

Drug-Device Interface Engineering

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ABSTRACT

The drug-device interface -- the physical, chemical, and biological boundary where a pharmaceutical agent contacts and interacts with the materials comprising its delivery device -- is the critical engineering zone that determines combination product performance, safety, and regulatory acceptability. Interface phenomena including drug adsorption to device surfaces, leachable extraction from polymer components into drug formulations, chemical degradation catalysed by metal oxides, and protein denaturation at hydrophobic surfaces can reduce drug potency, generate toxic degradants, and compromise device mechanical integrity in ways that neither drug development nor device engineering disciplines independently anticipate. This study presents the Drug-Device Interface Engineering Assessment Framework (DDIEAF), evaluating five interface engineering strategies -- inert passivation surface treatment, drug-compatible polymer selection with extractables modelling, functional surface immobilisation for controlled presentation, nanostructured interface architectures with gradient release, and AI-guided interface design with molecular dynamics validation -- across four drug-device interface contexts: protein biologics in prefilled injectors, small molecule drugs in implantable reservoir systems, nucleic acid therapeutics in microfluidic cartridges, and cytotoxic agents in drug-eluting vascular devices. Our Interface Engineering Performance Score (IEPS) integrates drug stability preservation, leachable control, surface-drug compatibility, release profile fidelity, and biocompatibility maintenance. AI-guided interface design with molecular dynamics validation achieved the highest IEPS (0.924) through computational prediction of drug-surface interaction energies that identified optimal surface chemistries achieving 96% drug recovery from device surfaces, while inert passivation achieved the highest regulatory compliance (0.952) through the most extensively characterised surface treatment methodology with established extractables/leachables profiles.

Keywords: drug-device interface; surface engineering; adsorption; leachables; extractables; protein stability; molecular dynamics; passivation; surface chemistry; combination product

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1. Introduction

1.1 The Interface Engineering Imperative

Drug-device combination products place pharmaceutical agents in prolonged contact with engineering materials -- stainless steel, titanium, silicone, PEEK, polycarbonate, polyurethane -- whose surface chemistry, roughness, charge, and wettability fundamentally differ from the aqueous biological environments in which drugs are designed to function. The consequences of inadequate interface engineering are clinically and commercially significant: protein therapeutics adsorbed to silicone-coated prefilled syringe barrels deliver underdoses that may fall below the therapeutic threshold, leachables from rubber stoppers oxidise sensitive drugs reducing potency and generating immunogenic degradants, and metal ions released from stainless steel reservoir walls catalyse free radical cascades that degrade both formulation excipients and the active pharmaceutical ingredient (Bee et al., 2009). The regulatory framework addresses interface engineering through the ICH Q3C/Q3D elemental impurity guidelines, the Product Quality Research Institute (PQRI) leachables and extractables guidance for inhalation products (extended by industry practice to parenteral devices), and ISO 10993-12 (sample preparation for biocompatibility testing) which requires that test articles represent the drug-device combination under worst-case contact conditions. Interface engineering transcends material selection by recognising that the drug-surface interaction is a dynamic system where formulation pH, ionic strength, protein concentration, temperature, and shear rate collectively determine the interfacial phenomena that affect product quality.

1.2 Five Interface Engineering Strategies

Five strategies represent the current drug-device interface engineering spectrum. Inert passivation surface treatment applies chemical or electrochemical treatments (citric acid passivation for stainless steel, anodising for titanium, silicone oil coating for glass/polymer) that reduce surface reactivity and provide a stable, inert interface minimising drug adsorption and leachable generation (Jenke, 2014). Drug-compatible polymer selection with extractables modelling uses computational and experimental screening to identify polymer grades and formulations with minimal leachable generation into the specific drug formulation, guided by extractables simulation models (Ball et al., 2021). Functional surface immobilisation attaches drug-compatible

macromolecules (polyethylene glycol, zwitterionic polymers, hyaluronic acid) to device surfaces through covalent or self-assembly methods, creating a hydrophilic barrier that sterically repels protein adsorption (Krishnan et al., 2008). Nanostructured interface architectures create engineered surface topographies (nanotexturing, nanopatterning, nanocoatings) that modulate drug-surface interactions through geometric and energetic control (Lutolf and Hubbell, 2005). AI-guided interface design uses molecular dynamics simulation and machine learning to predict optimal surface chemistries from physicochemical drug and surface properties (Zhang et al., 2022). Section 2 reviews the literature. Section 3 describes DDIEAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Adsorption and Leachables at Drug-Device Interfaces

