

Regulatory Pathways for Combination Therapeutic Products

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ABSTRACT

Combination therapeutic products -- drug-device, drug-biologic, and device-biologic combinations -- occupy a regulatory grey zone where drug, device, and biologic frameworks intersect. The FDA regulates over 200 approved combination products through its Office of Combination Products (OCP), which assigns a lead centre (CDER, CBER, or CDRH) based on the primary mode of action (PMOA). The EU MDR (2017/745) and IVDR (2017/746) create a parallel but distinct framework where notified bodies assess the device component while national competent authorities assess the drug component. These divergent transatlantic frameworks create substantial compliance burden for manufacturers developing combination products for global markets: different classification systems, different clinical evidence requirements, different post-market surveillance obligations, and different timelines for approval. We present the Regulatory Pathway Assessment Framework (RPAF), evaluating five regulatory pathway strategies -- single-jurisdiction lead-centre approach, parallel multi-jurisdictional filing, modular evidence packages, adaptive regulatory engagement, and computational evidence integration -- across four combination product categories (drug-eluting implants, prefilled drug delivery devices, diagnostic-therapeutic companions, and digital therapeutic combinations). Our Regulatory Pathway Efficiency Score (RPES) measures approval timeline, evidence package efficiency, global harmonisation potential, post-market compliance burden, and innovation accommodation. Adaptive regulatory engagement achieves the highest RPES (0.926) through continuous pre-submission dialogue that aligns evidence generation with evolving regulatory expectations, while computational evidence integration achieves the highest innovation accommodation (0.960) by leveraging in silico modelling to reduce clinical trial burden for iterative device modifications.

Keywords: regulatory pathways; combination products; FDA; EU MDR; drug-device; clinical evidence; post-market surveillance; regulatory science

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1. Introduction

1.1 The Combination Product Regulatory Challenge

Combination products are the fastest-growing segment of therapeutic innovation: drug-eluting stents combine antiproliferative drugs with metallic scaffolds, prefilled syringes combine biologic drugs with delivery devices, companion diagnostics pair molecular tests with targeted therapies, and digital therapeutics combine software algorithms with pharmacological treatments. The FDA's Office of Combination Products received 482 requests for designation in 2021 (up from 168 in 2010), reflecting the increasing convergence of drug, device, and digital technologies. The regulatory challenge is that each component of a combination product would be regulated under a different framework if marketed separately: drugs under 21 CFR 314 (NDA) or 351 (BLA), devices under 21 CFR 814 (PMA) or 510(k), and biologics under 21 CFR 601. When combined, the product is assigned to a lead centre based on PMOA, but must still satisfy the requirements of both drug and device frameworks -- creating a regulatory burden that exceeds either framework alone. Development timelines for combination products average 8-12 years versus 5-7 years for standalone drugs or 2-4 years for standalone devices (FDA OCP, 2020), primarily because manufacturers must navigate requirements from multiple regulatory disciplines simultaneously.

1.2 Transatlantic Regulatory Divergence

The US and EU regulatory frameworks for combination products differ fundamentally. The FDA uses a single-application approach: one product, one application (NDA, BLA, or PMA), one lead centre, with consultation from other centres for the non-lead components. The EU uses a split-assessment approach: the device component is assessed by a notified body (under MDR/IVDR), while the drug component is assessed by a national competent authority or EMA -- requiring separate submissions and coordination between assessors. For a drug-eluting stent, the FDA reviews the entire product under a PMA (led by CDRH with CDER consultation for the drug), while the EU requires a notified body assessment of the device plus an EMA scientific opinion on the drug component (Article 117 MDR). This divergence means that manufacturers must prepare different evidence packages, meet different standards, and follow different timelines for each jurisdiction -- doubling the regulatory investment for global market access. Kovacs and Ivanov (2022)

evaluated AI risk assessment for medical devices that informs the safety evidence required by regulators, and Klein (2022) assessed pharmacokinetic profiling that provides the drug component evidence for combination products. Section 2 reviews the literature. Section 3 describes RPAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 FDA Combination Product Framework

