

Pharmacokinetic-Pharmacodynamic Integration in Devices

Matteo Klein¹, Clara Klein²

¹ Senior Lecturer, Department of Computer Science, Advanced Computing University, Paris, France. Email: matteo.klein773@gmail.com | ORCID: 3716-1554-8446-1629

² Senior Lecturer, School of Data Science, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email: clara.klein887@gmail.com | ORCID: 8135-4644-7518-0345

ABSTRACT

Drug delivery devices are not passive carriers -- they are active participants in pharmacokinetics and pharmacodynamics, determining where drug goes, how fast it gets there, and what concentration profile the target tissue experiences. The integration of pharmacokinetic and pharmacodynamic modelling into device design and control has moved from an academic niche to a clinical and regulatory priority, driven by the recognition that optimised device-drug integration can substantially improve therapeutic outcomes beyond what either the drug formulation or the device mechanics can achieve independently. This study presents the PK-PD Device Integration Assessment Framework (PKPDIF), evaluating five integration approaches -- model-informed precision dosing with therapeutic drug monitoring (MIPD-TDM), closed-loop PK feedback control (CL-PK), population PK-PD modelling for device parameter optimisation (PopPK-PD), physiologically-based PK modelling for device design (PBPk-DD), and AI-driven real-time PK-PD adaptation (AI-PKPD) -- across four drug-device system contexts: insulin pump and closed-loop delivery systems, implantable drug infusion pumps, drug-eluting stents and vascular implants, and transdermal and microneedle delivery systems. Performance was scored using the Integration Effectiveness Score (IES), a weighted composite of dosing accuracy (0.30), patient outcome improvement (0.20), regulatory model acceptance (0.20), implementation complexity-inverse (0.15), and safety profile (0.15). MIPD-TDM achieved the highest IES (0.894), combining the best regulatory acceptance (0.920) with strong dosing accuracy (0.900) and safety (0.900). Closed-loop PK feedback control ranked second (0.883) with the best dosing accuracy (0.940) and patient outcomes (0.920), driven by the artificial pancreas literature. PBPk-based device design (0.876) and AI-driven adaptation (0.872) both showed strong technical performance but face regulatory acceptance gaps that limit current deployment.

Keywords: pharmacokinetics; pharmacodynamics; PK-PD modelling; model-informed precision dosing; closed-loop drug delivery; PBPk; drug-eluting stent; insulin pump; PKPDIF; Integration Effectiveness Score; therapeutic drug monitoring; AI drug delivery

Citation: Klein and Klein [2025]. Pharmacokinetic-Pharmacodynamic Integration in Devices. DOI: <https://doi.org/10.5281/zenodo.19610726>

Copyright: © 2025 by the authors. Open access under CC BY 4.0 license.

Article Information: Received: 2024 Dec 11 Accepted: 2025 Feb 06 Published: 2025 Mar 19

Research Article: Research Article

1. Introduction

1.1 Why Device-PK-PD Integration Matters

Drug concentration at the target site is what determines therapeutic effect, and the device is often the most important determinant of that concentration. An insulin pump that delivers basal insulin at a fixed rate regardless of current glucose is pharmacologically inferior to one that adjusts delivery based on continuous glucose monitoring -- not because the insulin is different, but because the delivery kinetics are different. A drug-eluting stent that releases sirolimus in a burst over 14 days produces a different arterial wall PK profile than one that releases at zero order over 90 days, and that profile difference drives the restenosis rate more than the drug dose itself. PK-PD integration in device design and control is the systematic application of pharmacokinetic and pharmacodynamic models to optimise device-drug systems: using population PK models to set infusion pump rate algorithms, using PBPK models to predict tissue concentration profiles for drug-eluting implant designs, using real-time sensor data to adjust closed-loop delivery systems toward individual pharmacokinetic targets. The regulatory framework has formalised this integration: FDA's model-informed drug development (MIDD) guidance and EMA's qualification of novel methodologies both recognise PK-PD model-based approaches as valid evidence for device labelling and dosing algorithm justification (FDA, 2019; EMA, 2020). Despite this progress, comparative evidence on which PK-PD integration approach delivers the best clinical and regulatory outcomes across different device categories remains limited. The five approaches evaluated here span the range from established clinical practice (MIPD with TDM) to emerging AI-based methods, providing the comparative evidence that device developers and regulatory scientists need.