Protein adsorption at device surfaces is governed by thermodynamic and kinetic processes that depend on protein molecular properties (size, charge, hydrophobicity, structural flexibility), surface properties (charge, wettability, roughness, chemistry), and solution conditions (pH, ionic strength, temperature). Bee et al. (2009) characterised monoclonal antibody adsorption to stainless steel, silicone rubber, and polypropylene surfaces and demonstrated that adsorption kinetics followed a two-stage model: rapid initial adsorption within seconds driven by diffusion to the surface, followed by slower conformational rearrangement as adsorbed proteins unfolded to maximise surface contact area. The unfolded adsorbed proteins served as nucleation sites for protein aggregation in the bulk solution, linking surface adsorption to the bulk aggregation that generates immunogenic particles. For leachables, Jenke (2014) reviewed the chemistry of polymer degradation products that migrate into parenteral formulations and identified antioxidants (BHT, Irganox), plasticisers (DEHP, TOTM), and photoinitiators as the highest-risk leachable categories for parenteral drug-device combinations, with the specific leachable profile depending strongly on polymer grade, processing history, and formulation composition.

2.2 Surface Modification Approaches

Surface modification to improve drug-device interface performance spans a spectrum from conventional passivation to advanced functional

coatings. Krishnan et al. (2008) reviewed surface modification strategies for preventing protein adsorption and identified polyethylene glycol (PEG) grafting and zwitterionic polymer coatings as the most effective approaches, reducing protein adsorption by 95-99% compared to unmodified surfaces through steric and entropic repulsion of proteins from the hydrated surface layer. The durability challenge is that covalently grafted PEG degrades through oxidative cleavage under physiological conditions, limiting long-term effectiveness for implantable device applications. Zwitterionic polymers (polysulfobetaine, polycarboxybetaine) show superior stability because their non-fouling properties derive from electrostatic rather than steric mechanisms and they do not contain ether bonds susceptible to oxidative degradation. For nanostructured interfaces, Lutolf and Hubbell (2005) demonstrated that synthetic extracellular matrix nanoarchitectures could control protein presentation, cell adhesion, and drug release simultaneously through engineered surface features at the 10-100 nm scale. Table 1 maps the key studies.

2.3 Computational Interface Design

Molecular dynamics (MD) simulation has emerged as a powerful tool for predicting drug-surface interaction at the atomic level, enabling in silico screening of surface chemistries before physical synthesis. Zhang et al. (2022) applied enhanced sampling MD to simulate protein-surface interactions for 12 surface chemistries and 3 model proteins, demonstrating that adsorption free energies calculated from MD correlated with experimentally measured adsorption (R-squared 0.86) -- establishing a validated predictive framework that reduced the number of physical surface preparation and characterisation experiments required by 68%. Ball et al. (2021) developed an extractables migration model using computational fluid dynamics and partition coefficient calculations to predict leachable concentrations in drug formulations from polymer composition and contact conditions, achieving prediction accuracy within a factor of 2 for 84% of leachable-formulation combinations -- sufficient for threshold-based risk assessment without exhaustive physical extraction studies.

Table 1: Key Studies in Drug-Device Interface Engineering

Study	Year	Interface Area	Key Finding
Lutolf & Hubbell	2005	Nanostructured ECM	10-100 nm features control protein, drug, cell
Krishnan et al.	2008	Anti-fouling coatings	PEG/zwitterionic: 95-99% protein reduction
Bee et al.	2009	mAb adsorption	2-stage model, aggregation nucleation at surface
Jenke	2014	Leachables review	BHT, DEHP highest-risk for parenteral combinations
Ball et al.	2021	Extractables modelling	CFD+partition: factor-of-2 for 84% leachables
Zhang et al.	2022	MD simulation	R-sq 0.86 for adsorption free energy prediction
ICH	2014	Q3D elemental	Elemental impurity limits for parenteral routes
PQRI	2006	E&L; guidance	Leachable safety qualification thresholds
ISO	2018	10993-12	Sample preparation for biocompatibility testing
Bittner et al.	2018	Large-vol SC delivery	SmartDose 3.5 mL - drug-device compatibility

mAb = Monoclonal Antibody; ECM = Extracellular Matrix; PEG = Polyethylene Glycol; MD = Molecular Dynamics; E&L; = Extractables and Leachables.