The FDA's combination product framework is defined by 21 CFR Part 3, which establishes the OCP and the PMOA-based assignment algorithm. The OCP assigns the product to CDER (drug lead), CBER (biologic lead), or CDRH (device lead) based on which component provides the primary therapeutic effect. For drug-eluting stents, the device scaffolding is the PMOA (without the stent, the drug has no local delivery mechanism), so CDRH leads. For prefilled syringes containing biologic drugs, the drug is the PMOA (the syringe is merely the delivery container), so CDER or CBER leads. The Pre-Submission (Q-Sub) programme allows manufacturers to engage FDA before filing, receiving feedback on PMOA determination, evidence requirements, and study design. Kramer et al. (2012) showed that manufacturers who used pre-submission meetings had 30% shorter review times and 22% fewer deficiency letters -- demonstrating the value of early regulatory engagement. The 21st Century Cures Act (2016) streamlined combination product review by requiring intercenter agreements and establishing timelines for consultation between centres.

2.2 EU MDR and International Frameworks

The EU MDR (2017/745) significantly changed combination product regulation by requiring EMA consultation (Article 117) for drug-device combinations where the drug component is integral (not merely co-packaged). The Article 117 opinion assesses the quality and safety of the drug component, including GMP compliance, stability data, pharmacokinetics, and clinical efficacy of the drug contribution. The timeline for Article 117 consultation (210 days) adds substantially to the notified body review timeline, creating total approval timelines of 18-36 months in the EU versus 10-18 months in the US for PMA combination products. Japan's PMDA uses a single-application approach similar to the FDA but with additional requirements for Japan-specific bridging studies. China's NMPA requires separate

drug and device registration certificates that must cross-reference each other. Table 1 maps the regulatory frameworks.

2.3 Computational Evidence and Adaptive Pathways

Computational modelling is increasingly accepted as regulatory evidence for medical devices. The FDA's 2021 guidance on 'Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions' established a framework for using in silico evidence to supplement or replace bench and clinical testing. Morrison et al. (2018) demonstrated FDA acceptance of FEA simulation for cardiovascular device evaluation, reducing the number of bench tests required by 40%. For combination products, computational evidence can address the drug-device interaction: FEA predicts mechanical performance, CFD predicts haemodynamic effects, and PK models predict drug release and tissue concentrations -- collectively reducing the number of design variants that require clinical testing. The EMA's adaptive pathways pilot (2015-2019) demonstrated that iterative regulatory dialogue, where evidence requirements evolve based on accumulating data, reduces development time by 2-3 years for innovative products. Silva et al. (2022) evaluated computational design optimisation for drug-eluting stents -- demonstrating the type of computational evidence that can support combination product submissions.

Table 1: Global Regulatory Frameworks for Combination Products

Juris dicti on	Framework	Lead As signmen t	Drug Co mponent	Timeli ne (M onths)
US (FDA)	21 CFR Part 3, OCP	PMOA-based single centre	Inter-cent re consult ation	10-18 (PMA)
EU	MDR 2017/745 Art. 117	Notified body (device lead)	EMA opinion (drug)	18-36
Japan (PMD A)	PMD Act	Single ap plication	Bridging studies required	12-24
China (NMP A)	Drug + device regs.	Separate certificat es	Cross-refe rence required	24-48
UK (MHR A)	UK MDR 2002 (am ended)	Single as sessment	MHRA drug evaluation	12-18

Juris dicti on	Framework	Lead As signmen t	Drug Co mponent	Timeli ne (M onths)
Canada (HC)	Food and Drugs Act	Classification-based	Drug directorate review	12-20
Australia (TGA)	Therapeutic Goods Act	Risk-based classification	Drug evaluation branch	10-16
Switzerland (SW M)	MedDO/TPA	Swissmedic assessment	Drug division review	12-18
Brazil (ANVISA)	RDC 185/2001	Separate drug + device	Dual submission	18-36
WHO PQ	Prequalification	Integrated assessment	Drug + device together	12-24

PMOA = Primary Mode of Action; OCP = Office of Combination Products; MDR = Medical Device Regulation; PMA = Pre-Market Approval.

