

Bioequivalence Studies in Controlled-Release Implants

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ABSTRACT

Controlled-release implants -- including biodegradable polymer rods, osmotic mini-pumps, reservoir-based subdermal systems, and drug-eluting stents -- deliver therapeutic agents over weeks to years from a single administration, yet demonstrating bioequivalence (BE) between a generic implant and its reference listed drug (RLD) remains one of the most complex challenges in regulatory science. Unlike oral dosage forms where plasma concentration-time profiles from single-dose crossover studies suffice, implantable systems exhibit release kinetics governed by polymer erosion, osmotic gradients, membrane diffusion, and local tissue response -- factors that decouple in vitro dissolution from in vivo performance. This study presents the Controlled-Release Implant Bioequivalence Assessment Framework (CRIBAF), evaluating five bioequivalence strategies -- conventional pharmacokinetic BE, in vitro-in vivo correlation (IVIVC)-based waiver, population pharmacokinetic modelling, mechanistic absorption simulation, and hybrid in vitro dissolution plus limited in vivo sampling -- across four implant categories: biodegradable PLGA rods, osmotic mini-pumps, reservoir subdermal systems, and drug-eluting coronary stents. Our Implant Bioequivalence Confidence Score (IBCS) integrates pharmacokinetic concordance, dissolution profile similarity, mechanistic plausibility, regulatory acceptance likelihood, and study feasibility. Population pharmacokinetic modelling achieved the highest IBCS (0.908) through nonlinear mixed-effects models that account for inter-subject variability in implant-site tissue perfusion, while IVIVC-based waiver achieved the highest regulatory acceptance score (0.950) for PLGA rod implants where Level A correlations have been established.

Keywords: bioequivalence; controlled-release implant; IVIVC; PLGA; pharmacokinetics; drug-eluting stent; population PK modelling; in vitro dissolution; regulatory science; generic drug approval

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1. Introduction

1.1 The Bioequivalence Challenge for Implantable Systems

Bioequivalence assessment for immediate-release oral dosage forms rests on a well-established scientific and regulatory foundation: the Biopharmaceutics Classification System (BCS) links in vitro dissolution to in vivo absorption, and single-dose crossover studies comparing C_{max} and AUC between test and reference products provide a statistically robust framework codified in FDA guidance and EMA guidelines (FDA, 2003). For controlled-release implants, however, this framework breaks down at multiple levels. First, the release mechanism is not dissolution from a solid matrix into gastrointestinal fluid but rather polymer degradation, membrane diffusion, or osmotic displacement into subcutaneous or intravascular tissue -- processes that depend on local tissue environment factors (pH, enzyme activity, blood flow) with no oral analogue (Burgess et al., 2004). Second, the duration of drug release spans weeks to years rather than hours, making conventional crossover study designs impractical because washout periods would need to match or exceed the release duration. Third, inter-subject variability in implant-site tissue response creates pharmacokinetic variability that dwarfs the formulation differences bioequivalence studies aim to detect -- the coefficient of variation for AUC from subcutaneous implants typically exceeds 40%, compared to 15-25% for oral products (Martinez et al., 2016). These challenges have left the regulatory pathway for generic controlled-release implants largely undefined, with only a handful of product-specific BE guidance documents issued by the FDA's Office of Generic Drugs.

1.2 Five Bioequivalence Strategies

Five approaches have been proposed or applied for implant bioequivalence assessment. Conventional pharmacokinetic BE applies standard C_{max}/AUC comparison with widened acceptance limits (e.g., 80-125% expanded to 75-133%) to accommodate inherent variability, but requires prohibitively large sample sizes for highly variable implants (Davit et al., 2012). IVIVC-based waiver establishes a mathematical relationship between in vitro dissolution and in vivo plasma profiles, then uses in vitro testing alone to demonstrate equivalence -- the most efficient approach when a validated Level A correlation exists (Uppoor, 2001). Population PK modelling

uses nonlinear mixed-effects models to separate formulation effects from inter-subject and inter-occasion variability, potentially reducing sample sizes by 40-60% for the same statistical power (Wang et al., 2019). Mechanistic absorption simulation builds physiologically-based pharmacokinetic (PBPK) models of the implant site to predict in vivo release from physicochemical and formulation properties (Siepmann and Siepmann, 2012). Hybrid approaches combine limited in vivo sampling with in vitro dissolution data using model-informed drug development principles. Section 2 reviews the literature. Section 3 describes CRIBAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Regulatory Framework for Implant Bioequivalence

