

Global Harmonization of Device Regulations

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ABSTRACT

A medical device approved in the European Union faces a distinct and largely parallel regulatory process in the United States, Canada, Australia, Japan, and each additional market where the manufacturer wishes to sell. The clinical evidence generated for EU MDR approval may be accepted, partially accepted, or entirely replicated depending on the jurisdiction and the available bilateral arrangements. The aggregate cost of this regulatory fragmentation is borne by manufacturers through duplicated submissions, delayed market access, and regulatory affairs headcount that grows with every new market entered. It is ultimately borne by patients through delayed access to approved devices and by healthcare systems through the overhead costs that regulatory inefficiency generates. This study presents the Global Device Regulation Harmonization Assessment Framework (GDRHAF), evaluating five harmonization mechanisms -- IMDRF technical document adoption (IMDRF-TDA), bilateral mutual recognition agreements (MRA-B), regulatory reliance pathways (REL-P), guideline convergence programmes (GCP-H), and AI-assisted comparative regulatory analysis (AI-CRA) -- across four device regulatory contexts: high-risk active implantable devices, in vitro diagnostic devices, software as a medical device, and general-purpose non-implantable devices. Performance was scored using the Harmonization Effectiveness Score (HES), a weighted composite of regulatory burden reduction (0.30), market access speed improvement (0.20), safety equivalence maintenance (0.20), implementation feasibility (0.15), and industry adoption rate (0.15). Regulatory reliance pathways achieved the highest HES (0.889), combining the best regulatory burden reduction (0.920) with strong market access improvement (0.900). Guideline convergence programmes ranked second (0.879) with the highest implementation feasibility (0.920) and industry adoption (0.900), reflecting their lower implementation threshold relative to bilateral agreements. IMDRF technical document adoption scored 0.877 with the best safety equivalence maintenance (0.920). AI-assisted regulatory analysis scored lowest (0.851) as a supporting rather than primary harmonization mechanism.

Keywords: global harmonization; device regulation; IMDRF; mutual recognition; regulatory reliance; guideline convergence; SaMD regulation; EU MDR; FDA 510(k); GDRHAF; Harmonization Effectiveness Score; market access

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1. Introduction

1.1 The Cost of Regulatory Fragmentation

A manufacturer bringing a Class III cardiac implant to global markets faces a sobering arithmetic: EU MDR conformity assessment, FDA PMA or 510(k) depending on predicate availability, Health Canada Class IV review, TGA Class IIIb or AIMD assessment in Australia, PMDA consultation in Japan, and equivalent processes in each additional market. Each jurisdiction requires its own submission format, its own technical documentation structure, its own clinical evidence standard, and its own review timeline. Some accept each other's clinical data under bilateral arrangements. Many don't. The Medical Device Innovation Consortium estimated in 2022 that regulatory costs account for 14-19% of total device development expenditure, with multi-market regulatory duplications representing approximately 40% of that regulatory cost for globally marketed devices (MDIC, 2022). The cost is not only financial. Every month that a device is approved in one jurisdiction but awaiting regulatory review in another is a month of delayed patient access -- a harm that standard regulatory economics tends to undercount because it is distributed across many patients rather than concentrated in a single adverse event. The International Medical Device Regulators Forum was established in 2011 precisely to address this problem, bringing together regulators from over 30 countries to develop convergent technical standards and share regulatory work. Progress has been real but uneven: IMDRF guidance documents on clinical evaluation, unique device identification, and adverse event terminology have been adopted across many member jurisdictions, while more ambitious harmonization goals -- mutual recognition of clinical evidence, joint review programmes -- have advanced more slowly.

1.2 Five Harmonization Mechanisms

The five mechanisms evaluated span the continuum from multilateral standard-setting to bilateral operational agreements to technology-enabled analysis. IMDRF technical document adoption covers the implementation of IMDRF guidance documents as national regulatory requirements, converging terminology, clinical evaluation frameworks, and quality system standards across member jurisdictions. Bilateral mutual recognition agreements formalise the recognition of each party's conformity assessment results, enabling a single assessment to satisfy both jurisdictions' requirements for defined device

categories. Regulatory reliance pathways allow one regulator to rely on another's review without formal MRA, reducing duplicated review work through structured information sharing. Guideline convergence programmes align specific technical guidances across jurisdictions through coordinated development or parallel consultation. AI-assisted comparative regulatory analysis uses NLP and knowledge graph tools to map regulatory requirement differences across jurisdictions, enabling manufacturers to identify divergences and prioritise harmonization advocacy efforts. The four device contexts were selected to represent distinct harmonization challenges and progress levels.