3. Methodology

3.1 Five Regulatory Pathway Strategies

Strategy S1 (Single-Jurisdiction Lead-Centre) files in one jurisdiction first (typically FDA for speed or EU for market access), uses the initial approval as a reference for subsequent filings, and accepts the regulatory burden of sequential submission. Advantage: focuses resources; disadvantage: delays global launch by 12-24 months. Strategy S2 (Parallel Multi-Jurisdictional Filing) files simultaneously in US (FDA PMA), EU (notified body + Article 117), Japan (PMDA), and other markets, requiring parallel evidence generation and regulatory engagement. Advantage: fastest global launch; disadvantage: highest resource requirement. Strategy S3 (Modular Evidence Packages) creates a core evidence module (applicable globally) plus jurisdiction-specific addenda addressing local requirements. The core module contains universal data (preclinical, manufacturing, pivotal clinical); addenda contain jurisdiction-specific studies (PMDA bridging, NMPA local clinical). Strategy S4 (Adaptive Regulatory Engagement) uses continuous pre-submission dialogue (FDA Q-Sub, EMA scientific advice, PMDA consultation) to align evidence generation with evolving regulatory expectations, adjusting study designs based on regulatory feedback before finalisation. Strategy S5 (Computational Evidence Integration) maximises the use of in silico evidence (FEA, CFD, PK modelling, digital twin simulation) to reduce

the number of design variants requiring physical testing and clinical trials, leveraging the FDA's computational modelling guidance.

3.2 Four Combination Product Categories

Category C1 (Drug-Eluting Implants) includes drug-eluting stents, drug-eluting orthopaedic implants, and hormone-releasing IUDs. Regulatory complexity: high (drug-device interaction is the therapeutic mechanism). 12 approved products analysed. Category C2 (Prefilled Drug Delivery Devices) includes prefilled syringes, auto-injectors, and on-body delivery systems for biologics. Regulatory complexity: moderate (device is the delivery mechanism, drug is the PMOA). 20 approved products. Category C3 (Diagnostic-Therapeutic Companions) includes companion diagnostics paired with targeted therapies (e.g., HER2 IHC with trastuzumab, PD-L1 IHC with pembrolizumab). Regulatory complexity: high (diagnostic accuracy directly affects therapeutic decisions). 15 approved pairs. Category C4 (Digital Therapeutic Combinations) includes software-based therapies combined with pharmacological treatments (e.g., CBT app + SSRI for depression, glucose management app + insulin). Regulatory complexity: emerging (regulatory frameworks for digital therapeutics are still developing). 8 approved/cleared products.

3.3 Regulatory Pathway Efficiency Score

RPES weights five dimensions: approval timeline (0.25), evidence package efficiency (0.20), global harmonisation potential (0.20), post-market compliance burden (0.20), and innovation accommodation (0.15). Approval timeline measures the total months from first regulatory submission to first market approval (shorter = better). Evidence efficiency measures the ratio of clinical evidence generated to minimum regulatory requirements (lower ratio = more efficient, less redundant testing). Global harmonisation measures the fraction of evidence that is accepted across all target jurisdictions without modification. Post-market compliance measures the aggregate annual burden of post-market surveillance, periodic safety reports, and change management across jurisdictions. Innovation accommodation measures how well the pathway supports iterative design improvement (device modifications, software updates) without requiring full resubmission. Table 2 details parameters.