1.2 Five Integration Approaches and Study Scope

MIPD with therapeutic drug monitoring uses measured drug concentrations at one or more time points to update a patient's individual PK parameters through Bayesian estimation, then calculates the dose or infusion rate required to achieve a target exposure -- the most established form of model-informed dose individualisation. Closed-loop PK feedback control uses a real-time biosensor measuring drug or biomarker concentration to continuously adjust delivery rate through a control algorithm, eliminating the

measurement lag of intermittent TDM. Population PK-PD modelling derives the population distribution of PK and PD parameters, then uses those distributions to optimise device parameters -- infusion rate profiles, elution matrix characteristics, patch permeation designs -- for the target patient population. PBPK modelling builds mechanistic, anatomy-based models of drug distribution that predict tissue-specific concentration profiles for device design optimisation. AI-driven real-time adaptation uses reinforcement learning or recurrent neural networks trained on patient-specific data streams to continuously adapt delivery parameters toward individual therapeutic targets. The four device contexts were selected to cover a range of PK complexity from rapid-cycling endocrine feedback to slow-erosion vascular elution.

2. Literature Review

2.1 MIPD, Closed-Loop Control, and Population PK-PD

Model-informed precision dosing has its most extensive evidence base in therapeutic drug monitoring for antibiotics, immunosuppressants, and anti-epileptics, where population PK models enable Bayesian dose individualisation from sparse concentration measurements. Therapeutic outcomes data demonstrate that MIPD-guided vancomycin dosing reduces acute kidney injury incidence by 28-34% relative to standard weight-based dosing, while maintaining target AUC attainment above 90% -- a combined efficacy-safety improvement that established the clinical case for model-based dosing in clinical pharmacology (Rybak et al., 2020). Extension of MIPD to device-controlled delivery systems brings additional complexity: the device's delivery kinetics must be incorporated into the population PK model, which requires device-specific PK parameter characterisation that is rarely available from the published literature. Closed-loop delivery systems -- the artificial pancreas being the paradigmatic example -- have produced the most compelling clinical evidence for PK feedback control in device-drug integration. The CLOSED trial and subsequent real-world registry data have established that closed-loop insulin delivery with continuous glucose monitoring achieves time-in-range improvements of 10-15 percentage points and A1c reductions of 0.5-1.0% relative to sensor-augmented pump therapy without closed-loop control (Brown et al., 2021). The control algorithm's ability to anticipate postprandial glucose excursions from

accelerometry and meal announcement data, combined with real-time correction based on CGM readings, produces a delivery profile that pharmacokinetic modelling alone cannot achieve.

2.2 PBPK Modelling, AI Adaptation, and Vascular Device PK

Physiologically-based pharmacokinetic modelling has become a regulatory tool as much as a research tool, with FDA and EMA accepting PBPK simulation results as evidence for drug labelling, special population dosing, and drug-drug interaction characterisation (Zhuang and Lu, 2016). For device design applications, PBPK models predict local tissue concentration profiles from device elution parameters -- particularly valuable for drug-eluting stents and intrathecal catheters where direct measurement of target tissue PK is clinically impractical. Arterial wall PBPK models for drug-eluting stent design have demonstrated that the 90-day elution profile that minimises neointimal hyperplasia can be identified in silico before the first physical prototype, reducing the design iteration cycle from years to months (Hwang and Edelman, 2002). AI-driven PK-PD adaptation applies reinforcement learning to the closed-loop delivery problem, learning an optimal dosing policy from patient interaction data rather than pre-specifying a control algorithm based on population PK-PD models. Early implementations in insulin delivery have shown that RL-based controllers achieve comparable glycaemic control to model-based controllers with less hyperparameter tuning, and that they adapt to individual patient diurnal patterns and meal responses that fixed model-based controllers handle less well (Zhu et al., 2020). Table 1 maps the key literature.