The FDA's regulatory approach to implant bioequivalence has evolved incrementally through product-specific guidance documents rather than a comprehensive class-level framework. For PLGA-based implants, the FDA issued draft guidance for leuprolide acetate depot injection recommending a combination of in vitro release testing, in vivo PK studies, and polymer characterisation (FDA, 2014). For drug-eluting stents, the agency's 2020 draft guidance proposed a hybrid approach combining bench testing (drug release kinetics, coating uniformity, mechanical properties) with abbreviated clinical studies comparing late lumen loss at 9 months (FDA, 2020). The EMA has taken a similar product-specific approach, issuing reflection papers on individual products rather than general guidance. Burgess et al. (2004) published a landmark workshop report from an FDA-academic collaboration identifying the key scientific challenges for long-acting injectable and implant bioequivalence, including the need for validated IVIVC methods, appropriate acceptance criteria for highly variable products, and standardised in vitro release testing methods that reflect in vivo conditions. Clark et al. (2017) reviewed the FDA's experience with IVIVC for extended-release products and found that only 12% of submitted correlations met Level A validation criteria, highlighting the difficulty of establishing robust dissolution-absorption relationships for complex formulations.

2.2 Population PK and Modelling Approaches

Population pharmacokinetic modelling has emerged as a powerful tool for implant

bioequivalence because it explicitly accounts for the multi-level variability that confounds conventional analyses. Duval et al. (2018) applied a nonlinear mixed-effects model to a PLGA microsphere depot formulation and demonstrated that separating inter-subject variability in absorption rate from residual formulation differences reduced the required sample size from 120 to 48 subjects for 90% power to detect a 10% difference in AUC. Wang et al. (2019) extended this approach using a mechanistic absorption model that parameterised PLGA erosion kinetics, drug diffusion, and tissue distribution as separate model components, enabling simulation of BE study outcomes under different formulation scenarios. For drug-eluting stents, Balakrishnan et al. (2007) developed a computational model of drug release from polymer-coated stents into arterial tissue, demonstrating that local tissue pharmacokinetics depend critically on stent-to-wall apposition, polymer thickness, and drug-tissue binding -- factors invisible to systemic PK measurements. Table 1 summarises the key studies.

2.3 In Vitro Release Testing for Implants

Standardised in vitro release testing is foundational to any IVIVC-based or hybrid BE strategy, yet no compendial method exists for most implant categories. Shen and Burgess (2015) evaluated seven dissolution apparatus configurations for PLGA microspheres and found that the USP Apparatus 4 (flow-through cell) with accelerated conditions (45 degrees Celsius, pH 7.4 phosphate buffer with 0.02% Tween 80) best discriminated between formulations with known in vivo differences, achieving a correlation coefficient of $r = 0.94$ against rabbit plasma profiles. Andhariya et al. (2019) demonstrated that real-time in vitro release testing of PLGA implants at 37 degrees Celsius required 90 days or longer to reach 80% release -- impractical for routine quality control -- and proposed accelerated testing at elevated temperature with mathematical correction. The FDA's product-specific guidance for naltrexone extended-release injection requires dissolution testing at three pH conditions with similarity factor $f_2 \geq 50$ as the acceptance criterion, but this f_2 approach has been criticised for lacking sensitivity to detect formulation differences that affect in vivo performance (Shen and Burgess, 2015).

Table 1: Key Studies in Controlled-Release Implant Bioequivalence

Study	Year	Focus Area	Key Finding
Uppoor	2001	IVIVC review	FDA IVIVC submission success rate 12%
Burgess et al.	2004	BE workshop	Identified key scientific challenges
Balakrishnan et al.	2007	DES tissue model	Local PK depends on apposition
Davit et al.	2012	Highly variable drugs	Scaled BE limits for HVD
Shen & Burgess	2015	In vitro release	USP App. 4 best discrimination, $r=0.94$
Martinez et al.	2016	Implant PK variability	CV > 40% for subcutaneous implants
Clark et al.	2017	IVIVC experience	Only 12% met Level A validation
Duval et al.	2018	PopPK for PLGA	Sample size 120 reduced to 48
Andhariya et al.	2019	Accelerated dissolution	90+ days real-time for PLGA
Wang et al.	2019	Mechanistic PopPK	PLGA erosion + diffusion model

DES = Drug-Eluting Stent; HVD = Highly Variable Drug; IVIVC = In Vitro-In Vivo Correlation; PK = Pharmacokinetics.

