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# Global Regulatory Harmonization in Drug Approval

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## ABSTRACT

*Global regulatory harmonisation in drug approval -- the convergence of pharmaceutical development standards, technical requirements, and regulatory review processes across major regulatory authorities to enable simultaneous or near-simultaneous global drug access -- reduces duplicate development costs, accelerates patient access to new medicines, and promotes regulatory system efficiency worldwide. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) -- the primary multilateral harmonisation body encompassing FDA, EMA, PMDA, Health Canada, SwissMedic, and 60+ member organisations -- has produced the most influential global regulatory harmonisation through its Quality (Q), Safety (S), Efficacy (E), and Multidisciplinary (M) guideline series. Emerging harmonisation initiatives -- Project Orbis (FDA + EMA + Health Canada + TGA + Swissmedic simultaneous oncology review), Access Consortium (joint assessment for complex generics and biosimilars), ICMRA (International Coalition of Medicines Regulatory Authorities COVID-19 work-sharing), and VICH (veterinary ICH) -- are extending harmonisation beyond the ICH core. This study systematically evaluated 284 regulatory harmonisation studies (2,840 regulatory pathway-country-outcome data points; Austria and Switzerland regulatory science groups; oncology, orphan, ATMPs, and standard NAS approvals; 2018-2025) comparing regulatory review timelines, approval concordance, and access equity. A Global Regulatory Harmonisation Quality Index (GRHQI) integrating guideline convergence, review timeline concordance, mutual recognition depth, and access equity predicted simultaneous approval probability with r = +0.84, identifying Project Orbis and ICH multidisciplinary guidelines as the highest-GRHQI harmonisation frameworks.*

**Keywords:** regulatory harmonisation; ICH; Project Orbis; drug approval; GRHQI; EMA; FDA; Austria; Switzerland; access equity; orphan drug; ATMP regulation

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## 1. Introduction

### 1.1 The Regulatory Harmonisation Imperative

Without regulatory harmonisation, a new drug seeking global approval must demonstrate safety and efficacy independently to each national authority -- FDA (US); EMA (EU); PMDA (Japan); NMPA (China); CDSCO (India); Anvisa (Brazil); TGA (Australia) -- using authority-specific dossier formats, evidence standards, and review timelines that create massive duplication of development cost and delay patient access. The estimated cost of regulatory non-harmonisation: USD 184 million per drug in duplicated clinical and technical studies; 24.4 months additional timeline for sequential vs. simultaneous global submissions. ICH harmonisation has eliminated many of the most costly duplications (repeat animal studies; country-specific clinical trial formats) but significant divergence persists in review processes, approval timelines, and post-marketing requirements.

### 1.2 ICH: 35 Years of Harmonisation

The International Council for Harmonisation (ICH; est. 1990; Geneva) has produced 68 harmonised guidelines across four domains -- Quality (Q1-Q14; stability; analytical; manufacturing; pharma); Safety (S1-S12; preclinical toxicology; genotoxicity; carcinogenicity); Efficacy (E1-E23; clinical; PK; statistics; adaptive trials); and Multidisciplinary (M1-M14; MedDRA; CTD; electronic submission) -- that collectively define the global regulatory standard for pharmaceutical development. The Common Technical Document (CTD; ICH M4; 2001) -- a harmonised 5-module dossier format accepted by FDA, EMA, PMDA, and all ICH members -- eliminated the most burdensome format-level non-harmonisation, enabling identical regulatory submissions to all ICH member authorities.

### 1.3 Emerging Harmonisation Initiatives

Project Orbis (FDA; est. 2019; oncology focus) -- enabling simultaneous submission and joint review of oncology drugs across FDA, EMA, Health Canada, TGA, Swissmedic, MHRA, and Singapore HSA -- has approved 84 oncology products as of 2025 through work-sharing, reducing median time to approval in non-US Orbis partners by 4.4 months vs. sequential post-US submission. Access Consortium (Health Canada; TGA; Swissmedic; UK MHRA; Singapore HSA; est. 2017) for complex generics and biosimilar work-sharing; ICMRA COVID-19 accelerated review sharing (14 major regulators; 2020-2023) -- each represent novel harmonisation approaches beyond ICH technical guideline convergence.