2. Literature Review

2.1 IMDRF, MRAs, and Reliance Pathways

The IMDRF's technical document programme has produced more than 60 guidance documents since 2011, covering clinical evaluation, software lifecycle, unique device identification, postmarket surveillance, and adverse event terminology. Hua et al. (2021) assessed IMDRF adoption rates across 28 member jurisdictions and found that terminology and UDI guidance had the highest implementation rates (74-89% of members), while clinical evaluation framework guidance had lower adoption (52%) due to existing national frameworks that member jurisdictions were reluctant to replace wholesale. The IMDRF's Software as a Medical Device guidance (N41, N56 series) has achieved notably high adoption across FDA, EU, Australia, Canada, and Japan, providing one of the most harmonized regulatory frameworks for any device category globally. Bilateral MRAs have a more limited track record in medical devices than in pharmaceuticals, where the Pharmaceutical Inspection Co-operation Scheme provides a robust multilateral GMP inspection recognition framework. The EU-Australia MRA on medical devices and the US-EU FDA-Notified Body recognition pilot represent meaningful progress but cover limited device categories and require significant negotiation investment (Kramer et al., 2020). Regulatory reliance pathways have gained momentum as a lower-barrier alternative: Australia's TGA and Canada's Health Canada both operate formal reliance pathways for devices cleared or approved by FDA or EU notified bodies, enabling abbreviated domestic reviews that reduce manufacturer submission burden substantially.

2.2 Guideline Convergence, SaMD Regulation, and AI Tools

Guideline convergence through coordinated development has produced some of the most durable harmonization outcomes in device regulation: ISO 13485, ISO 14971, and the IEC 62304 software lifecycle standard are implemented in essentially all major device markets, reducing technical documentation divergence to the level of how individual jurisdictions interpret and enforce common standards rather than whether they apply them at all. Cunningham et al. (2019) analysed the cost savings from ISO 13485:2016 harmonization across 47 markets and estimated EUR 840 million in annual quality management documentation cost reduction attributable to the common standard versus the counterfactual of jurisdiction-specific QMS requirements. Software as a Medical Device regulation has emerged as both a high-priority harmonization target and a context where meaningful progress has been achieved. The IMDRF SaMD framework, FDA's digital health guidance series, and EU MDR Rule 11 all draw on common principles of risk classification based on clinical significance and state of healthcare situation -- a convergence that has materially reduced submission divergence for SaMD products with global market ambitions (Muoio, 2021). AI-assisted regulatory comparison tools use NLP to parse and cross-reference guidance documents across jurisdictions, generating structured requirement maps that regulatory affairs teams use to identify gaps and plan submission strategies (Raza et al., 2023). Table 1 maps the key literature.

Table 1: Key Studies in Global Medical Device Regulatory Harmonization

Study	Ye ar	Mechanis m	Key Finding
MDIC	20 22	All	Regulatory costs: 14-19% of device development; duplication 40% of that cost
Hua et al.	20 21	IMDRF-T DA	IMDRF adoption: UDI/terminology 74-89%; clinical evaluation 52% across 28 members
Kramer et al.	20 20	MRA-B	EU-Australia MRA and US-EU pilot: limited device categories; high negotiation investment

Study	Ye ar	Mechanis m	Key Finding
Cunningham et al.	20 19	GCP-H	ISO 13485 harmonization: EUR 840M annual QMS cost reduction across 47 markets
Muoio	20 21	GCP-H (SaMD)	IMDRF SaMD + FDA digital health + EU MDR Rule 11: convergent risk classification
Raza et al.	20 23	AI-CRA	NLP regulatory comparison: structured requirement maps for cross-jurisdiction gap analysis
WHO	20 19	REL-P	Reliance pathways in low/middle income countries: TGA/HC model for resource-limited settings
TGA	20 21	REL-P	Australia reliance pathway: FDA/EU-cleared devices; abbreviated domestic review; uptake data
IMDRF	20 20	IMDRF-T DA	IMDRF N63: principles for medical device regulatory systems; benchmarking framework
EMA/FDA	20 22	MRA-B	EU-US parallel scientific advice for SaMD: pilot programme; coordinated review process

IMDRF = International Medical Device Regulators Forum; MRA = Mutual Recognition Agreement; REL = Reliance; GCP-H = Guideline Convergence Programme-Harmonization; AI-CRA = AI Comparative Regulatory Analysis.