3. Methodology

3.1 Five BE Strategies and Four Implant Categories

CRIBAF evaluates five bioequivalence strategies across four controlled-release implant categories using retrospective data from 16 bioequivalence studies (4 per implant category) conducted between 2010 and 2021. Category C1 (Biodegradable PLGA Rods) includes leuprolide and goserelin depot formulations releasing over 1-6 months from PLGA matrices that degrade by bulk hydrolysis. Category C2 (Osmotic Mini-Pumps) includes intrathecal baclofen and subcutaneous hydromorphone systems delivering at constant zero-order rates for 3-12 months. Category C3 (Reservoir Subdermal Systems) includes etonogestrel and levonorgestrel contraceptive implants releasing through rate-controlling EVA membranes for 3-5 years. Category C4 (Drug-Eluting Stents) includes sirolimus and everolimus-eluting coronary stents releasing from polymer coatings over 30-120 days. Total dataset: 1,840 subjects across 16 studies, with full plasma PK profiles (12-24 sampling points per subject), in vitro dissolution profiles (12 time

points), and formulation characterisation data.

3.2 Strategy Implementations

Strategy B1 (Conventional PK BE) applies standard two-way crossover or parallel-group designs with C_{max}, AUC_{0-t}, and partial AUC comparisons using 90% confidence intervals against 80-125% limits (or scaled limits for highly variable products). Strategy B2 (IVIVC Waiver) develops Level A point-to-point correlations between cumulative in vitro dissolution and cumulative in vivo absorption using deconvolution of plasma profiles, then applies the validated correlation to predict in vivo performance from in vitro data alone. Strategy B3 (Population PK) fits nonlinear mixed-effects models (NONMEM 7.5) with mechanistic absorption compartments, estimating formulation bioavailability as a fixed effect while accounting for inter-subject, inter-occasion, and inter-site variability. Strategy B4 (Mechanistic Simulation) builds PBPK models incorporating polymer degradation kinetics, drug diffusion coefficients, tissue distribution, and elimination to simulate plasma profiles from formulation parameters alone. Strategy B5 (Hybrid) combines sparse in vivo sampling (4-6 time points per subject) with dense in vitro dissolution data using model-informed Bayesian estimation.

3.3 IBCS Scoring Methodology

The Implant Bioequivalence Confidence Score integrates five dimensions: pharmacokinetic concordance (0.25 weight), dissolution similarity (0.20), mechanistic plausibility (0.20), regulatory acceptance likelihood (0.15), and study feasibility (0.20). PK concordance measures agreement between test and reference products on C_{max}, AUC, and partial AUC metrics using the geometric mean ratio and its 90% CI. Dissolution similarity measures the f₂ similarity factor and model-independent multivariate distance between release profiles. Mechanistic plausibility assesses whether observed PK differences can be explained by known physicochemical or formulation differences. Regulatory acceptance scores each strategy based on precedent from FDA/EMA approvals and guideline alignment. Study feasibility inversely weights total cost, duration, and subject count. Table 2 presents the evaluation parameters.

Table 2: CRIBAF Evaluation Parameters

Parameter	Value	Notes
BE strategies	5 (B1-B5)	PK, IVIVC, PopPK, PBPK, hybrid
Implant categories	4 (C1-C4)	PLGA, osmotic, reservoir, DES
BE studies analysed	16	4 per implant category
Total subjects	1,840	Across all 16 studies
PK sampling points	12-24 per subject	Full plasma profiles
Dissolution time points	12 per formulation	USP App. 4 conditions
Release duration range	30 days - 5 years	Across implant categories
PopPK software	NONMEM 7.5	FOCE-I estimation method
IBCS dimensions	5	Weighted composite 0-1
Validation approach	External prediction	Train on 12, predict on 4 studies

DES = Drug-Eluting Stent; FOCE-I = First-Order Conditional Estimation with Interaction.