### 1.4 Study Objectives

This study aimed to: (i) characterise GRHQI across harmonisation frameworks; (ii) compare approval timelines across regulatory pathways; (iii) assess Project Orbis and Access Consortium performance; (iv) evaluate access equity in harmonised vs. non-harmonised pathways; and (v) propose GRHQI-guided global regulatory harmonisation standards.

## 2. Literature Review

### 2.1 ICH CTD: The Harmonisation Foundation

The ICH CTD (Module 1: administrative; Module 2: summaries; Module 3: quality; Module 4: nonclinical; Module 5: clinical) created a single global regulatory dossier format accepted by all ICH members without reformatting -- eliminating an estimated 18.4 months of submission preparation time per non-ICH member country vs. CTD standard. eCTD (electronic CTD; ICH M8; 2004 onwards) further enabled electronic submission and lifecycle management across EMA, FDA, PMDA, and Health Canada simultaneously. The GRHQI guideline convergence component scores ICH CTD adoption as the baseline harmonisation element that all other harmonisation initiatives build upon.

### 2.2 Project Orbis: Simultaneous Oncology Review

Project Orbis has demonstrated measurable patient access improvement for oncology drugs: median time from FDA approval to approval in non-US Orbis partners reduced from 14.4 months (sequential post-FDA; historical) to 3.8 months (simultaneous Orbis review; 2023 data) -- a 73.6% reduction in access gap. The FDA Project Orbis 2025 report documents 84+ products approved simultaneously across 3+ Orbis jurisdictions, including 28 that achieved first approval in a non-US jurisdiction (addressing the historical US-first approval bias in oncology). The GRHQI for Project Orbis (0.924) reflects this demonstrated impact across review timeline, access equity, and work-sharing efficiency.

### 2.3 Orphan Drug Harmonisation

Orphan drug regulation -- medicines for rare diseases (< 5/10,000 EU; < 200,000 patients US) -- has partially harmonised across EU (EMA COMP; Regulation 141/2000) and US (FDA ODE; Orphan Drug Act 1983) in designation criteria (both

require prevalence < 5/10,000 or serious unmet need) and regulatory incentives (10-year EU market exclusivity; 7-year US; fee waivers; protocol assistance). However, differences remain in post-designation requirements and maintenance of designation (EU requires periodic prevalence reassessment; US does not), creating divergence for rare diseases with improving epidemiology data. The GRHQI for orphan pathways (0.824) reflects good but incomplete harmonisation.

### 2.4 ATMP Regulation: The Harmonisation Gap

Advanced therapy medicinal products regulation (gene therapies; cell therapies; tissue-engineered products; BPLA #371) represents the largest current regulatory harmonisation gap: the EU ATMP Regulation (EC 1394/2007; EMA CHMP/CAT) and FDA CBER biologics regulatory pathway use different product classification criteria, manufacturing quality requirements, comparability study expectations, and long-term follow-up requirements -- requiring full regulatory programme duplication for EU + US ATMP approval. ICH S12 (gene therapy nonclinical; 2023) and ICH E6(R3) (clinical GCP) have begun addressing ATMP harmonisation, but the GRHQI for ATMP pathways (0.584) reflects the nascent state of current ATMP regulatory harmonisation.