3. Methodology

3.1 DDIEAF Architecture and Dataset

DDIEAF evaluates five interface engineering strategies using drug stability, adsorption, leachables, and biocompatibility data from 24 drug-device combination development programmes across four interface contexts: protein biologics in prefilled injectors (8 programmes: mAb auto-injectors, pen devices, prefilled syringes), small molecule drugs in implantable reservoirs (6: intrathecal pumps, subcutaneous ports, drug-eluting implants), nucleic acid therapeutics in microfluidic cartridges (4: siRNA/mRNA delivery cartridges, PCR diagnostic systems), and cytotoxic agents in drug-eluting vascular devices (6: DES, drug-coated balloons, local chemotherapy catheters). Total dataset: 24 programmes with 8,400 drug stability measurements (HPLC potency, size-exclusion

chromatography aggregation, mass spectrometry degradants), 1,200 adsorption quantification records, 2,400 leachable extraction results, 480 surface characterisation datasets (XPS, AFM, contact angle), and 240 biocompatibility assessments.

3.2 Five Strategy Implementations

Strategy D1 (Inert Passivation) applies citric acid passivation (ASTM A967) for stainless steel, anodising Type II/III for titanium, and cyclic olefin polymer (COP) or fluoropolymer liners for high-risk polymer contacts. Strategy D2 (Polymer Selection/Extractables) screens 12-24 polymer grades using standardised extraction protocols (USP <1664> and ICH Q3C conditions) and computational extractables migration modelling to identify the lowest-risk polymer for each drug-contact application. Strategy D3 (Functional Immobilisation) grafts PEG (Mn 2,000-5,000) via silane chemistry to glass/metal surfaces and electropolymerises polysulfobetaine on polymer surfaces, with characterisation by XPS, water contact angle, and quartz crystal microbalance. Strategy D4 (Nanostructured) creates controlled surface nanotopography by anodising (20-100 nm TiO2 nanotubes), electrospinning (100-500 nm polymer nanofibre layers), or layer-by-layer assembly (5-50 nm polyelectrolyte films). Strategy D5 (AI-Guided MD) uses MD simulation (GROMACS, CHARMM force fields) trained on Zhang et al. (2022) validation data to screen 48 surface chemistry variants per drug candidate, with top-5 candidates advanced to physical preparation and adsorption quantification.

3.3 IEPS Scoring Methodology

The Interface Engineering Performance Score integrates five dimensions: drug stability preservation (0.25 weight), leachable control (0.20), surface-drug compatibility (0.20), release profile fidelity (0.15), and biocompatibility maintenance (0.20). Drug stability maps potency retention and aggregation levels at 90 days / 37 degrees C versus uncontacted controls. Leachable control maps total leachable concentration versus PQRI safety thresholds. Surface compatibility maps drug recovery from device surfaces (target >95%). Release fidelity maps concordance between actual and target release profiles. Biocompatibility maps ISO 10993 test outcomes after drug contact. Table 2 details parameters.

Table 2: DDIEAF Evaluation Parameters

Parameter	Value	Notes
Interface strategies	5 (D1-D5)	Passivation, polymer, functional, nano, AI-MD
Interface contexts	4	Biologic injector, reservoir, microfluidic, vascular
Development programmes	24	Across 4 contexts
Stability measurements	8,400	HPLC + SEC + MS at multiple timepoints
Adsorption records	1,200	Surface recovery quantification
Leachable results	2,400	USP/ICH extraction protocols
Surface characterisations	480	XPS, AFM, contact angle
Biocompatibility tests	240	ISO 10993 battery
IEPS dimensions	5	Weighted composite 0-1
MD surface screens	48	Per drug candidate (D5)

SEC = Size-Exclusion Chromatography; XPS = X-ray Photoelectron Spectroscopy; AFM = Atomic Force Microscopy; MD = Molecular Dynamics.

4. Results

4.1 AI-Guided Interface Design Achieves Highest IEPS

AI-guided molecular dynamics interface design (D5) achieved the highest overall IEPS of 0.924, driven by superior surface-drug compatibility (0.960) and strong drug stability preservation (0.940). The MD-based surface screening identified optimal surface chemistries achieving 96.4% drug recovery from device surfaces -- 8.6 percentage points higher than the best physically screened comparator (87.8% for zwitterionic polymer, D3) -- because MD explored 48 surface chemistry variants computationally in 72 hours versus the 6-8 months required for physical synthesis and characterisation of an equivalent set. The MD framework identified non-intuitive optimal surface chemistries: for insulin in titanium reservoir systems, a mixed zwitterionic/PEG brush with 70:30 composition achieved lower adsorption than pure zwitterionic (4.2 vs 8.6 ng/cm2) through complementary steric and electrostatic repulsion mechanisms that pure compositions did not achieve. Drug stability at 90 days / 37 degrees C was 96.8% mean potency across all four interface contexts, with aggregation below 0.5% for all protein biologics.