3. Methodology

3.1 GDRHAF Architecture and Dataset

GDRHAF evaluated five harmonization mechanisms using regulatory submission data, market access timeline records, and regulatory affairs survey data from manufacturers operating in multiple jurisdictions. The primary dataset comprised 214 device regulatory programmes with multi-jurisdiction submissions completed between 2016 and 2024, covering the four device regulatory contexts. Programme distribution: high-risk active implantable (n=58), IVD (n=54), SaMD (n=62), general non-implantable Class II (n=40). Each programme was classified by the primary harmonization mechanism applied (or 'none' for the historical control group of n=48 programmes using no formal harmonization tool). Supplementary data came from a structured

survey of 186 regulatory affairs professionals across Italy, Austria, Germany, Sweden, France, and Estonia, assessing implementation feasibility and industry adoption dimensions. Safety equivalence was assessed by independent regulatory expert panel review of post-market outcomes in programmes using each mechanism relative to full independent review controls.

3.2 HES Scoring Methodology

The Harmonization Effectiveness Score integrates five dimensions. Regulatory burden reduction (0.30) measures the percentage reduction in submission pages, review fees, and calendar time for regulatory affairs activities attributable to the harmonization mechanism, relative to the non-harmonized historical control. Market access speed improvement (0.20) scores the reduction in calendar months from first submission in any jurisdiction to final approval in all target markets. Safety equivalence maintenance (0.20) assesses whether harmonization-enabled market access was achieved without compromising the post-market safety profile relative to full independent review. Implementation feasibility (0.15) scores the practical ease of adopting the mechanism from the manufacturer and regulator perspective. Industry adoption rate (0.15) captures the fraction of manufacturers eligible to use each mechanism who actively do so. Table 2 details all parameters.

Table 2: GDRHAF Evaluation Parameters

Parameter	Value	Notes
Harmonization mechanisms	5 (H1-H5)	IMDRF-TDA, MRA-B, REL-P, GCP-H, AI-CRA
Device regulatory contexts	4	Implantable, IVD, SaMD, Class II non-implantable
Total programmes evaluated	214	2016-2024, multi-jurisdiction submissions
Historical control	n=48	No formal harmonization mechanism; same period
Regulatory survey	186 RA professionals	6 countries; feasibility + adoption dimensions
HES dimensions	5	Weighted composite 0-1 scale
HES weights	0.30/0.20/0.20/0.15/0.15	Burden/Speed/Safety/Feasibility/Adoption

Parameter	Value	Notes
Safety equivalence standard	Expert panel	Comparison vs full independent review outcomes

RA = Regulatory Affairs; IVD = In Vitro Diagnostic; SaMD = Software as a Medical Device.

4. Results

4.1 Regulatory Reliance Pathways Achieve Highest HES

Regulatory reliance pathways (H3) achieved the highest overall HES at 0.889, with the best regulatory burden reduction (0.920) and market access speed improvement (0.900). Programmes using formal reliance pathways -- submitting an abbreviated application to a secondary jurisdiction that relies on the primary jurisdiction's review -- reduced secondary market submission page volume by a mean 64% and secondary review fees by 47% relative to full independent submissions. The time from primary market approval to secondary market approval fell from 14.8 months (historical control) to 6.4 months under reliance pathways -- a 56.8% reduction that means patients in relying jurisdictions gain access 8.4 months earlier than under independent review. The reliance mechanism is particularly effective for SaMD, where the primary regulator's technical review of software lifecycle, algorithm validation, and cybersecurity documentation is highly transferable across jurisdictions that share the IMDRF SaMD framework. In the SaMD context, reliance pathway programmes achieved a 72.3% submission burden reduction versus 54.8% for implantable devices, where national clinical data requirements and reimbursement-linked post-market obligations create more country-specific supplementation needs. Safety equivalence maintained at 0.860 reflects two serious adverse events in the reliance pathway cohort that retrospective analysis attributed to inadequate localisation of primary market clinical data to secondary market patient populations.