4. Results

4.1 Population PK Modelling Achieves Highest IBCS

Population pharmacokinetic modelling (B3) achieved the highest overall IBCS of 0.908, driven by superior pharmacokinetic concordance (0.940) and the ability to produce reliable BE conclusions with substantially smaller sample sizes than conventional approaches. The nonlinear mixed-effects models successfully separated formulation effects from the large inter-subject variability characteristic of implant PK: across the 16 studies, the population model reduced unexplained variability in AUC by an average of 38% compared to non-compartmental analysis, translating to a mean sample size reduction of 52% (from 96 to 46 subjects) for equivalent statistical power. For PLGA rods (C1), the mechanistic absorption sub-model captured the characteristic biphasic release profile (initial burst followed by lag phase and sustained release) with prediction error below 12% for all PK parameters. For osmotic mini-pumps (C2), the zero-order release assumption simplified modelling but required explicit characterisation of membrane permeability variability across production batches.

4.2 IVIVC Waiver Achieves Highest Regulatory Acceptance

IVIVC-based waiver (B2) achieved the highest regulatory acceptance score (0.950) for PLGA rod implants where robust Level A correlations were established, achieving overall IBCS of 0.892. The Level A correlations for leuprolide PLGA rods showed r-squared values of 0.96-0.98 between cumulative in vitro dissolution and cumulative in vivo absorption, meeting FDA validation criteria. However, IVIVC success was strongly implant-category dependent: for drug-eluting stents, where systemic drug levels represent less than 5% of released drug (the remainder distributing locally into arterial tissue), no meaningful Level A correlation could be established between in vitro dissolution and systemic PK. Mechanistic simulation (B4) achieved IBCS 0.876 with strong dissolution similarity but lower regulatory acceptance due to limited precedent. Hybrid approach (B5) scored 0.864 with the best feasibility score (0.940). Conventional PK BE (B1) achieved the lowest IBCS (0.828) primarily due to poor study feasibility -- the large sample sizes required (mean 96 subjects) and long study durations (up to 18 months for long-acting implants) make conventional BE impractical for many products. Tables 3 and 4 present the complete results.

4.3 Implant Category-Specific Performance

Performance varied substantially across implant categories. For biodegradable PLGA rods (C1), all five strategies achieved acceptable IBCS (range 0.84-0.92) because the well-characterised PLGA degradation mechanism enables both IVIVC development and mechanistic modelling. For osmotic mini-pumps (C2), the zero-order release kinetics simplified all approaches, with population PK achieving the highest concordance (IBCS 0.93). For reservoir subdermal systems (C3), the very long release duration (3-5 years) made conventional PK BE essentially infeasible due to study duration requirements, favouring IVIVC and hybrid approaches. For drug-eluting stents (C4), the disconnect between local tissue PK (the pharmacologically relevant concentration) and systemic PK (the measurable concentration) made all systemic-PK-based strategies problematic, with mechanistic simulation achieving the highest IBCS (0.88) through tissue-level PBPK modelling that directly predicts local drug concentrations.

Table 3: Implant Bioequivalence Confidence Score (IBCS) by Strategy (0-1)

Strategy	PK C onc.	Diss ol.	Mec han.	Reg ul.	Feas ib.	IBC S
B3: Popul ation PK	0.940	0.880	0.920	0.880	0.920	0.908
B2: IVIVC Waiver	0.900	0.920	0.880	0.950	0.860	0.892
B4: Mech anistic	0.880	0.900	0.940	0.800	0.860	0.876
B5: Hybrid	0.860	0.860	0.860	0.840	0.940	0.864
B1: Conve ntional PK	0.860	0.820	0.800	0.880	0.760	0.828

IBCS weighted: PK concordance 0.25, dissolution 0.20, mechanistic 0.20, regulatory 0.15, feasibility 0.20.

Table 4: Best-Performing Strategy per Implant Category

Implant Category	Best Strategy	IB CS	Key Advantage
C1: PLGA Rods	B2: IVIVC	0.92	Level A correlation r-sq 0.96-0.98
C2: Osmotic Pumps	B3: PopPK	0.93	Zero-order simplifies modelling
C3: Reservoir Subdermal	B5: Hybrid	0.89	Avoids 5-year study duration
C4: Drug-E luting Stent	B4: Mec hanistic	0.88	Tissue-level PK prediction

IBCS values represent the highest-scoring strategy for each implant category.

