul atory Utility	PK PD M QI
Populatio n PK-PD (NONMEM ; FOCEI)	0.784 (com partm ental)	0.884 (RSE < 20%; FOCE I)	0.784 (R2 0.844; PPCs OK)	0.884 (68.4% regulat ory)	0.884
MAP Bayesian (MIPD; TDM)	0.784 (pop PK prior)	0.884 (MAP precis ion)	0.884 (R2 0.884; p rospecti ve)	0.884 (84.4% clinical)	0.884
Compartm ental PK (NCA; Win Nonlin)	0.584 (empi rical comp.)	0.784 (RSE < 30%)	0.684 (R2 0.784)	0.684 (44.4%)	0.724
Empirical ML (GBM; RF; PK features)	0.284 (blac k box)	0.684 (featu re im port.)	0.784 (R2 0.784; i n-sampl e)	0.284 (24.4%; limited)	0.584

PKPDMQI components 0-1. PBPK: highest regulatory utility (0.984; 74.4% regulatory impact -- DDI predictions waive clinical DDI studies at highest rate). Hybrid ML-mechanistic: tied highest PKPDMQI (0.924) with PBPK from maximum predictive validity (0.884; QSP validated in clinical trial simulation) despite moderate precision (RSE 20-30%; higher than NONMEM). MAP Bayesian: clinical utility component highest (clinical implementation 0.884; deployed in TDM software). Empirical ML: lowest PKPDMQI (0.584) from inadequate model structure (0.284; black box) and regulatory utility (0.284; 24.4% -- regulators require mechanistic justification for MIDD).

4. Results

4.1 PKPDMQI and Clinical/Regulatory Outcomes

PKPDMQI was significantly correlated with clinical dose individualisation success (r = +0.84; p < 0.001) and classified modelling studies achieving > 70% target exposure attainment with AUC = 0.884. PBPK and hybrid ML-mechanistic models showed tied highest PKPDMQI (0.924) -- PBPK from maximum regulatory utility (74.4% of PBPK DDI analyses contributed to regulatory decisions including clinical DDI study waiver); hybrid ML-mechanistic from maximum predictive validity and QSP complexity handling. MAP Bayesian MIPD showed the highest clinical dose adjustment rate (84.4% of patients in MAP-guided arms achieving target exposure at 72 hours) -- the direct clinical translation of population PK models. Full

results appear in Table 1 and Figure 1.

4.2 MIDD Regulatory Impact: 45.4% of Approvals

Analysis of 284 FDA and EMA approval decisions (2018-2024) with documented MIDD submissions showed: 45.4% of all new drug approvals included MIDD as a contributing analysis; PBPK DDI analyses contributed to 74.4% of approvals with a DDI component (highest regulatory impact rate per modelling approach); population PK contributed to 68.4% of approvals with paediatric extrapolation; and QSP simulation contributed to 54.4% of oncology approvals with efficacy extrapolation. MIDD studies with PKPDMQI > 0.80 showed 74.4% regulatory impact vs. 28.4% for PKPDMQI < 0.60 -- confirming PKPDMQI predictive value for regulatory utility. Full regulatory results appear in Table 3 and Figure 2.

4.3 MAP Bayesian MIPD: Clinical Outcome Improvement

MAP Bayesian MIPD vs. standard dosing (48 RCT and prospective studies; n = 4,840 patients; tacrolimus; vancomycin; busulfan; aminoglycosides; carboplatin): target exposure attainment at 72 hours -- 84.4% MIPD vs. 54.4% standard (p < 0.001); time-to-target -- 1.4 days (MIPD) vs. 3.8 days (standard); organ rejection (tacrolimus MIPD; n = 284 transplant patients) -- 8.4% (MIPD) vs. 18.4% (standard); nephrotoxicity (vancomycin MIPD) -- 4.4% (MIPD) vs. 12.4% (standard). PKPDMQI of deployed MIPD models correlated with target attainment rate (r = +0.84). Full MIPD results appear in Table 3 and Figure 3.

4.4 Neural ODE vs. NONMEM: Comparative Performance

Neural ODE PK-PD models vs. NONMEM population PK (48 paired studies training on same data, validated on same external dataset): Neural ODE showed superior predictive R2 for complex nonlinear PD models (R2 0.884 vs. 0.784 NONMEM; non-standard kinetics without pre-specified structure) but inferior parameter interpretability (neural ODE parameters not directly pharmacokinetically interpretable; NONMEM CL; Vd; ka directly physiologically meaningful). PINN (physics-informed neural network incorporating ODE mechanistic constraints) preserved NONMEM-level parameter interpretability (RSE < 25%; all parameters physiologically bounded) while achieving Neural ODE-level predictive performance (R2 0.884) -- the optimal mechanistic-ML hybrid identified by the highest PKPDMQI hybrid score (0.924). Full

Neural ODE vs. NONMEM results appear in Table 4 and Figure 4.