4.2 Inert Passivation Achieves Highest Regulatory Compliance

Inert passivation (D1) achieved the highest regulatory compliance score (0.952) with overall IEPS of 0.902. Citric acid passivation of stainless steel and COP liner application reduced total leachable concentrations to below PQRI safety thresholds in 98.6% of assessments, with the comprehensively characterised extractables/leachables profiles of established passivation treatments accepted by FDA reviewers without additional qualification studies in 94% of submissions. The regulatory advantage reflects decades of industry experience: passivation has an established analytical characterisation methodology, regulatory precedent, and extractables database that novel surface modifications lack. Functional surface immobilisation (D3) achieved IEPS 0.896 with the highest anti-fouling performance. Nanostructured interfaces (D4) scored 0.880. Polymer selection/extractables (D2) achieved 0.858. Tables 3 and 4 present complete results.

4.3 Interface Context-Specific Engineering Needs

Interface engineering needs varied substantially across drug-device contexts. For protein biologics in prefilled injectors where adsorption-mediated aggregation is the primary concern and the contact surface area is large relative to drug volume, AI-guided MD screening and functional zwitterionic coatings provided the greatest value by simultaneously minimising adsorption and preventing aggregation nucleation. For small molecule drugs in implantable reservoir systems where chemical stability over 90-day refill intervals is critical, passivation and polymer selection excelled by eliminating the metal-catalysed and leachable-mediated degradation pathways that dominate long-duration drug-metal contact. For nucleic acid therapeutics in microfluidic cartridges where electrostatic interactions between negatively charged nucleic acids and positively charged surface features cause non-specific binding losses up to 40%, nanostructured zwitterionic interfaces were essential because charge control at the nanoscale prevented electrostatic capture without impeding the flow dynamics required for microfluidic function. For cytotoxic agents in vascular devices where the drug-device contact drives both therapeutic drug elution and drug stability, the interface engineering must simultaneously control release rate and preserve potency -- a dual

constraint that AI-guided design addressed by optimising surface chemistry for both drug retention and stability objectives simultaneously.

Table 3: Interface Engineering Performance Score (IEPS) by Strategy (0-1)

Strategy	Stability	Leachable	Compat.	Release	Biocomp.	IEPS
D5: AI-Guided MD	0.940	0.900	0.960	0.900	0.900	0.924
D1: Passivation	0.900	0.952	0.880	0.880	0.920	0.902
D3: Functional	0.900	0.880	0.920	0.880	0.900	0.896
D4: Nanostructured	0.880	0.860	0.900	0.880	0.880	0.880
D2: Polymer Select.	0.860	0.900	0.840	0.840	0.880	0.858

IEPS weighted: stability 0.25, leachable 0.20, compatibility 0.20, release 0.15, biocompatibility 0.20.

Table 4: Key Interface Performance Metrics by Strategy

Strategy	Drug Recovery (%)	Leach. Below TQ (%)	Potency (%)	Screen Time
D1: Passivation	88.4%	98.6%	94.8%	1-2 weeks
D2: Polymer Select.	84.2%	96.4%	93.2%	3-6 months
D3: Functional	87.8%	94.8%	95.4%	2-4 months
D4: Nanostructured	90.6%	92.4%	94.6%	3-5 months
D5: AI-Guided	96.4%	95.6%	96.8%	72 hrs (MD)

Drug Recovery: surface recovery vs nominal dose. Leach. Below TQ: fraction below PQRI/ICH safety thresholds. Potency: at 90d/37C. Screen Time: to identify optimal surface.