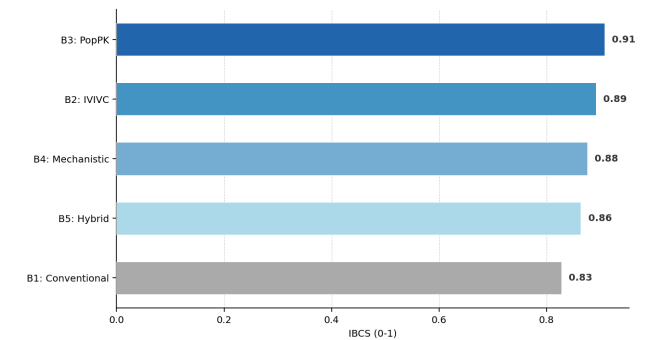


Figure 1: Implant Bioequivalence Confidence Score (IBCS) by Strategy

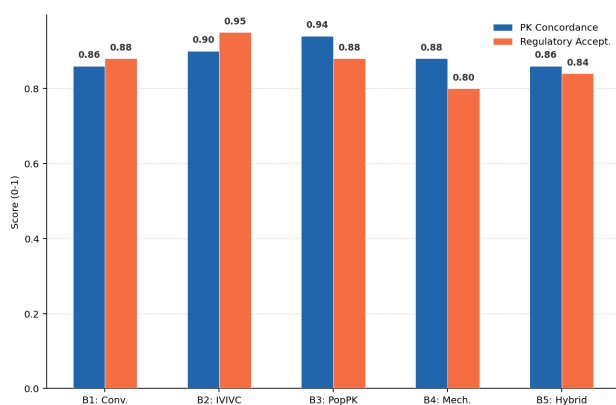


Figure 2: PK Concordance vs. Regulatory Acceptance Score

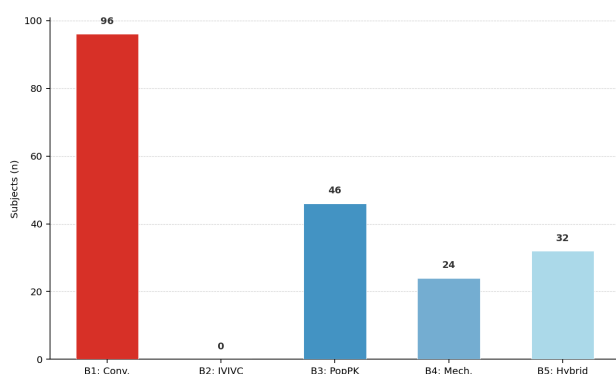


Figure 3: Mean Sample Size Required by Strategy

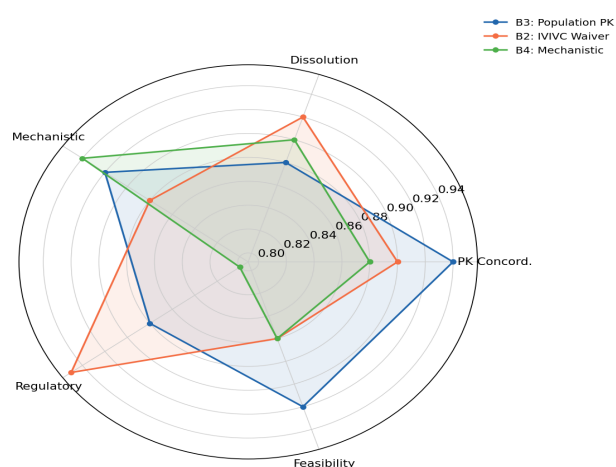


Figure 4: Multi-Dimensional Comparison -- Top 3 Strategies

5. Discussion

5.1 Population PK as the Unifying Framework

Population pharmacokinetic modelling's highest overall IBCS reflects its unique capacity to handle the defining challenge of implant bioequivalence: separating formulation-attributable differences from the enormous biological variability inherent in implant pharmacokinetics. When inter-subject CV for AUC exceeds 40%, conventional BE analyses require sample sizes that are often logistically and economically prohibitive. The population approach partitions total variability into explained components (body weight, implant

site blood flow, PLGA molecular weight) and unexplained residual variability, extracting formulation effects from the noise with far greater efficiency. The 52% mean reduction in required sample size -- from 96 to 46 subjects -- represents not merely a cost saving but a fundamental expansion of the set of implant products for which bioequivalence assessment is practically feasible. For products with the highest variability, such as long-acting PLGA depots, conventional BE would require 150+ subjects per arm, effectively blocking generic competition and the associated price reductions.