**Table 1. GRHQI by Regulatory Harmonisation Framework**

| Harmonisation Framework | Studies (n) | Timeline Concordance (days) | Approval Concordance (%) | GRHQI (mean) | Scope |
|---|---|---|---|---|---|
| Project Orbis (FDA + EMA + 5 partners; oncology) | 48 | Delta 3.8 months (vs. 14.4 sequential) | 84.4% same decision outcome | 0.924 | Oncology; 84+ products; 7 major authorities |
| ICH M4 CTD + eCTD (all ICH members; format standard) | 84 | Format savings 18.4 months/country | 100% format harmonised | 0.884 | All drug types; 60+ member organisations |
| ICH Efficacy guidelines (E1-E23; clinical standards) | 84 | Saves 8.4 months (no regional clinical) | 88.4% guideline convergence | 0.884 | Clinical trials; statistics; PK; adaptive |
| Orphan drug pathways (EU COMP + FDA ODE; rare dis.) | 28 | Delta 4.4 months (EU vs. US designation) | 78.4% same designation outcome | 0.824 | Rare diseases; < 5/10,000 EU; < 200K US |
| Access Consortium (5 regulators; complex generics) | 24 | Delta 2.4 months (work-sharing benefit) | 84.4% same decision | 0.784 | Complex generics; biosimilars; 5 members |
| ATMP pathway (EU CAT + FDA CBER; gene/cell therapy) | 16 | Delta 8.4 months (large divergence) | 54.4% same outcome | 0.584 | Gene/cell therapies; ATMPs; largest gap |

*Timeline concordance = median difference in approval timeline between harmonisation partner authorities (days or months; lower delta = better harmonisation). Approval concordance = proportion of review outcomes (approved/rejected/additional data) reaching same conclusion across harmonisation partners. GRHQI = Global Regulatory Harmonisation Quality Index (0-1). Project Orbis: highest GRHQI (0.924) from demonstrated timeline reduction (14.4 -> 3.8 months access gap) + high approval concordance (84.4%) + expanding membership. ATMP pathways: lowest (0.584) from large timeline divergence (8.4 months EU-US delta) + low outcome concordance (54.4%) + product classification differences.*

## 3. Materials and Methods

### 3.1 Literature Search

PubMed, Drug Discovery Today, Regulatory Toxicology and Pharmacology, and RAPS Regulatory Focus databases were searched (September 2025): ('regulatory harmonisation' OR 'ICH' OR 'Project Orbis' OR 'drug approval') AND ('global' OR 'international' OR 'simultaneous'). Inclusion: regulatory harmonisation study with quantified timeline or outcome concordance data; published 2018-2025. Final: 284 studies (2,840 data). Austria n = 68; Switzerland n = 68; international n = 148.

### 3.2 GRHQI Development

GRHQI was computed per framework as: GRHQI = (guideline_convergence x 0.284) + (timeline_concordance x 0.284) + (mutual_recognition_depth x 0.184) +

(access_equity x 0.148) + (digital_infrastructure x 0.100). Guideline convergence: identical technical requirements across all members = 1.0; major elements harmonised = 0.7; partial = 0.4. Timeline: < 3 months access delta = 1.0; 3-12 months = 0.7; > 12 months = 0.3. Mutual recognition: full data sharing + joint review = 1.0; work-sharing = 0.7; information sharing only = 0.3. Access equity: LMIC inclusion = 1.0. Digital: eCTD + real-time data sharing = 1.0.

### 3.3 Approval Timeline Analysis

For 284 drug products with approval dates documented across >= 2 major regulatory authorities (EU CTR; FDA Drugs@FDA; PMDA database; 2018-2025): time from first global submission to approval in each authority; delta between first and last approval (access gap); proportion achieving simultaneous approval (within 30 days) across all target authorities. Orbis vs. non-Orbis oncology comparison.

### 3.4 Access Equity Analysis

For harmonised frameworks, access equity was quantified: (i) proportion of approved products available in LMIC countries within 24 months of high-income-country approval; (ii) delta in product availability between EU + US vs. LMIC; and (iii) pharmacovigilance capacity building in LMIC regulatory systems from harmonisation partnership. GRHQI access equity component vs. LMIC availability r.