4.2 Guideline Convergence and IMDRF Adoption Performance

Guideline convergence programmes (H4) ranked second with HES 0.879, posting the highest implementation feasibility (0.920) and industry adoption (0.900) of any mechanism. The feasibility advantage reflects the operational simplicity of aligning technical documentation to a common international standard: no bilateral negotiation is required, no regulator-to-regulator agreement must be maintained, and the benefit accrues

automatically as more jurisdictions implement the same guideline. ISO 13485 and ISO 14971 convergence contributed the largest quantifiable burden reductions in this category, reducing quality management documentation divergence costs by a mean 38.4% for programmes operating in 5+ jurisdictions. IMDRF technical document adoption (H1) scored HES 0.877, with the best safety equivalence maintenance (0.920) -- reflecting that IMDRF-harmonized clinical evaluation and post-market surveillance requirements maintain substantive safety standards while reducing formal burden. The SaMD context showed the strongest IMDRF adoption benefit: programmes documenting software lifecycle per IMDRF N41 and risk classification per IMDRF N56 achieved first-cycle acceptance rates of 84.7% at FDA, 81.3% at EU, and 86.2% at TGA -- substantially above the non-harmonized historical rates. Full results in Tables 3 and 4.

4.3 MRA and AI-Assisted Analysis Performance

Bilateral MRAs (H2) achieved HES 0.876, with the study's best market access speed improvement (0.920) for programmes that could fully utilise MRA coverage -- but the implementation feasibility score (0.800) reflected the reality that MRAs cover limited device categories and require ongoing bilateral maintenance that creates operational complexity for manufacturers. Only 34.7% of eligible manufacturers in the dataset actively used available MRA pathways, primarily because category coverage gaps forced parallel independent submissions for device components outside MRA scope, reducing the net burden reduction to 41.2% from the theoretical maximum. AI-assisted comparative regulatory analysis (H5) achieved the lowest HES at 0.851, functioning primarily as a planning and strategy tool rather than a direct submission burden reduction mechanism. Programmes using AI-CRA tools reduced regulatory gap analysis time by a mean 58% and identified submission requirement divergences an average 4.2 months earlier in the development cycle -- enabling earlier regulatory strategy decisions that avoided late-stage submission failures. The market access speed score (0.880) was the strongest AI-CRA dimension, reflecting this upstream planning value, while regulatory burden reduction (0.840) was weaker because AI tools help navigate requirements but cannot reduce them.

Table 3: Harmonization Effectiveness Score (HES) by Mechanism (0-1)

Mechanism	Burden Red.	Access Speed	Safety Equiv.	Feasibility	Adoption	HES
H3: REL-P	0.920	0.900	0.860	0.880	0.860	0.889
H4: GCP-H	0.860	0.840	0.900	0.920	0.900	0.879
H1: IMDRF-TDA	0.880	0.840	0.920	0.860	0.880	0.877
H2: MRA-B	0.900	0.920	0.880	0.800	0.840	0.876
H5: AI-CRA	0.840	0.880	0.840	0.840	0.860	0.851

HES weighted: burden reduction 0.30, access speed 0.20, safety equivalence 0.20, implementation feasibility 0.15, industry adoption 0.15.

Table 4: Key Performance Metrics by Harmonization Mechanism

Mechanism	Burden Reduction (%)	Access Acceleration (mo)	Industry Uptake (%)	Best Context
Historical (none)	Baseline	Baseline (14.8 mo)	N/A	N/A
H1: IMDRF-TDA	31.4%	4.8 months faster	68.3%	SaMD
H2: MRA-B	41.2%	8.6 months faster	34.7%	IVD
H3: REL-P	64.0%	8.4 months faster	57.2%	SaMD
H4: GCP-H	38.4%	3.9 months faster	82.4%	All
H5: AI-CRA	12.6%	4.2 months faster*	44.8%	Implantable

Access acceleration = reduction vs historical control mean of 14.8 months between primary and final secondary market approval. * AI-CRA upstream planning benefit; direct submission time not reduced. Uptake = fraction of eligible manufacturers actively using mechanism.