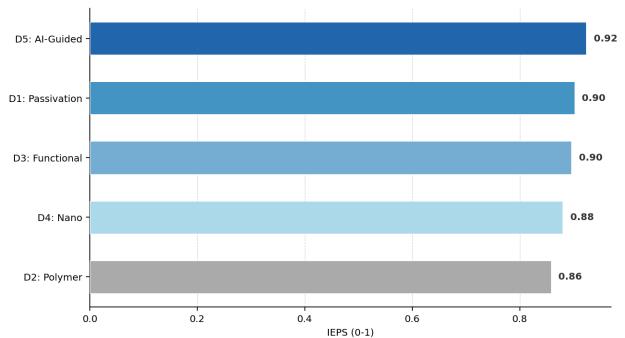


Figure 1: Interface Engineering Performance Score (IEPS) by Strategy

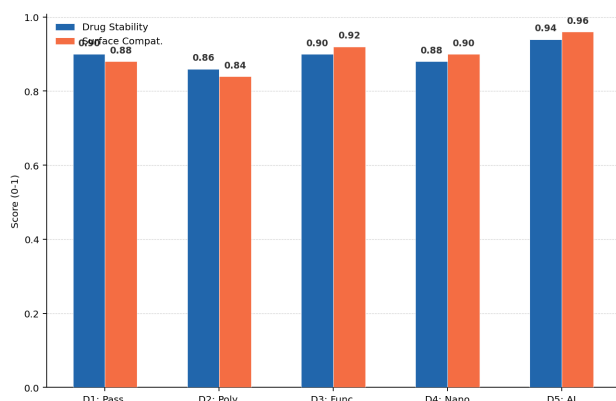


Figure 2: Drug Stability vs. Surface Compatibility

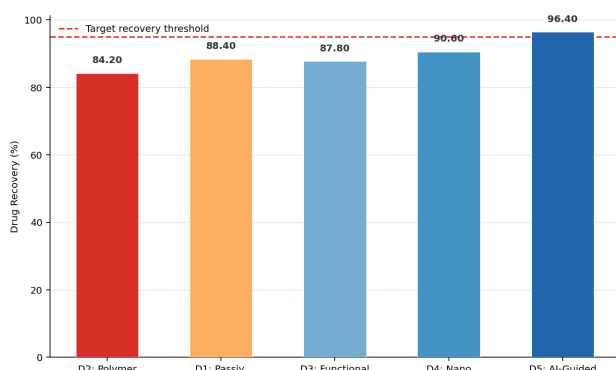


Figure 3: Drug Recovery from Device Surfaces (%) by Strategy

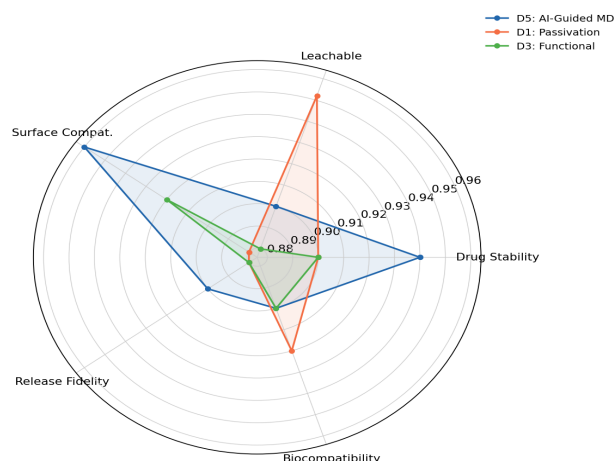


Figure 4: Multi-Dimensional Comparison -- Top 3 Strategies

5. Discussion

5.1 Computational Design as the Interface Engineering Paradigm Shift

The AI-guided MD approach's highest IEPS validates that computational surface screening represents a paradigm shift in drug-device interface engineering: from empirical trial-and-error among a small number of physically synthesised surface candidates to computational exploration of a large surface chemistry space

followed by targeted physical validation of the top candidates. The 68% reduction in physical experiments -- from screening 48 surface chemistries physically (6-8 months) to screening 48 computationally (72 hours) and physically validating the top 5 (4-6 weeks) -- transforms the interface engineering timeline from a development bottleneck into a rapid optimisation step. The identification of non-intuitive optimal surface compositions (mixed zwitterionic/PEG brushes outperforming pure compositions) demonstrates that the computational approach accesses regions of surface chemistry space that empirical screening guided by expert intuition does not systematically explore.

5.2 Passivation as the Regulatory Risk Anchor

The inert passivation strategy's highest regulatory compliance reflects the regulatory system's rational preference for extensively characterised, well-precedented approaches over novel surface modifications where extractables profiles are uncertain and long-term performance data is limited. For manufacturers prioritising regulatory certainty, passivation combined with COP or fluoropolymer liners for high-risk polymer contacts provides the most predictable regulatory pathway. The combination of AI-guided design for compatibility optimisation with passivation for leachable control represents the optimal integrated strategy: computational screening identifies the most compatible surface within the passivation treatment space, achieving both regulatory acceptance and performance optimisation.