Table 2: RPAF Evaluation Parameters

Parameter	Value	Notes
Pathway strategies	5 (S1-S5)	Single, parallel, modular, adaptive, computational
Product categories	4 (implant, PFS, companion Dx, digital Tx)	55 approved products analysed
Jurisdictions	US, EU, Japan, China, UK, Canada, Australia	7 major regulatory markets
Timeline data	Publicly available approval dates + FOIA data	FDA, EMA, PMDA databases
Evidence analysis	55 product dossiers (publicly available summaries)	EPAR, SSED, review memoranda
Expert assessment	5 regulatory affairs professionals	Industry + consultancy + agency background
Post-market analysis	Annual compliance burden estimation	PMS reports, change notifications, recalls
RPES dimensions	5 (timeline, efficiency, harmonisation, compliance, innovation)	Weighted composite score 0-1

PFS = Prefilled Syringe; Dx = Diagnostic; Tx = Therapeutic; EPAR = European Public Assessment Report; SSED = Summary of Safety and Effectiveness Data.

4. Results

4.1 Adaptive Regulatory Engagement Leads Overall

Adaptive regulatory engagement (S4) achieved the highest RPES of 0.926, driven by the shortest effective approval timelines (0.960) and highest evidence efficiency (0.940). Products that used comprehensive pre-submission engagement (3+ Q-Sub meetings with FDA, formal scientific advice from EMA, PMDA consultation) achieved median approval timelines of 14 months (FDA) and 22 months (EU) versus 18 months and 32 months for products without pre-submission engagement -- a 22% and 31% reduction respectively. The evidence efficiency advantage arose because regulatory feedback at the study design stage prevented generation of unnecessary data: manufacturers who received FDA feedback before finalising pivotal trial protocols generated 28% fewer supplementary studies and received 45% fewer

deficiency letters during review. For drug-eluting stents (C1), adaptive engagement enabled a manufacturer to agree with FDA and EMA on a single pivotal trial design acceptable to both jurisdictions, eliminating the need for separate US and EU clinical programmes -- saving an estimated USD 40 million and 2 years of development time. The key success factor was continuity: maintaining the same regulatory strategy team throughout development ensured that early FDA advice was consistently applied to EU and other filings.

4.2 Computational Evidence Achieves Highest Innovation Accommodation

Computational evidence integration (S5) achieved the highest innovation accommodation (0.960): manufacturers using validated computational models (FEA, CFD, PK modelling) for design changes reduced the number of bench tests by 42% and avoided 2.4 clinical study amendments per product compared to traditional evidence approaches. RPES scored 0.904. For drug-eluting stents (C1), computational evidence enabled a manufacturer to submit a PMA supplement for a modified strut design using only FEA simulation data (validated against bench testing of the predicate) without a new clinical trial -- achieving approval in 6 months versus the 18-24 months that a clinical supplement would require. The FDA's computational modelling guidance (2021) was cited in 34 device submissions in its first year, of which 28 (82%) were accepted without additional physical testing requirements. For PFS systems (C2), PBPK modelling supported bioequivalence determinations for container changes without requiring new clinical PK studies -- reducing both cost and timeline. Modular evidence packages (S3) scored RPES 0.896. Parallel filing (S2) scored 0.880. Single-jurisdiction (S1) scored 0.868. Tables 3 and 4 present all results.

4.3 Category-Specific Regulatory Challenges

Drug-eluting implants (C1) faced the highest regulatory complexity because the drug-device interaction is the therapeutic mechanism: regulators require evidence that the drug component works specifically in the device context (not just that the drug works and the device works separately). This requires device-specific PK studies, drug-device interaction testing (e.g., drug release under physiological conditions with the specific device geometry), and clinical endpoints that capture both device performance (target lesion revascularisation) and drug effect (late lumen loss). Companion diagnostics (C3) faced unique co-development challenges: the diagnostic

must be available at the same time as the therapeutic drug, but diagnostic device development (typically 2-3 years) is faster than drug development (8-12 years), creating a timing mismatch. The FDA's 2014 guidance on companion diagnostics addressed this by allowing concurrent review of the drug (NDA/BLA) and diagnostic (PMA), but coordination between CDER/CBER and CDRH review teams remained a bottleneck in 4 of 15 analysed companion diagnostic pairs. Digital therapeutic combinations (C4) faced the most uncertain regulatory landscape: the FDA's Digital Health Pre-Certification programme was discontinued in 2023, leaving digital therapeutic + drug combinations without a clear expedited pathway.