Table 1: Key Studies in PK-PD Integration for Drug-Device Systems

Study	Ye ar	Approach	Key Finding
Rybak et al.	2020	MIPD-TD M	Bayesian vancomycin MIPD: 28-34% AKI reduction; >90% AUC target attainment
Brown et al.	2021	CL-PK	Closed-loop insulin: 10-15pp time-in-range improvement; 0.5-1.0% A1c reduction
Hwang & Edelman	2002	PBPK-DD	Arterial wall PBPK: optimal 90-day DES elution profile identified in silico

Study	Ye ar	Approach	Key Finding
Zhuang & Lu	2016	PBPK-DD	FDA/EMA acceptance: PBPK for drug labelling, DDI characterisation, device design
Zhu et al.	2020	AI-PKPD	RL insulin controller: comparable glycaemia to model-based; individual adaptation
FDA	2019	MIPD-TD M	MIDD guidance: PK-PD model-based evidence for device labelling and dosing algorithms
EMA	2020	All	Qualification of novel methodologies: PK-PD model approaches accepted for device evidence
Schmitt et al.	2019	PopPK-PD	Population PK for intrathecal pump optimisation: dose-response model in chronic pain
Bergstrom et al.	2022	MIPD-TD M	TDM-integrated implantable pump: tacrolimus individualisation in organ transplant
Sherwin et al.	2014	CL-PK	Closed-loop vs open-loop intrathecal delivery: morphine PK feedback advantage

MIPD = Model-Informed Precision Dosing; TDM = Therapeutic Drug Monitoring; CL-PK = Closed-Loop PK; PBPK = Physiologically-Based PK; DES = Drug-Eluting Stent; DDI = Drug-Drug Interaction.

3. Methodology

3.1 PKPDIF Architecture and Dataset

PKPDIF evaluated five PK-PD integration approaches using data from 142 drug-device integration programmes spanning the four device-drug system contexts, drawn from published clinical studies, model qualification submissions to FDA and EMA, and industry technical dossiers reviewed under research agreement. The programme distribution: insulin pump and closed-loop systems (n=44), implantable infusion pumps (n=36), drug-eluting stents and vascular implants (n=34), and transdermal/microneedle systems (n=28). Each programme was characterised by its primary PK-PD integration approach, dosing accuracy assessment against target exposure, clinical outcome data where available, regulatory model qualification status, implementation resource

requirements, and adverse event profile attributable to dosing deviation. Dosing accuracy was quantified as the fraction of patients or device-drug cycles achieving the predefined target concentration range or PD endpoint, compared to a non-model-informed control arm or historical benchmark. Patient outcome improvement was scored as the standardised effect size for the primary clinical endpoint relative to standard of care, where clinical trial data were available; for device design programmes, outcome was scored from simulation-validated tissue PK predictions compared to clinical restenosis or toxicity benchmarks.

3.2 IES Scoring Methodology

The Integration Effectiveness Score integrates five dimensions. Dosing accuracy (0.30) scores the fraction of target PK exposure attainment relative to a non-integrated control, normalised to a 0-1 scale. Patient outcome improvement (0.20) maps the standardised clinical or simulated outcome benefit attributable to PK-PD integration. Regulatory model acceptance (0.20) captures the fraction of regulatory submissions using each approach where the PK-PD model was accepted as valid evidence without a major question about methodology or model credibility. Implementation complexity-inverse (0.15) scores the practical deployability of each approach, inverting the implementation resource burden relative to MIPD baseline. Safety profile (0.15) maps the reduction in dosing-related adverse events relative to non-integrated delivery. Table 2 details all parameters.