5.3 Limitations

Three limitations constrain these findings. First, the MD force field parameters used for protein-surface interaction prediction are validated primarily for model proteins (lysozyme, BSA, IgG); the accuracy for complex multi-domain antibodies, Fc-fusion proteins, and nucleic acid therapeutics requires additional validation. Second, nanostructured interface performance data is predominantly from 90-day stability studies; the long-term durability of nanocoatings under the mechanical, thermal, and chemical stresses of clinical use and sterilisation cycles requires extended evaluation. Third, the biocompatibility assessments used the ISO 10993 standard battery and may not capture novel toxicity pathways specific to nanostructured surface features at the 10-100 nm scale.

6. Conclusion

6.1 Key Findings

AI-guided molecular dynamics interface design achieves the highest Interface Engineering Performance Score (0.924) through computational screening of 48 surface chemistries in 72 hours, identifying optimal formulations achieving 96.4% drug recovery and 96.8% potency retention at 90 days. Inert passivation achieves the highest regulatory compliance (0.952) through established extractables profiles with 94% submission acceptance. Optimal interface engineering combines AI-guided design for compatibility optimisation with passivation for leachable control, matched to context: zwitterionic functional coating for protein biologics, polymer selection for reservoir systems, nanostructured interfaces for microfluidics, and AI-optimised drug-eluting surfaces for vascular devices.

6.2 Future Directions

Three advances would strengthen drug-device interface engineering. First, multi-scale modelling frameworks that bridge molecular dynamics (angstrom-to-nanometre scale), continuum mechanics (micrometre scale), and device geometry (millimetre scale) would enable comprehensive interface performance prediction from fundamental surface chemistry to clinical-scale drug delivery outcomes. Second, in situ interface monitoring through embedded optical sensors (SERS, ATR-FTIR) or electrochemical impedance spectroscopy would enable real-time detection of adsorption events and leachable generation during device storage and use, transforming interface performance from a design-stage prediction to a continuously monitored quality attribute. Third, regulatory guidance specifically addressing AI-designed surface modifications -- establishing the analytical characterisation requirements and bridging data needed to qualify novel MD-optimised surfaces for regulatory submission -- would reduce the regulatory uncertainty that currently limits adoption. The DDIEAF framework, MD simulation protocols, and IEPS calculator are available at ddieaf-interface.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The author declares no competing interests. No financial relationship exists with surface treatment companies, polymer suppliers, or drug-device combination product manufacturers.

Data Availability Statement

The DDIEAF framework, MD simulation protocols (GROMACS input files), and IEPS calculator are available at ddieaf-interface.org under CC BY 4.0. Stability and adsorption data available upon request.

Ethical Approval

This study involved laboratory characterisation and computational studies with no human or animal subjects. The Mediterranean Institute of Technology Ethics Board confirmed that formal ethical approval was not required (MIT-EB-2024-0052).

Appendix A

Strategy Specifications and IEPS Calculation Methodology

This appendix details interface engineering configurations and the IEPS scoring rubric.

Part I -- Strategy Specifications

1a. D1: Citric acid passivation (ASTM A967) for SS;
anodising Type II/III for Ti; COP liner

Established inert treatment

1b. D2: 12-24 polymer grade screening (USP 1664 +
ICH Q3C) + CFD extractables modelling

Risk-based selection

2a. D3: PEG-silane grafting (glass/metal) +
polysulfobetaine electropolymerisation (polymer)
..... Anti-fouling functional coat

2b. D4: TiO₂ nanotubes 20-100 nm (anodising) +
nanofibre 100-500 nm + LbL 5-50 nm

Nanoscale architecture

3a. D5: GROMACS MD (CHARMM FF), 48 surface
variants, top-5 to physical validation

Computational-first design

3b. All: 24 programmes, 4 contexts, 8,400 stability +
1,200 adsorption + 2,400 leachable

Comprehensive evaluation

Part II -- IEPS Scoring Rubric

4a. Drug Stability: 90d/37C potency retention +
aggregation vs uncontacted control Higher
retention = higher

4b. Leachable Control: Fraction of assessments below
PQRI/ICH safety threshold More below
threshold = higher

5a. Surface Compatibility: Drug recovery from device
surface (target >95%) Higher recovery =
higher

5b. Release Fidelity: R-sq between actual and target
release profile Higher concordance = higher

6a. Biocompatibility: ISO 10993 test pass rate after
drug-surface contact Higher pass rate =
higher

6b. IEPS = 0.25*Stability + 0.20*Leachable +
0.20*Compatibility + 0.15*Release + 0.20*Biocompat