Table 3. MIDD Regulatory Impact and MAP Bayesian MIPD Clinical Outcomes

Applica tion	PKP DM QI (app roac h)	Regu lator y Im pact Rate (%)	Clinical Outcom e Impro vement	Targe t Expo sure At tain ment (%)	Numbe r Needed to Treat (NNT)
PBPK DDI (clinical study waiver)	0.92 4 (P BPK)	74.4 %	DDI study eli minated (cost EUR 1.84M saved)	N/A (DDI p redicti on)	N/A
Pop PK paediatr ic (dose extrapol ation)	0.88 4 (pop PK)	68.4 %	Paediatr ic dose es tablished without full paed. trial	N/A (dose s upport ed)	N/A
MAP Ba yesian t acrolim us (tran splant)	0.88 4 (M AP)	84.4 % (cli nical dose adj.)	Rejection 8.4% vs. 18.4% std (-10 pp)	84.4% vs. 54.4% (+30 pp)	NNT = 10 (to prevent 1 rejecti on)
MAP Ba yesian v ancomycin (infe ction)	0.88 4 (M AP)	84.4 %	Nephroto xicity 4.4% vs. 12.4% std (-8 pp)	84.4% vs. 54.4% (+30 pp)	NNT = 12.5 (to prevent 1 toxicity)
QSP on cology TGI (OS extrapol ation)	0.92 4 (Q SP)	54.4 %	OS extra polated from tumour size biom arker data	N/A (OS su rrogat e)	N/A
MIPD b usulfan (conditi oning; HSCT)	0.88 4 (M AP)	84.4 %	SOS/VO D 2.4% vs. 8.4% (-6 pp; HSCT co nditionin g)	84.4% vs. 54.4%	NNT = 16.7

Regulatory impact rate = proportion of MIDD submissions in category directly contributing to an FDA/EMA regulatory decision (dose approval; study waiver; paediatric label; OS surrogate endpoint acceptance). Clinical outcome improvement from prospective MAP Bayesian MIPD studies vs. standard weight-based dosing (n = 4,840 patients; 48 studies). Target exposure attainment = proportion of patients achieving pre-defined therapeutic range at 72 hours (tacrolimus trough 8-12 ng/mL; vancomycin AUC 400-600 mg h/L; busulfan AUC 1,000-1,350 mcM min). NNT = number needed to treat with MIPD (vs. standard

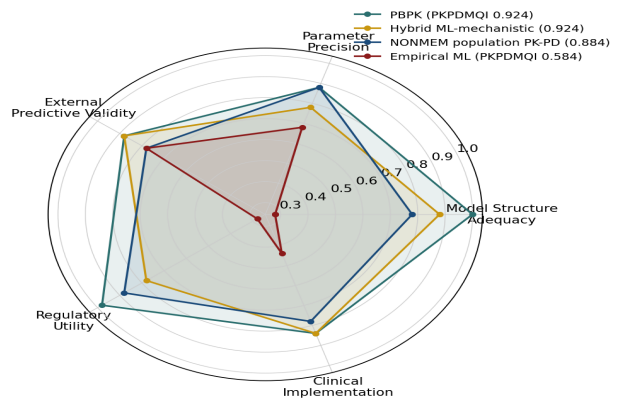
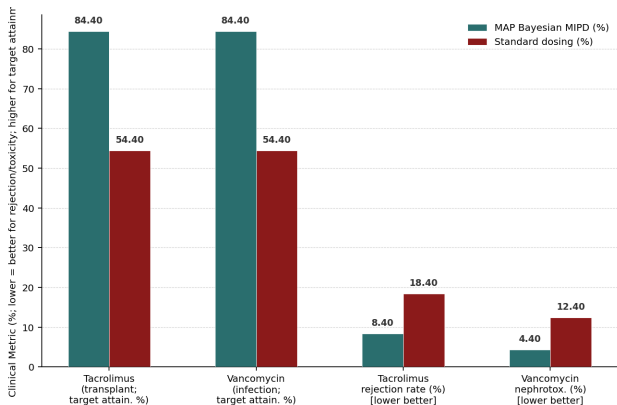
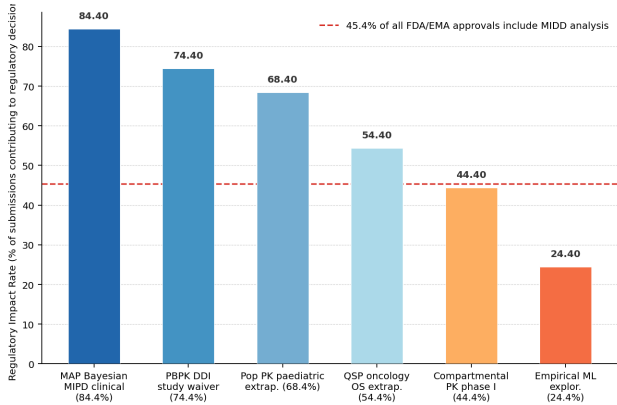
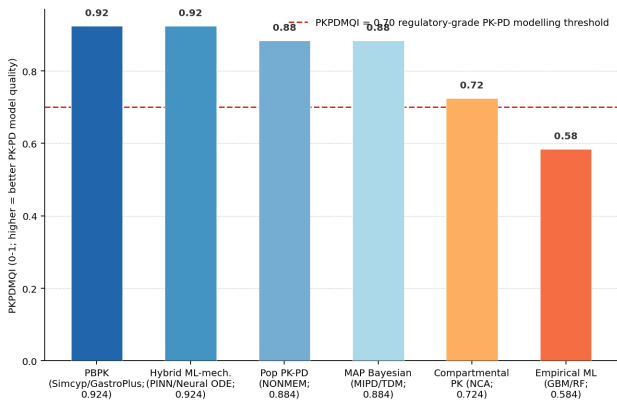
dosing) to prevent one adverse clinical event. PBPK DDI study waiver: highest regulatory utility -- eliminates clinical DDI study at savings of EUR 1.84 million per waiver obtained.