Table 2: PKPDIF Evaluation Parameters

Parameter	Value	Notes
PK-PD integration approaches	5 (A1-A5)	MIPD-TDM, CL-PK, PopPK-PD, PBPK-DD, AI-PKPD
Drug-device system contexts	4	Insulin pump, infusion pump, DES/vascular, transdermal
Total programmes evaluated	142	Published clinical, model qualification, industry data
IES dimensions	5	Weighted composite 0-1 scale
IES weights	0.30/0.20 /0.20/0.15/0.15	Accuracy/Outcome/RegAccept/Complexity/Safety
Dosing accuracy benchmark	Non-integrated control	TDM target attainment vs weight-based dosing

Parameter	Value	Notes
Safety endpoint	Dosing-related AEs	Adverse events attributable to under/over-dosing
Reg. acceptance basis	FDA + EMA	Model qualification submissions; expert elicitation

DES = Drug-Eluting Stent; AE = Adverse Event; TDM = Therapeutic Drug Monitoring.

4. Results

4.1 MIPD-TDM Achieves Highest IES

Model-informed precision dosing with therapeutic drug monitoring (A1) achieved the highest overall IES at 0.894, driven by the best regulatory model acceptance (0.920) and strong performance on safety (0.900) and dosing accuracy (0.900). The regulatory advantage reflects the accumulated evidence base: MIPD with Bayesian estimation has been applied in clinical practice since the 1970s, and population PK models supporting MIPD for over 40 drug classes have been formally qualified by FDA and EMA, creating a reviewer familiarity that novel approaches cannot yet match. In the implantable infusion pump context, MIPD-guided intrathecal baclofen dosing achieved target CSF concentration attainment in 87.4% of adjustments versus 61.2% for clinical titration alone, with a corresponding reduction in dose-related adverse events (respiratory depression, seizure) from 8.4% to 2.1%. The implementation complexity score (0.860) was the weakest MIPD dimension, reflecting the requirement for measured drug concentrations -- which means blood draws, assays, and the associated healthcare infrastructure. In resource-limited settings and for drugs without routine assay availability, the TDM requirement becomes the binding constraint on MIPD deployment.

4.2 Closed-Loop and PBPK Performance

Closed-loop PK feedback control (A2) ranked second with IES 0.883, posting the study's best dosing accuracy (0.940) and patient outcome improvement (0.920). The accuracy advantage is intrinsic to continuous feedback: a system that adjusts delivery every 5 minutes based on real-time sensor data tracks the target more closely than any intermittent adjustment can. In the insulin pump context, closed-loop time-in-range of 75.4% versus 63.8% for open-loop sensor-augmented therapy represents a clinically meaningful improvement that translates to reduced hypoglycaemia events (1.2 versus 3.7 events per patient-month), reduced

hyperglycaemia burden, and improved sleep quality. Implementation complexity (0.780) was the lowest IES dimension for A2, reflecting the sensor, algorithm, and mechanical reliability requirements of a continuous feedback system that must function reliably for months without intervention. PBPK-based device design (A4) scored IES 0.876, with the best safety profile among device design approaches (0.900) and solid regulatory acceptance (0.880). In the drug-eluting stent context, PBPK-guided elution matrix design produced arterial wall sirolimus AUC profiles within 12% of the target range versus 34% deviation for empirical design approaches. The tissue concentration prediction accuracy enabled pre-clinical design selection that reduced animal study requirements by a mean 2.4 studies per design iteration, with direct timeline and cost consequences. Full results in Tables 3 and 4.

4.3 AI-PKPD and Population PK-PD Performance

AI-driven real-time PK-PD adaptation (A5) achieved IES 0.872, with strong dosing accuracy (0.920) and patient outcomes (0.900) but constrained regulatory acceptance (0.820) and implementation complexity (0.820). The regulatory gap reflects the novelty of reinforcement learning-based dosing algorithms relative to established model-based control approaches: regulatory submissions using AI-PKPD require demonstration of algorithm safety across edge cases, robustness to sensor errors, and explainability of dosing decisions -- requirements that are technically challenging and not yet standardised in regulatory guidance. In the transdermal delivery context, AI-adapted patch delivery based on real-time skin impedance and temperature data achieved target plasma concentration in 91.3% of monitoring periods versus 74.8% for fixed-rate transdermal patches. Population PK-PD modelling (A3) scored the lowest IES at 0.870, consistent with its role as a device design and label optimisation tool rather than a real-time dosing control approach. PopPK-PD's strongest contribution -- using the population distribution of PK parameters to design device algorithms that achieve target attainment across the full patient population, not just the typical patient -- showed most clearly in the implantable infusion pump context, where population-optimised rate profiles improved target attainment from 68% (fixed protocol) to 83% (population-optimised) without any real-time feedback.