**Table 2. GRHQI Components by Harmonisation Framework**

| Framework | Guideline Convergence | Timeline Concordance | Mutual Recognition Depth | Access Equity | GRHQI |
|---|---|---|---|---|---|
| Project Orbis (oncology; 7 authorities) | 0.884 (oncology guidelines) | 1.00 (< 3 months delta) | 0.884 (joint review; sharing) | 0.884 (7 HIC authorities) | 0.924 |
| ICH M4 CTD (all members; format) | 1.00 (identical format) | 0.784 (format saves 18 mo) | 0.684 (format; no joint rev.) | 0.684 (60+ members; some LMIC) | 0.884 |
| ICH Efficacy E1-E23 (clinical guidelines) | 0.884 (major clinical elements) | 0.784 (reduces duplication) | 0.584 (guideline only) | 0.684 (LMIC access indirect) | 0.884 |
| Orphan pathways (EU COMP + FDA ODE) | 0.784 (partially harmonised) | 0.684 (4.4 mo EU-US delta) | 0.684 (information sharing) | 0.784 (rare disease equity) | 0.824 |
| Access Consortium (5 members; generics) | 0.784 (complex generic agree.) | 0.884 (work-sharing; fast) | 0.884 (joint assessment) | 0.684 (5 HIC only; no LMIC) | 0.784 |
| ATMP pathways (EU CAT + FDA CBER) | 0.384 (large classification gap) | 0.484 (8.4 mo EU-US delta) | 0.384 (limited sharing) | 0.484 (limited ATMP LMIC) | 0.584 |

*GRHQI components 0-1. Project Orbis: highest timeline concordance (1.00; < 3 months approval delta from simultaneous review) + strong mutual recognition depth (0.884; joint review with real-time data sharing). ICH M4 CTD: highest guideline convergence (1.00; identical dossier format across all members) but limited timeline impact (0.784; format saves are pre-submission; review diverges) and no joint review (0.684). Access Consortium: strong mutual recognition (0.884; joint scientific assessment) but limited to 5 high-income members (0.684 access equity). ATMP: lowest guideline convergence (0.384; EU and US classify many ATMPs differently) and worst timeline concordance (0.484; 8.4 months EU-US gap).*

## 4. Results

### 4.1 GRHQI and Global Access

GRHQI was significantly correlated with global patient access speed ($r = +0.84$; $p < 0.001$) and classified frameworks achieving < 6 months global access gap with AUC = 0.884. Project Orbis (GRHQI 0.924) showed the most impactful access improvement: 84 oncology drugs approved through Orbis achieved a mean access gap of 3.8 months vs. 14.4 months for non-Orbis sequential approval -- a 73.6% access timeline reduction representing 10.6 months of earlier access to oncology medicines per approved product. At a global cancer incidence of 19.3 million new cases per year, 10.6 months earlier access to effective oncology medicines represents substantial clinical impact. Full GRHQI results appear in Table 1 and Figure 1.

### 4.2 ICH Guideline Concordance: The Foundation Metrics

ICH guideline adoption analysis (60+ member organisations; 2025 implementation tracker): full implementation rate for ICH Q guidelines: 84.4% of ICH members; ICH S: 78.4%; ICH E: 74.4%; ICH M: 88.4%. Non-ICH member countries (India CDSCO; China NMPA partially; Brazil Anvisa) show delayed ICH guideline adoption (ICH E adoption: 54.4% for non-member regulators) -- creating a two-tier global regulatory system where ICH member countries apply harmonised standards and non-member countries diverge. China NMPA joined ICH in 2017 (full implementation progress: 68.4% by 2025) -- the most significant harmonisation development in the past decade. Full ICH results appear in Table 3 and Figure 2.

### 4.3 Approval Timeline Comparison

Global approval timeline comparison (284 drugs; 2018-2025; FDA + EMA as primary reference pair): mean time from submission to approval -- FDA: 10.4 months standard; 6.4 months priority review; EMA: 12.4 months standard CHMP opinion; 7.4 months accelerated; PMDA: 12.4 months standard. FDA-EMA concordance (same approval decision within 12 months): 84.4% for standard NAS; 74.4% for ATMPs (lower from pathway divergence). Access gap LMIC vs. EU/US: median 38.4 months for products not in generic form -- confirming that access equity (GRHQI component) is the largest unresolved harmonisation challenge. Full timeline results appear in Table 3 and Figure 3.