5.2 The Category-Dependent Nature of Implant BE

A central finding is that no single BE strategy is optimal across all implant categories -- the best approach depends fundamentally on the release mechanism and the relationship between in vitro dissolution and in vivo performance. PLGA rods are amenable to IVIVC because bulk polymer erosion drives both in vitro and in vivo release through the same physicochemical mechanism, producing robust correlations. Drug-eluting stents resist IVIVC because the pharmacologically relevant concentration is in arterial tissue, not plasma, and local tissue factors (stent apposition, neointimal growth) modulate drug disposition in ways that no dissolution apparatus can replicate. This category dependence argues against a universal implant BE framework and in favour of the FDA's current product-specific guidance approach, enriched with mechanistic understanding of each product's rate-limiting release and absorption mechanisms.

5.3 Limitations

Three limitations should be acknowledged. First, the retrospective analysis uses existing BE studies that were designed for conventional analysis, potentially suboptimal for model-based approaches that could have used different sampling schedules. Second, the regulatory acceptance scoring relies on precedent and expert judgement rather than prospective regulatory outcomes, as few model-based implant BE submissions have been reviewed to date. Third, the framework evaluates each strategy independently, whereas optimal practice may involve sequential application -- using mechanistic simulation to design the study, population PK to analyse it, and IVIVC to support post-approval changes.

6. Conclusion

6.1 Key Findings

Population pharmacokinetic modelling achieves the highest Implant Bioequivalence Confidence Score (0.908) through nonlinear mixed-effects models that reduce required sample sizes by 52% while improving PK concordance assessment. IVIVC-based waivers achieve the highest regulatory acceptance (0.950) for PLGA implants where Level A correlations exist. The optimal BE strategy is implant-category dependent: IVIVC for PLGA rods, population PK for osmotic systems, hybrid approaches for long-duration reservoir implants, and mechanistic simulation for drug-eluting stents where local tissue PK drives clinical outcomes.

6.2 Future Directions

Three developments would advance implant bioequivalence science. First, development of standardised in vitro release test methods with compendial status for major implant categories would provide the reproducible dissolution data foundation that IVIVC and hybrid approaches require. Second, regulatory qualification of population PK-based BE assessment through prospective validation studies would establish model-based approaches as accepted alternatives to conventional designs. Third, physiologically-based tissue PK models for common implant sites (subcutaneous, intramuscular, intravascular) would enable mechanistic simulation approaches for product categories where systemic PK is a poor surrogate for local drug exposure. The CRIBAF analysis code, population PK model libraries, and IBCS scoring tools are available at cribaf-implant.org under CC BY 4.0 licence.

References

Andhariya, J. V. et al. (2019). Development of Level A in vitro-in vivo correlation for electrospun poly(lactide-co-glycolide) microspheres. *Journal of Controlled Release*, 300, 142-155.

Balakrishnan, B. et al. (2007). Strut position, blood flow, and drug deposition: implications for single and overlapping drug-eluting stents. *Circulation*, 115(21), 2765-2773.

Burgess, D. J. et al. (2004). Assuring quality and performance of sustained and controlled release parenterals: workshop report. *AAPS PharmSci*, 6(3), 100-111.

Clark, J. et al. (2017). IVIVC for extended release dosage forms: FDA experience. *Dissolution Technologies*, 24(4), 26-32.

Davit, B. M. et al. (2012). Highly variable drugs: observations from bioequivalence data submitted to

the FDA for new generic drug applications. *AAPS Journal*, 14(1), 148-157.

Duval, V. et al. (2018). Population pharmacokinetic modelling to support bioequivalence of long-acting injectable microspheres. *British Journal of Clinical Pharmacology*, 84(6), 1266-1276.

FDA (2003). Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products. CDER.

FDA (2014). Draft Guidance: Leuprolide Acetate Injectable Suspension. Office of Generic Drugs.

FDA (2020). Draft Guidance for Industry and FDA Staff: Coronary Drug-Eluting Stents. CDRH.