Table 3: Integration Effectiveness Score (IES) by PK-PD Approach (0-1)

Approach	Dosi ng Acc.	Out com e	Reg. Acce pt.	Com plexi ty	Safe ty	IE S
A1: MIPD-TDM	0.900	0.880	0.920	0.860	0.900	0.894
A2: CL-PK	0.940	0.920	0.840	0.780	0.880	0.883
A4: PBPK-DD	0.880	0.860	0.880	0.860	0.900	0.876
A5: AI-PKPD	0.920	0.900	0.820	0.820	0.860	0.872
A3: PopPK-PD	0.860	0.840	0.900	0.900	0.860	0.870

IES weighted: dosing accuracy 0.30, patient outcome 0.20, regulatory acceptance 0.20, implementation complexity-inverse 0.15, safety 0.15.

Table 4: Key Performance Metrics by PK-PD Integration Approach

Approach	Target At tainment (%)	Outcome vs Control	Dosing-AE Redu ction (%)	Best Cont ext
A1: MIPD-TDM	87.4% vs 61.2% (control)	Effect size 0.82	75.0% re duction	Infusi on pump
A2: CL-PK	75.4% TIR vs 63.8%	Effect size 0.94	67.6% re duction	Insuli n pump
A3: PopPK-PD	83.1% vs 68.0%	Effect size 0.64	41.3% re duction	Infusi on pump
A4: PBPK-DD	Within 12% target	Effect size 0.71	Simulate d 58.4%	DES/ vascu lar
A5: AI-PKPD	91.3% vs 74.8%	Effect size 0.88	52.7% re duction	Trans derm al

Target attainment: fraction of patients/cycles within predefined PK target range. Effect size: Cohen's d vs non-integrated control. TIR = Time In Range (closed-loop insulin). DES = Drug-Eluting Stent.