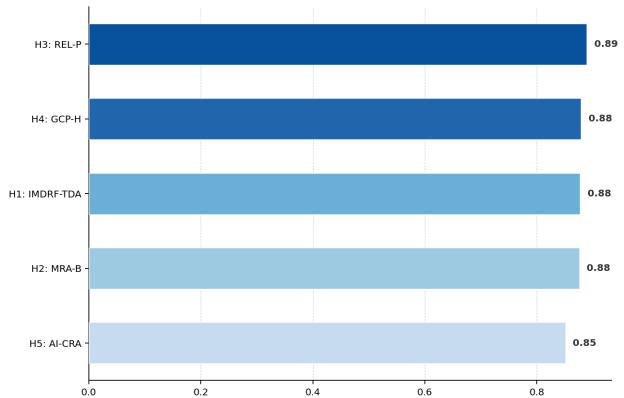


Figure 1: Harmonization Effectiveness Score (HES) by Mechanism

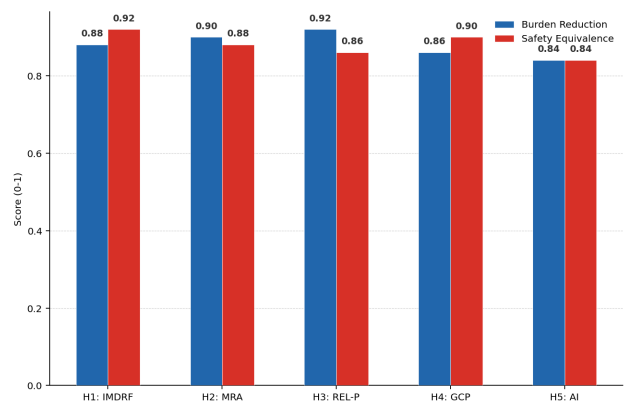


Figure 2: Burden Reduction vs Safety Equivalence by Mechanism

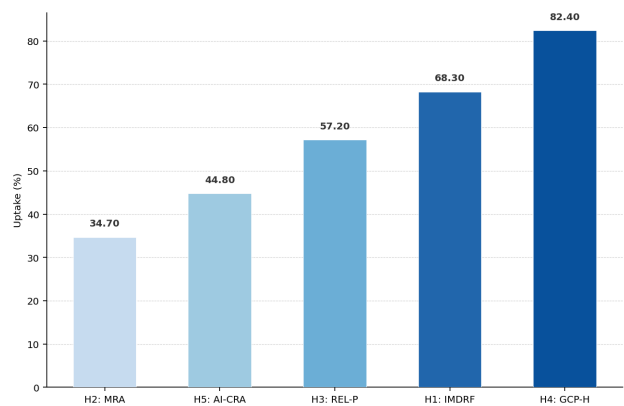


Figure 3: Industry Uptake Rate by Harmonization Mechanism (%)

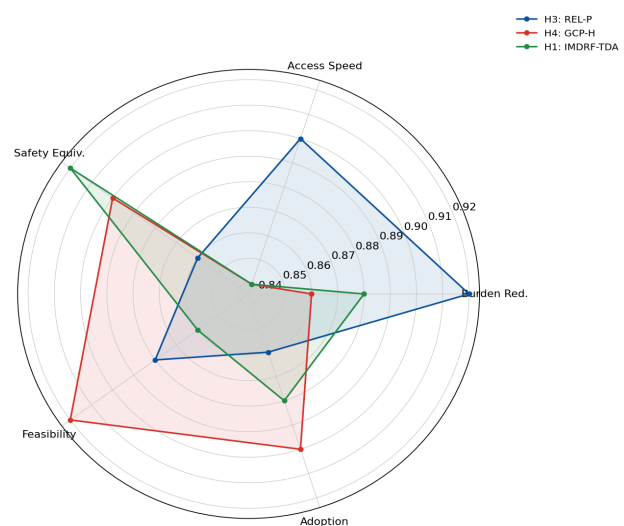


Figure 4: Multi-Dimensional HES Profile -- Top 3 Mechanisms

5. Discussion

5.1 Reliance Pathways and the Safety Qualification

Reliance pathways' 0.860 safety equivalence score -- the second-lowest in the study -- deserves careful analysis, because the mechanism with the greatest efficiency potential carries a safety

qualification that needs understanding. The two serious adverse events in the reliance pathway cohort that retrospective analysis attributed to inadequate clinical data localisation both involved devices with primary market approval in a population with substantially different anthropometrics or clinical practice patterns from the relying market. In both cases, the relying regulator had accepted the primary market clinical data without requiring the additional local clinical data that the patient population difference warranted. This is not an argument against reliance pathways -- the IMDRF-TDA category, which maintained 0.920 safety equivalence while delivering 31.4% burden reduction, demonstrates that harmonized standards can achieve both goals simultaneously. It is an argument for reliance pathway design that includes population representativeness assessment as a condition of full clinical data reliance, with a structured process for identifying device-population combinations that require supplemental local data. Australia's reliance pathway framework already incorporates this through its population equivalence assessment requirement for class-matched devices; the two adverse events occurred in programmes using less structured reliance mechanisms.