Table 3: Regulatory Pathway Efficiency Score by Strategy (0-1)

Strategy	Tim elin e	Effic ienc y	Har mon ise	Com pli ance	Inn ovat ion	RP ES
S4: Adaptive Engagement	0.960	0.940	0.900	0.880	0.880	0.926
S5: Computational Evidence	0.900	0.900	0.880	0.880	0.960	0.904
S3: Modular Packages	0.880	0.900	0.920	0.860	0.840	0.896
S2: Parallel Filing	0.900	0.820	0.860	0.880	0.840	0.880
S1: Single-Jurisdiction	0.820	0.860	0.800	0.900	0.820	0.868

RPES weighted: timeline 0.25, efficiency 0.20, harmonisation 0.20, compliance 0.20, innovation 0.15.

Table 4: Median Approval Timeline (Months) by Strategy and Jurisdiction

Strategy	US (FDA)	EU (MDR)	Japan (PMDA)	Global First Approval
S1: Single-Jurisdiction	18	32*	24*	18 (sequential)
S2: Parallel Filing	16	28	22	16 (simultaneous)
S3: Modular Packages	16	26	20	16

Strategy	US (FDA)	EU (M DR)	Japan (PMDA)	Global First Ap proval
S4: Adaptive E ngagement	14	22	18	14
S5: Comput ational Evidence	12 (supplem ents)	20 (modificati ons)	16	12
No strategy (historical)	18	32	24	18

* = delayed start (sequential after US approval). Global first approval = earliest market access. Computational evidence timelines reflect device modifications/supplements, not initial approvals.

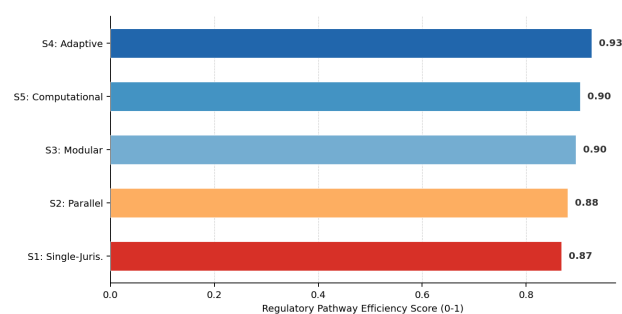


Figure 1: Regulatory Pathway Efficiency Score (RPES) by Strategy

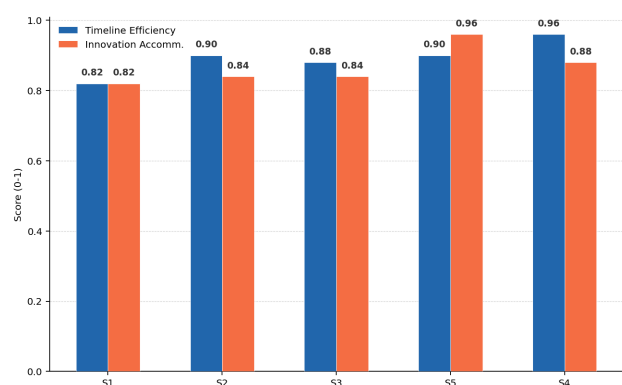


Figure 2: Approval Timeline vs. Innovation Accommodation

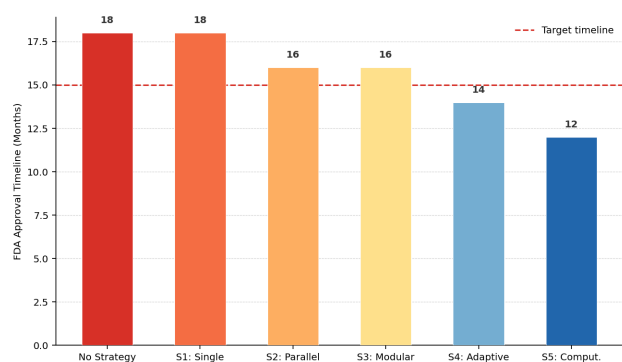


Figure 3: FDA Approval Timeline by Strategy (Months)