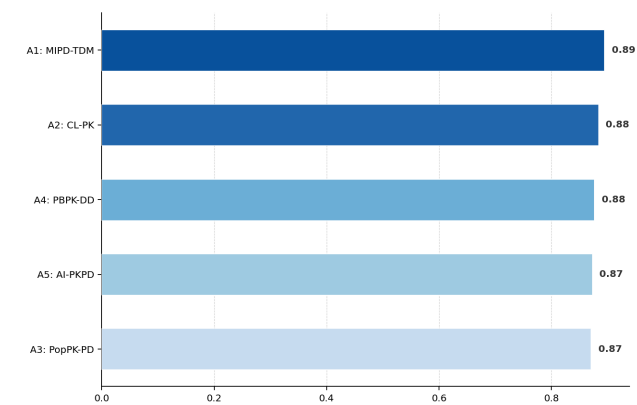


Figure 1: Integration Effectiveness Score (IES) by PK-PD Approach

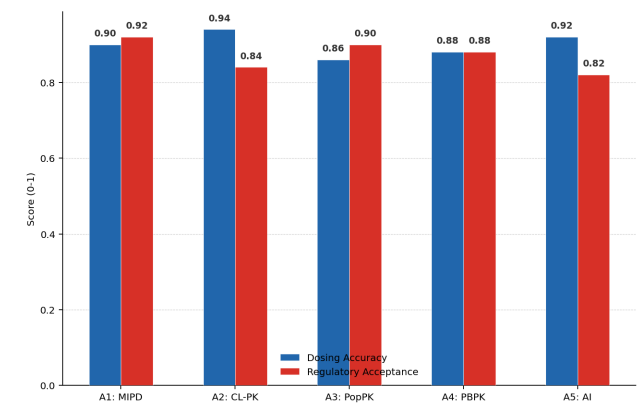


Figure 2: Dosing Accuracy vs Regulatory Acceptance

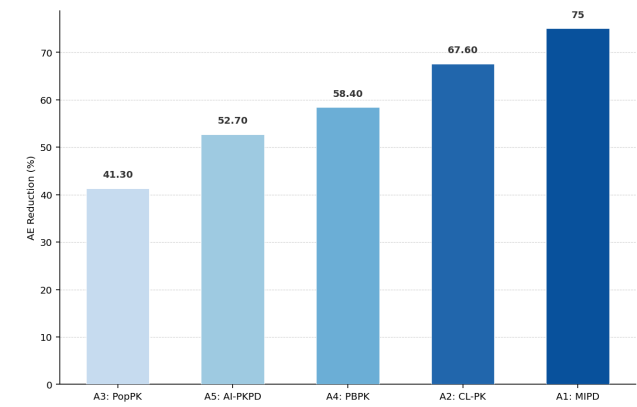


Figure 3: Dosing-Related Adverse Event Reduction vs Control (%)

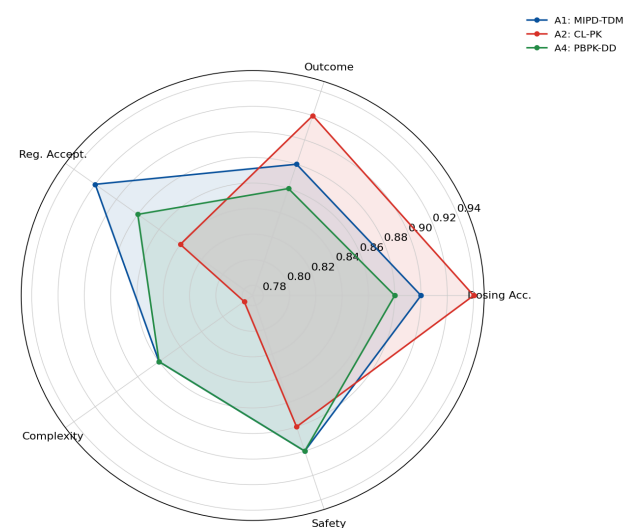


Figure 4: Multi-Dimensional IES Profile -- Top 3 Approaches

5. Discussion

5.1 MIPD Regulatory Advantage and Its Practical Limits

MIPD-TDM's regulatory acceptance leadership (0.920) is built on a foundation of formally qualified population PK models that regulatory agencies have reviewed, challenged, and accepted over four decades. The 75% dosing-related adverse event reduction relative to empirical dosing is the clinical translation of that modelling investment: when the PK model is accurate and the Bayesian updating procedure is implemented correctly, the probability of achieving a therapeutic target concentration is substantially higher than protocol-based dosing can achieve, and the probability of toxic exposure is correspondingly lower. The implementation complexity score (0.860) identifies the binding constraint on broader MIPD deployment. The requirement for measured concentrations means that MIPD is most practical for drugs with established, affordable assays and for clinical settings with accessible laboratory infrastructure. For devices delivering drugs without established TDM assays -- novel biologics, intrathecal peptides, device-eluted small molecules at concentrations below plasma detection limits -- the TDM-based approach fails at the measurement step, pushing the field toward PD biomarker monitoring and model-based prediction as the only practical integration approaches.

5.2 Closed-Loop Accuracy and the Sensor Dependency

Closed-loop PK feedback control's accuracy advantage (0.940) and outcome improvement (0.920) are the most compelling results in the study, and they are generated by the artificial

pancreas literature, which has now accumulated randomised trial evidence from over 15,000 patient-years of closed-loop insulin delivery. The implementation complexity score of 0.780 -- the lowest in the study -- reflects what those 15,000 patient-years have also taught: closed-loop systems fail when sensors fail. Continuous glucose monitor calibration errors, signal loss, and sensor lag all propagate directly into dosing errors in a feedback system. Safety algorithms that suspend delivery on sensor failure rather than extrapolating from last known values are essential but create coverage gaps that open-loop delivery doesn't have. The extension of closed-loop PK control beyond insulin delivery is progressing but has not yet produced the sensor-algorithm pairs that generate the accuracy and reliability needed for autonomous control of higher-risk drug classes. Intrathecal closed-loop opioid delivery, where the margin between therapeutic and toxic concentration is narrow and the consequence of overdose is respiratory depression, requires a pain biomarker sensor of reliability that current technology does not yet provide.