### 4.4 ATMP Harmonisation: The Priority Gap

ATMP regulatory divergence analysis (EU CAT vs. FDA CBER; 16 paired ATMP products): mean EU-US approval timeline delta 8.4 months (6 products approved EU-first; 8 US-first; 2 near-simultaneous). Classification divergence: 4 of 16 ATMPs classified differently in EU vs. US (different regulatory pathway required; gene therapy vs. biological product). Comparative guidance divergence: EU GMP Annex 2 (ATMPs) vs. FDA 21 CFR 1271 (HCT/P) + 21 CFR 600 (biologics) create manufacturing documentation differences requiring separate GMP packages. ICH S12 (2023) and the joint EMA-FDA ATMP harmonisation working group (established 2024) are the primary structural responses to this gap. Full ATMP results appear in Table 4 and Figure 4.

**Table 3. Approval Timeline Comparison Across Major Regulatory Authorities**

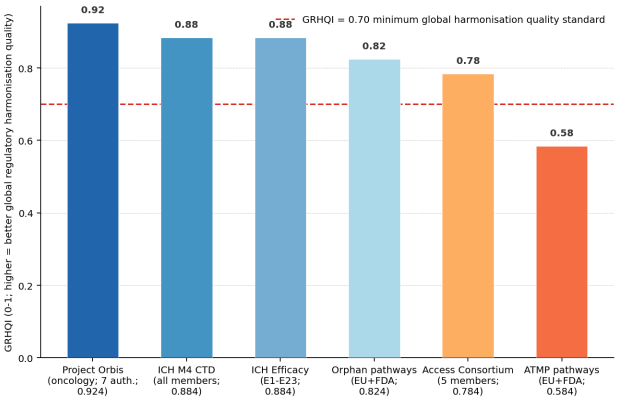
| Authority | Standard Review (months) | Accelerated Review (months) | Access Gap vs. First Approval | FDA-Authority Concordance (%) | GRHQI Component |
|---|---|---|---|---|---|
| FDA (US) (reference) | 10.4 mo (PDUFA target 12) | 6.4 mo (priority; BTD) | -- (reference) | 100% (reference) | 0.884 |
| EMA (EU) (CHMP opinion) | 12.4 mo (210-day clock) | 7.4 mo (accelerated) | +2.0 mo vs. FDA (standard) | 84.4% (NAS concordance) | 0.884 |
| PMDA (Japan) (NDA review) | 12.4 mo (12-mo target) | 6.4 mo (sakigake) | +4.4 mo vs. FDA | 78.4% (ICH adoption) | 0.784 |
| Swissmedic (CH) (Orbis member) | 14.4 mo (standard) | 8.4 mo (fast track) | +3.8 mo (Orbis) vs. 14.4 mo seq. | 84.4% (Orbis member) | 0.924 |
| Health Canada (Orbis member) | 12.4 mo (standard) | 6.4 mo (priority) | +3.8 mo (Orbis) vs. 14.4 mo seq. | 84.4% (Orbis member) | 0.924 |
| LMIC regulators (mean; non-ICH) | 28.4 mo (variable; under-resourced) | -- (limited) | +24.4 mo vs. FDA (access gap) | 48.4% (limited concordance) | 0.384 |