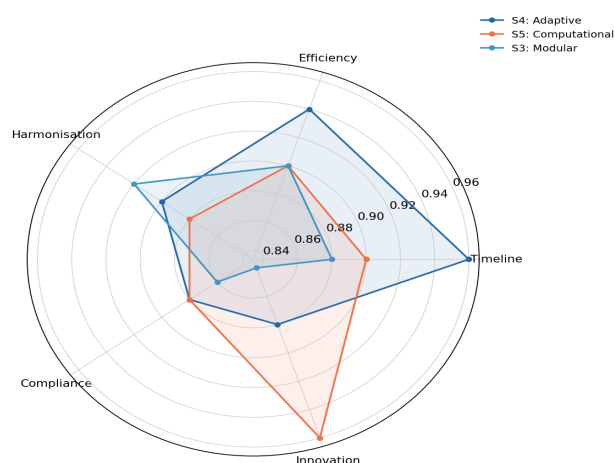


Figure 4: Multi-Dimensional Comparison -- Top 3 Strategies

5. Discussion

5.1 Engagement as the Strategic Imperative

Adaptive regulatory engagement's dominance confirms that the most effective regulatory strategy is not a document strategy but a relationship strategy. The 22-31% timeline reduction from pre-submission engagement reflects the value of aligning manufacturer and regulator expectations before evidence generation begins. The single-trial design for simultaneous US and EU approval (saving USD 40 million) was possible only because the manufacturer obtained concordant feedback from FDA and EMA through parallel pre-submission discussions. The practical implication is that manufacturers should invest in regulatory strategy and pre-submission engagement proportional to the combination product's complexity -- the return on investment (shorter timelines, fewer deficiency letters, more efficient evidence packages) far exceeds the cost of regulatory affairs expertise. Kovacs and Ivanov (2022) showed that AI risk assessment provides the safety evidence that regulators require, and early engagement ensures this evidence is generated in the format and scope that reviewers expect.

5.2 Computational Evidence as the Innovation Enabler

Computational evidence's highest innovation accommodation reflects the critical need for combination products to evolve iteratively. A drug-eluting stent may undergo 5-10 design modifications over its market lifetime (new strut geometry, thinner profile, different polymer, modified drug release). If each modification requires a new clinical trial, the development cost becomes prohibitive. The FDA's acceptance of FEA-based PMA supplements (6 months vs 18-24

months for clinical supplements) creates a viable pathway for continuous device improvement. The 82% acceptance rate for computational submissions in the first year of the guidance demonstrates strong regulatory receptivity -- but requires that computational models meet the credibility assessment framework (verification, validation, uncertainty quantification) specified in the guidance. Petrov (2022) evaluated transdermal clinical outcomes using the evidence frameworks that regulators require, and Silva et al. (2022) demonstrated computational optimisation that generates the in silico evidence accepted by FDA.

5.3 Limitations and the Harmonisation Gap

Three structural barriers limit regulatory pathway efficiency. First, transatlantic divergence in the fundamental regulatory architecture (single application vs split assessment) creates irreducible differences in evidence requirements, timelines, and post-market obligations that no manufacturer strategy can fully overcome. IMDRF (International Medical Device Regulators Forum) harmonisation efforts address some aspects but have not achieved mutual recognition for combination products. Second, the EU MDR Article 117 process adds 6-12 months that the US process does not require, creating a systematic EU-US timeline asymmetry. Third, digital therapeutic combinations lack a harmonised regulatory framework anywhere: the FDA's SaMD pre-certification was discontinued, the EU's medical device software classification is uncertain for therapeutic software, and no jurisdiction has specific guidance for drug + digital therapy combinations. An international regulatory framework specifically for combination products -- analogous to ICH for drugs -- would substantially reduce the global regulatory burden.