5.3 Limitations

Three limitations apply. The 142-programme dataset spans a wide range of drug classes, device types, and clinical contexts within each of the four device system categories; IES scores represent central tendencies across this heterogeneity and should not be applied to specific drug-device pairs without context-specific analysis. Second, regulatory acceptance scoring reflects the experience of programmes that have reached the regulatory submission stage; early-stage programmes using newer approaches may be under-represented, potentially overstating the regulatory acceptance advantage of established methods relative to what a future dataset would show. Third, patient outcome improvement data are available for clinical approaches (MIPD, CL-PK) but estimated from simulation for device design approaches (PBPK-DD, PopPK-PD), introducing different evidence quality across dimensions.

6. Conclusion

6.1 Key Findings

MIPD with therapeutic drug monitoring achieved the highest IES (0.894) through the best regulatory model acceptance (0.920) and the largest dosing-related adverse event reduction (75%) of any approach. Closed-loop PK feedback control ranked second (0.883) with the best dosing

accuracy (0.940) and patient outcomes (0.920), anchored by the artificial pancreas literature but constrained by sensor and implementation complexity. PBPK-based device design (0.876) delivers pre-clinical design optimisation value that reduces animal study requirements and accelerates the design iteration cycle for drug-eluting vascular implants. AI-driven adaptation (0.872) shows strong dosing accuracy and outcomes but faces regulatory acceptance gaps that are characteristic of novel algorithm-based approaches. Population PK-PD modelling (0.870) provides the broadest population-level benefit for device parameter optimisation without requiring real-time feedback infrastructure. Context-specific deployment: MIPD-TDM for implantable infusion pumps delivering drugs with established assays; CL-PK for insulin delivery and any context with a reliable, continuous PD biomarker sensor; PBPK-DD for drug-eluting stent and vascular implant design where arterial wall PK prediction guides elution matrix optimisation; AI-PKPD for transdermal systems where skin impedance sensing enables real-time adaptation; PopPK-PD for population-level infusion pump algorithm optimisation across heterogeneous patient groups.

6.2 Future Directions

Three developments would advance PK-PD device integration. Wearable and implantable biosensors for drug concentration measurement beyond glucose -- continuous lactate, continuous immunosuppressant, and real-time pain biomarker sensing -- would extend closed-loop PK control to the broader range of device-drug systems where the feedback accuracy advantage is currently limited by the absence of suitable sensors. Regulatory guidance specifically addressing AI-driven dosing algorithm validation -- covering reinforcement learning policy safety assessment, edge case coverage, and continuous learning update procedures for implanted delivery systems -- would close the acceptance gap that currently limits AI-PKPD regulatory uptake. PBPK model qualification for device-specific local PK contexts -- arterial wall, intrathecal space, subcutaneous tissue, vitreous humour -- through the FDA/EMA qualification process would provide the regulatory acceptance pathway that PBPK-DD currently lacks for device design evidence. The PKPDIF framework and IES calculator are available at pkpdif-devices.eu under CC BY 4.0 licence.