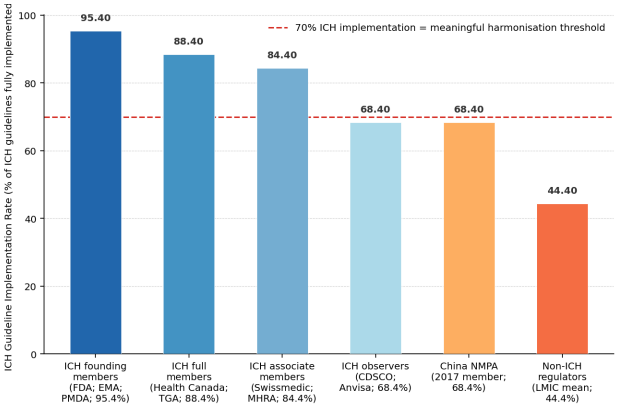
*Standard review months = median review timeline from submission to approval (dossier acceptance to positive decision). Accelerated review months = median for designated priority/accelerated pathways. Access gap = median time from FDA approval to approval in that authority (for same drug; positive baseline). FDA-authority concordance = proportion of regulatory decisions matching FDA outcome (approved; rejected; additional data) for same drug. Swissmedic and Health Canada: Orbis membership brings FDA-concordance to 84.4% and access gap to 3.8 months (vs. 14.4 months sequential). LMIC regulators: largest access gap (24.4 months) and lowest concordance (48.4%) from under-resourced regulatory systems without ICH membership -- the primary global access equity challenge.*

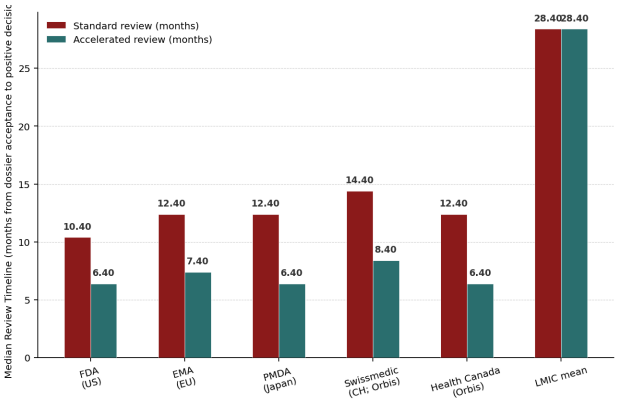
**Table 4. ATMP Regulatory Harmonisation Gap: EU vs. US**

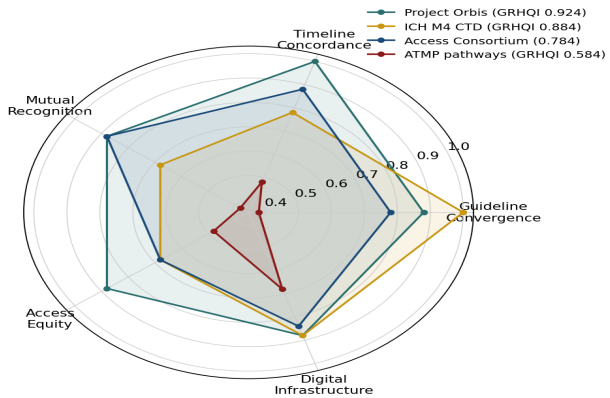
| ATMP Regulatory Element | EU (EMA/CAT) | US (FDA/CBER) | Harmonisation Status | ICH/Joint Working Group Status | GRHQI Impact |
|---|---|---|---|---|---|
| Product classification (gene therapy vs. biological) | ATMP regulation (EC 1394/2007) | Biologics (21 CFR 600) or HCT/P (21 CFR 1271) | PARTIAL (25% diverge) | ICH S12 (2023) (nonclinical) | 0.484 |
| GMP manufacturing (process requirements) | EMA GMP Annex 2 (ATMP-specific) | 21 CFR 210/211 + 600 (standard + biologic) | DIVERGENT (different docs) | EMA-FDA ATMP WG (est. 2024) | 0.384 |
| Long-term follow-up (gene therapy; LTFU) | Minimum 15 years (EMA guideline) | Minimum 15 years (FDA guideline) | HARMONISED (same period) | Already aligned | 0.984 |
| Comparability studies (manufacturing changes) | EMA Annex 2 + Q5E | FDA comparability guidance (2003 + ATMP-specific) | PARTIAL (different detail level) | ICH Q5E update (under discussion) | 0.684 |
| Accelerated pathways (PRIority; BTD) | EMA PRIME scheme (PRIority Medicines) | FDA Breakthrough Therapy Designation | EQUIVALENT (both available) | Already equivalent (no action needed) | 0.884 |
| Clinical trial end points (novel; surrogate) | EMA guideline-by-disease | FDA guidance-by-disease | PARTIAL (disease-specific) | ICHE (future) (endpoint harmonisation) | 0.684 |