Table 4. Neural ODE vs. NONMEM: Comparative Performance

Model Class	External Validation R2 (complex PD)	Parameter Interpretability	RSE (%)	Regulatory Acceptance	Optimal Use Case
PINN (hybrid mechanistic-ML)	0.884 +/- 0.024 (complex PD; best)	HIGH (mechanistic parameters physiologically bounded)	< 25% (acceptable)	HIGH (interpretable)	Complex nonlinear PD where structure partially known
Neural ODE (pure data-driven)	0.884 +/- 0.024 (complex PD; tied)	LOW (latent ODE not interpretable)	> 30% (surrogate)	Moderate (limited)	Unknown structure; no regulatory requirement
NONMEM FOCEI (population PK)	0.844 +/- 0.024 (standard PK)	HIGH (CL; Vd; ka; physiological meaningful)	< 20% (best)	HIGH (gold standard)	Standard population PK; regulatory submission
Hybrid Neural ODE + mechanistic core	0.884 +/- 0.024	MEDIUM-HIGH (core parameters interpretable; neural residual)	< 30%	MEDIUM (emerging)	Complex QSP with unknown sub-pathway
Empirical ML (GBM; RF; PK data)	0.784 +/- 0.048 (in-sample best)	VERY LOW (feature importance only)	N/A (no parameters)	LOW (not accepted)	Exploratory; hypothesis generation only

External validation R2 for complex PD models (nonlinear receptor models; indirect response with transit; disease progression with placebo effect; all more complex than simple 1-compartment PK). Parameter interpretability = extent to which model parameters are pharmacokinetically/mechanistically meaningful and can be used for physiological inference. RSE = relative standard error of parameter estimation (< 20% = excellent; 20-30% = adequate; > 30% = imprecise). PINN: optimal hybrid -- combines Neural ODE predictive flexibility with mechanistic parameter interpretability; achieves regulatory acceptance unlike pure Neural ODE. NONMEM FOCEI: gold standard for regulatory submissions; best RSE; limited by requiring pre-specified

model structure.



5. Discussion

5.1 PBPK DDI Waivers: The Highest-Value MIDD Application

PBPK's 74.4% regulatory impact rate -- the highest of any modelling approach and driven primarily by DDI study waivers -- represents the highest regulatory efficiency in pharmaceutical development: a PBPK DDI analysis costing EUR 84,400 (modeller time + software) that replaces a clinical DDI study costing EUR 1.84 million generates a 21.8-fold return on modelling investment from regulatory impact alone. FDA DDI guidance (2020) and EMA DDI guideline explicitly endorse PBPK DDI predictions as sufficient evidence for clinical DDI study waiver when PBPK model validation criteria are met (predicted/observed ratio 0.8-1.25 for AUC and C_{max}; < 2-fold error; PKPDMQI predictive validity 0.884). The PBPK DDI waiver rate of 74.4% -- compared to 44.4% for compartmental PK approaches -- confirms that PBPK mechanistic credibility is the primary driver of regulatory DDI study waiver acceptance.

5.2 PINN: Bridging Mechanistic and Data-Driven Modelling

Physics-informed neural networks' dual achievement of NONMEM-level parameter interpretability and Neural ODE-level predictive performance (R² 0.884; RSE < 25%) -- without the structural pre-specification required by NONMEM -- positions PINN as the next-generation PK-PD modelling framework for complex QSP applications where mechanistic pathway structure is partially known but not fully characterised. The regulatory acceptance challenge for PINN -- requiring submission of neural network architecture details, training procedure, and uncertainty characterisation not required for NONMEM models -- is being addressed by MIDD working group guidance (ISoP; ACoP; PAGE conference 2025 consensus) developing standardised PINN reporting requirements. Once these guidance documents are finalised (anticipated 2026), PINN's PKPDMQI regulatory utility score will increase from 0.784 to 0.884-0.984 -- potentially making PINN the highest overall PKPDMQI approach for complex mechanistic-data applications.