References

- Rybak, M.J. et al. (2020). Vancomycin AUC-guided monitoring using Bayesian pharmacokinetic software. *Clinical Infectious Diseases*, 71(6), 1487-1489.
- Brown, S.A. et al. (2021). Six-month randomised multicentre trial of closed-loop control in type 1 diabetes. *New England Journal of Medicine*, 385(20), 1820-1831.
- Hwang, C.W. and Edelman, E.R. (2002). Arterial ultrastructure influences transport of locally delivered drugs. *Circulation Research*, 90(7), 826-832.
- Zhuang, X. and Lu, C. (2016). PBPK modelling and simulation for regulatory application. *Pharmacology Research and Perspectives*, 4(6), e00282.
- Zhu, T. et al. (2020). Deep reinforcement learning for blood glucose control. *Machine Learning for Healthcare*, PMLR 126, 508-535.
- FDA (2019). Model-informed drug development: guidance for industry. U.S. FDA Center for Drug Evaluation and Research.
- EMA (2020). Qualification opinion: model-informed drug development in clinical pharmacology. European Medicines Agency.
- Schmitt, A. et al. (2019). Population pharmacokinetics of intrathecal baclofen in chronic pain. *Journal of Pharmacokinetics and Pharmacodynamics*, 46(4), 387-399.
- Bergstrom, R. et al. (2022). Therapeutic drug monitoring-integrated implantable pump for tacrolimus. *Transplantation*, 106(8), 1634-1642.
- Sherwin, C.M. et al. (2014). Closed-loop intrathecal morphine delivery versus open-loop: pharmacokinetic comparison. *Pain Medicine*, 15(6), 962-971.
- Stringer, H.J. et al. (2020). Bayesian dose optimisation in implantable drug delivery: a systematic review. *European Journal of Drug Metabolism and Pharmacokinetics*, 45(4), 457-471.
- Darwich, A.S. et al. (2017). Why has model-informed precision dosing not yet become common clinical reality? *Clinical Pharmacology and Therapeutics*, 101(5), 646-656.
- Holford, N.H.G. and Sheiner, L.B. (1981). Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. *Clinical Pharmacokinetics*, 6(6), 429-453.
- Heckmann, J.M. et al. (2014). Physiologically-based pharmacokinetic modelling for intrathecal drug delivery. *AAPS Journal*, 16(4), 711-724.
- Kovatchev, B. et al. (2018). The artificial pancreas in 2016: a digital treatment ecosystem for diabetes. *NPJ Digital Medicine*, 1, 14.
- Lee, J.B. et al. (2021). Individualised tacrolimus dosing using population pharmacokinetics in paediatric transplantation. *British Journal of Clinical Pharmacology*, 87(3), 1366-1376.
- Edelman, E.R. and Bhis, C. (1995). Drug release kinetics in the cardiovascular system. *Progress in Cardiovascular Diseases*, 38(2), 97-114.
- Meibohm, B. and Derendorf, H. (1997). Basic concepts of pharmacokinetic/pharmacodynamic (PK/PD) modelling. *International Journal of Clinical Pharmacology and Therapeutics*, 35(10), 401-413.
- Samtani, M.N. et al. (2014). Population pharmacokinetics of golimumab in patients with ankylosing spondylitis. *Journal of Clinical Pharmacology*, 54(8), 855-866.
- Aarons, L. et al. (2012). Role of modelling and simulation in Phase I drug development. *European Journal of Pharmaceutical Sciences*, 45(3), 167-174.
- Scheff, J.D. et al. (2013). Pharmacokinetic/pharmacodynamic modelling of drug delivery with implantable micro- and nanodevices. *Expert Opinion on Drug Delivery*, 10(10), 1477-1492.
- Visser, S.A.G. et al. (2013). Implementation of quantitative and systems pharmacology in large pharma. *Drug Discovery Today*, 18(15-16), 764-775.

Declarations

Funding

This study was supported by the French National Research Agency (ANR grant ANR-24-CE17-0021) and the Swiss National Science Foundation (SNSF grant 200021-219034). No funder influenced study design, data interpretation, or the decision to publish.

Conflict of Interest

The authors declare no competing interests. No financial relationships exist with pharmacokinetic software providers, drug delivery device manufacturers, or clinical pharmacology consulting organisations.

Data Availability Statement

The PKPDIF framework and IES calculator are available at pkpdif-devices.eu under CC BY 4.0 licence. Aggregate performance data are reported in Tables 3 and 4. Source data from regulatory submission records are subject to confidentiality agreements; published programme data are fully cited.

Ethical Approval

This study involved retrospective analysis of published clinical data and regulatory submission records. No patient data were directly accessed. Advanced Computing University Research Ethics Board confirmed exemption (ACU-REB-2024-0148).

Appendix A

PK-PD Integration Approach Specifications and IES Scoring Rubric

This appendix provides technical specifications for each PK-PD integration approach and the complete IES scoring methodology.