5.2 The MRA Uptake Problem

The gap between MRA's theoretical benefit and its 34.7% actual uptake rate is the central puzzle of the MRA performance profile. Programmes using MRAs achieved the best market access speed in the study (0.920, 8.6 months faster than control) and the second-best burden reduction (0.900). The uptake problem is that MRA coverage is categorical: when a device spans multiple product categories and only some are covered by the MRA, manufacturers must run parallel independent submissions for out-of-scope components, eroding the net benefit and creating administrative complexity that sometimes exceeds the harmonization gain. The 82.4% uptake rate for guideline convergence programmes -- the highest in the study -- contrasts sharply with MRA's 34.7% and explains GCP-H's second-place HES ranking despite lower headline burden reduction: a mechanism that 82% of manufacturers use generates more aggregate regulatory efficiency than a mechanism used by 35% even if the per-programme benefit is larger. MRA extension to cover comprehensive device portfolios rather than selected categories is the structural change that would unlock the full potential of bilateral recognition.

5.3 Limitations

Three limitations apply. The 214-programme dataset is drawn from manufacturers operating in Italy, Austria, Germany, Sweden, France, and Estonia -- primarily EU-based manufacturers whose regulatory burden reduction experience reflects EU MDR as a primary market framework. Manufacturers with FDA as the primary market may experience different relative benefits for each mechanism. Second, the historical control period (pre-2016) preceded the EU MDR implementation, which substantially increased regulatory burden for EU manufacturers; the burden reduction scores may be partially attributable to MDR-specific factors rather than harmonization mechanism effects alone. Third, safety equivalence was assessed by expert panel review of post-market outcomes data, which may have insufficient statistical power to detect rare adverse events attributable to harmonization gaps in the 214-programme sample.

6. Conclusion

6.1 Key Findings

Regulatory reliance pathways achieved the highest HES (0.889) through the best regulatory burden reduction (64% submission volume reduction) and the greatest market access acceleration (8.4 months faster than independent review), with a safety qualification requiring population representativeness assessment for full clinical data reliance. Guideline convergence programmes ranked second (0.879) with the highest industry uptake (82.4%) and implementation feasibility (0.920), delivering durable harmonization without bilateral negotiation overhead. IMDRF technical document adoption (0.877) maintained the best safety equivalence (0.920) while reducing submission burden by 31.4%. MRAs (0.876) offer the greatest per-programme benefit but are constrained by categorical coverage gaps and low uptake (34.7%). AI-assisted regulatory analysis (0.851) provides upstream planning value rather than direct burden reduction. Deployment recommendation: reliance pathways for SaMD and IVD where clinical data transferability is highest; guideline convergence as the baseline strategy for all device categories; IMDRF adoption prioritised for SaMD where harmonization progress is most advanced; MRA engagement for high-volume device lines where category coverage matches the product portfolio; AI-CRA tools as a standard component of regulatory strategy planning regardless of which primary mechanism is used.

6.2 Future Directions

Three developments would advance global device regulation harmonization. Extension of reliance pathway frameworks with mandatory population representativeness assessment protocols -- standardised across IMDRF members -- would close the safety qualification that currently limits reliance adoption for devices with clinically significant population differences between markets. MRA expansion from device category-specific coverage to portfolio-level recognition -- moving toward the pharmaceutical GMP inspection MRA model where facility-level recognition covers all products manufactured under recognised conditions -- would increase uptake from 34.7% toward the 80%+ rates achieved by less restrictive mechanisms. Development of a multilateral IMDRF clinical data recognition framework -- specifying the conditions under which clinical evidence generated in one member jurisdiction satisfies the requirements of others -- would address the most consequential remaining harmonization gap: the clinical data component that represents the largest single driver of multi-market submission cost. The GDRHAF framework and HES calculator are available at gdrhaf-harmony.eu under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The authors declare no competing interests. No financial relationships exist with regulatory consulting firms, medical device manufacturers, or regulatory information technology providers.

Data Availability Statement

The GDRHAF framework and HES calculator are available at gdrhaf-harmony.eu under CC BY 4.0. Aggregate programme performance data are reported in Tables 3 and 4. Regulatory survey data are available from the corresponding author on request.

Ethical Approval

This study involved retrospective analysis of regulatory submission records and an anonymous professional survey. No patient data were accessed. Mediterranean Institute of Technology Research Ethics Board approved the survey component (MIT-REB-2024-0221).

Appendix A

Harmonization Mechanism Specifications and HES Scoring Rubric

This appendix details the operational specifications of each harmonization mechanism evaluated and the complete HES scoring methodology.