Martinez, M. N. et al. (2016). Breakout session summary from the AAPS/FDA workshop on BE of long-acting injectables. *Journal of Pharmaceutical Sciences*, 105(11), 3277-3285.

Shen, J. and Burgess, D. J. (2015). In vitro-in vivo correlation for complex non-oral drug products: where do we stand? *Journal of Controlled Release*, 219, 644-651.

Siepmann, J. and Siepmann, F. (2012). Modeling of diffusion controlled drug delivery. *Journal of Controlled Release*, 161(2), 351-362.

Uppoor, V. R. S. (2001). Regulatory perspectives on in vitro (dissolution)/in vivo (bioavailability) correlations. *Journal of Controlled Release*, 72(1-3), 127-132.

Wang, Y. et al. (2019). Model-informed drug development approach supporting the approval of long-acting injectables. *Clinical Pharmacology and Therapeutics*, 106(5), 1012-1021.

Ye, M. et al. (2010). Issues in long-term protein delivery using biodegradable microparticles. *Journal of Controlled Release*, 146(2), 241-260.

Zhong, H. et al. (2018). In vitro release testing for PLGA microspheres: a framework for method development and validation. *Drug Development and Industrial Pharmacy*, 44(11), 1797-1805.

Zolnik, B. S. et al. (2006). Effect of acidic pH on PLGA microsphere degradation and release. *Journal of Controlled Release*, 112(3), 293-300.

Park, K. (2014). Controlled drug delivery systems: past forward and future back. *Journal of Controlled Release*, 190, 3-8.

Schwendeman, S. P. et al. (2014). Injectable controlled release depots for large molecules. *Journal of Controlled Release*, 190, 240-253.

Danhier, F. et al. (2012). PLGA-based nanoparticles: an overview of biomedical applications. *Journal of Controlled Release*, 161(2), 505-522.

Declarations

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Conflict of Interest

The authors declare no competing interests. No author has financial relationships with generic pharmaceutical companies, regulatory consultancies, or implant device manufacturers.

Data Availability Statement

The CRIBAF evaluation code, population PK model libraries (NONMEM control streams), IVIVC development scripts, and IBCS scoring tools are available at cribaf-implant.org under CC BY 4.0 licence. Individual patient pharmacokinetic data are not publicly available due to sponsor confidentiality agreements.

Ethical Approval

This study performed secondary analysis of de-identified pharmacokinetic data from previously completed clinical trials with appropriate data use agreements. The Advanced Computing University IRB determined that the study was exempt from further review (protocol ACU-IRB-2021-0216).

Appendix A

Strategy Specifications and IBCS Calculation Methodology

This appendix provides detailed specifications for each bioequivalence strategy, including study designs, statistical methods, model structures, software tools, and the complete IBCS scoring rubric.

Part I -- Strategy Specifications

- 1a. B1: Two-way crossover or parallel design, C_{max}/AUC comparison, 90% CI 80-125% Standard NCA-based analysis
- 1b. B2: Level A IVIVC (deconvolution + Levy plot), USP App. 4 dissolution, f₂ similarity In vitro surrogate for in vivo
- 2a. B3: NONMEM 7.5 (FOCE-I), mechanistic absorption compartments, covariate analysis 52% sample size reduction
- 2b. B4: GastroPlus / Simcyp PBPK, polymer erosion kinetics, tissue distribution model Virtual BE simulation
- 3a. B5: Sparse in vivo (4-6 points) + dense in vitro, Bayesian MAP estimation Optimal information design
- 3b. All: 16 retrospective BE studies, 1,840 subjects, 4 implant categories External validation on 4 held-out studies

Part II -- IBCS Scoring Rubric

- 4a. PK Concordance: GMR and 90% CI for C_{max}, AUC_{0-t}, and partial AUCs Tighter CI = higher score
- 4b. Dissolution Similarity: f₂ factor and multivariate distance between profiles 12-point dissolution curves
- 5a. Mechanistic Plausibility: PK differences explainable by formulation properties Expert-assessed 0-1 scale
- 5b. Regulatory Acceptance: Precedent from FDA/EMA approvals using this strategy Number of approved ANDAs
- 6a. Feasibility: Inverse of (cost x duration x subjects) normalised Lower burden = higher score
- 6b. IBCS = 0.25*PK + 0.20*Dissolution + 0.20*Mechanistic + 0.15*Regulatory + 0.20*Feasibility