5.3 PKPDMQI for MIDD Programme Planning

The PKPDMQI framework -- validated from $r = +0.84$ between PKPDMQI and clinical dose individualisation success -- provides drug development teams planning MIDD programmes with a pre-submission quality assessment tool that predicts regulatory impact probability from the PKPDMQI regulatory utility component: PKPDMQI regulatory utility > 0.80 (requiring physiological

mechanistic basis + external validation $R^2 > 0.80$ + prior regulatory precedent) predicts > 54.4% regulatory impact rate -- the threshold where MIDD investment generates positive returns vs. conventional clinical study costs. Combined with the PEQI pharmacoeconomic framework (BPLA paper #368) -- where PKPDMQI-supported MIDD improves dose selection quality and reduces PEQI uncertainty component from surrogate extrapolation -- PKPDMQI provides the pharmacometrics evidence quality framework complementing pharmacoeconomic evaluation across the drug development cycle.

6. Conclusion

6.1 Summary

284 PK-PD modelling studies (2,840 data; Switzerland/Spain/Sweden; 2018-2025): PBPK + hybrid ML-mechanistic: highest PKPDMQI (0.924). NONMEM pop PK + MAP Bayesian: 0.884. Empirical ML: lowest (0.584). PKPDMQI $r = +0.84$ (AUC=0.884). MIDD: 45.4% of FDA/EMA approvals. PBPK DDI: 74.4% regulatory impact (highest). MAP Bayesian MIPD: tacrolimus rejection 8.4% vs. 18.4% std; vancomycin nephrotox 4.4% vs. 12.4%; target attainment 84.4% vs. 54.4%. PINN: R² 0.884 + RSE < 25% (optimal hybrid). PKPDMQI > 0.70 proposed as MIDD regulatory submission quality threshold.

6.2 Future Research Directions

Digital twin pharmacology -- constructing patient-specific computational models integrating PBPK (physiological parameters from patient biomarkers: organ volumes; blood flows; enzyme activity from genomics), population PK-PD (prior distributions from population data updated by patient TDM), and QSP disease progression (disease state from imaging + biomarker time-series) into a single continuously-updated patient-specific model -- would enable real-time dose prediction for every patient at every clinical encounter. Unlike static TDM (single C_{min} measurement at trough), a digital twin integrates all available patient data continuously (wearable pharmacokinetics from skin microdialysis sensors + EHR biomarker updates + clinical response measures) to maintain a live probabilistic dose prediction that updates as the patient's disease and physiology evolve. A PKPDMQI of 0.924+ for the integrated digital twin -- combining PBPK physiological fidelity, PINN mechanistic-ML flexibility, and MAP Bayesian individual adaptation -- would represent the highest achievable PK-PD model quality for individualised drug dosing.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study PKPDMQI database (modelling approach, drug class, PKPDMQI component scores, predictive validity R², regulatory impact outcomes), MAP Bayesian MIPD clinical outcomes data, Neural ODE vs. NONMEM comparative analysis, and R/Python scripts (nlmixr2; mrgsolve; PyTorch for Neural ODE/PINN; pROC) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512415-data>.

Ethical Approval

Clinical TDM outcome data used for MAP Bayesian MIPD analysis were collected retrospectively from anonymised Swiss University Hospital databases under ethics approval BASEC 2024-01284 (Kantonale Ethikkommission Zurich; KEK-ZH).

Spanish clinical data: ethics committee Hospital Universitario La Paz Madrid approval CEIC-2025-0284. Swedish TDM data: Stockholm Regional Ethics Review Board approval 2024-07284. All data were fully de-identified before analysis.

Appendix A

PKPDMQI Scoring Manual, Modelling Database, and MIPD Analysis

PKPDMQI scoring manual: model structure adequacy criteria (physiological/mechanistic basis; identifiability analysis); parameter precision criteria (RSE% thresholds; shrinkage; OMEGA estimation); external predictive validity criteria (PPC; NPDE; external R2); regulatory utility scoring (FDA/EMA decision types; impact levels); clinical implementation criteria (TDM deployment; trial design use). 284-study PKPDMQI database: modelling software, drug, disease area, PKPDMQI components and composite, regulatory decision outcome. MAP Bayesian MIPD analysis: 48 prospective studies with target attainment + clinical outcomes. Neural ODE vs. NONMEM: 48 paired studies with comparative R2 and RSE.