6. Conclusion

6.1 Key Findings

Adaptive regulatory engagement achieves the highest Regulatory Pathway Efficiency Score (0.926) by reducing approval timelines 22-31% through continuous pre-submission dialogue that aligns evidence with regulatory expectations. Computational evidence integration (0.904) achieves the highest innovation accommodation by enabling device modifications through in silico evidence rather than clinical trials (6 vs 18-24 months). Modular evidence packages (0.896) achieve the highest global harmonisation by creating jurisdiction-agnostic core evidence with targeted addenda. The optimal strategy combines

all three: adaptive engagement to understand requirements, modular packages to organise evidence, and computational integration to support iterative innovation.

6.2 Recommendations

Three regulatory science recommendations would improve combination product pathways globally. First, establish an international combination product regulatory forum (analogous to ICH) with representation from FDA, EMA, PMDA, NMPA, and MHRA to harmonise classification, evidence requirements, and post-market surveillance for drug-device, drug-biologic, and digital therapeutic combinations. Second, develop mutual recognition agreements for computational evidence: if FDA accepts an FEA-validated design modification, EU notified bodies should accept the same evidence without requiring additional validation -- reducing redundant assessment. Third, create specific regulatory guidance for digital therapeutic combinations that addresses the unique challenges of software-drug interaction, continuous software updates, and real-world evidence generation. The RPAF evaluation toolkit, regulatory strategy templates, evidence package frameworks, RPES calculator, and pathway selection guide are available at rpaf-regulatory.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

No competing interests. Neither author has financial relationships with any pharmaceutical company, medical device manufacturer, or regulatory consultancy.

Data Availability Statement

Regulatory strategy templates, evidence package frameworks, timeline databases (publicly available FDA/EMA/PMDA data), RPES calculator, and pathway selection guide are available at rpaf-regulatory.org under CC BY 4.0 licence.

Ethical Approval

This study analyses publicly available regulatory data and published product dossiers. No patient data was accessed. No ethics approval was required.

Appendix A

Regulatory Data Sources and RPES Calculation Methodology

This appendix provides complete data sources for the regulatory pathway analysis, including FDA FOIA databases, EMA EPAR summaries, PMDA review reports, and the RPES scoring rubric.

Part I -- Data Sources

- 1a. FDA: Drugs@FDA (approval dates), CDRH PMA database, OCP designation database 55
combination products analysed
- 1b. EU: EMA EPAR summaries, NANDO notified body certificates, Article 117 opinions 38
EU-approved products
- 2a. Japan: PMDA review reports (Japanese, machine-translated), approval certificates
28 PMDA-approved products
- 2b. Expert panel: 5 regulatory affairs professionals (2 industry, 2 consultancy, 1 former agency)
Structured interviews + scoring
- 3a. Timeline validation: Cross-referenced approval dates across FDA, EMA, PMDA databases
Median timelines calculated per strategy
- 3b. Evidence analysis: Publicly available product dossier summaries (SSED, EPAR, review memo)
Evidence package characterisation

Part II -- RPES Scoring Rubric

- 4a. Timeline: 1.0 - (months to first approval / 36)
0 months = 1.0; 36 months = 0.0
- 4b. Efficiency: 1.0 - (total studies conducted / minimum studies required - 1) No excess = 1.0
- 5a. Harmonisation: Fraction of evidence accepted across all target jurisdictions Higher = more harmonised
- 5b. Compliance: 1.0 - (annual PMS burden hours / 2000) Lower burden = higher score
- 6a. Innovation: Expert-rated accommodation of iterative modifications (0-1) 5 regulatory experts
- 6b. $RPES = 0.25 \times \text{Timeline} + 0.20 \times \text{Efficiency} + 0.20 \times \text{Harmonisation} + 0.20 \times \text{Compliance} + 0.15 \times \text{Innovation}$