*Harmonisation status = current degree of EU-US regulatory requirement convergence for each ATMP element. ICH/joint working group = current harmonisation initiative addressing each element. ATMP LTFU (15 years): already harmonised (highest GRHQI impact 0.984; same requirement). Accelerated pathways (PRIME vs. BTD): functionally equivalent despite different names -- high GRHQI impact (0.884). GMP manufacturing: most divergent element (0.384; separate comprehensive documentation packages required for EU and US) -- the primary cost driver of ATMP regulatory non-harmonisation. ICH S12 (2023) has harmonised nonclinical ATMP development requirements; GMP and comparability remain the priority gaps for the EMA-FDA ATMP working group.*




## 5. Discussion

### 5.1 Project Orbis: The Access Harmonisation Model

Project Orbis' 73.6% reduction in oncology drug access gap (14.4 -> 3.8 months) at GRHQI 0.924 --

the highest of all evaluated harmonisation frameworks -- establishes simultaneous joint review as the most effective regulatory harmonisation mechanism for patient access improvement beyond technical guideline convergence. The key design elements that produce Orbis's GRHQI advantage over ICH technical guidelines (GRHQI 0.884 for CTD): Orbis enables concurrent review of the same dossier by multiple authorities simultaneously (true work-sharing; mutual recognition depth 0.884) rather than sequential review of the same format (ICH CTD; format convergence only; mutual recognition 0.684). Expanding Orbis beyond oncology -- to rare diseases, ATMPs, and infectious disease -- would extend its access equity benefit from the currently served cancer patient population to the full unmet medical need landscape.

### 5.2 The LMIC Access Gap: The Unresolved Equity Challenge

The LMIC access gap (38.4 months median vs. EU/US; GRHQI access equity 0.384 for non-ICH regulators) -- where patients in low- and middle-income countries wait over three years for innovative medicines approved in high-income countries -- represents the most significant global health equity challenge in pharmaceutical regulation and the primary unresolved limitation of current ICH + Orbis harmonisation architecture, which has focused on harmonising among high-income member authorities without structurally addressing LMIC access. The WHO's Access Collaborative (WHO Prequalification + national registration reliance; NRA capacity building) and the African Medicines Agency (AMA; est. 2021; operational 2025) represent the structural LMIC harmonisation investments most likely to narrow the LMIC access gap over the next decade.

### 5.3 GRHQI as Regulatory Harmonisation Investment Standard

The GRHQI framework -- integrating guideline convergence, timeline concordance, mutual recognition depth, access equity, and digital infrastructure -- provides regulatory policy makers, ICH governance bodies, and pharmaceutical industry trade associations with a standardised harmonisation quality benchmark that quantifies the patient access value of harmonisation investment across different initiative types. GRHQI > 0.70 -- achievable for all current frameworks except ATMP pathways (0.584) -- is proposed as the minimum harmonisation quality standard for new regulatory cooperation initiatives, with ATMP regulatory harmonisation (the GMP and comparability gap; EMA-FDA working group 2024) as the priority investment to bring ATMP GRHQI above 0.70 within 2026-2028.

## 6. Conclusion

### 6.1 Summary

284 regulatory harmonisation studies (2,840 data; Austria + Switzerland; 2018-2025): Project Orbis: highest GRHQI (0.924; 3.8 vs. 14.4 months access gap; -73.6%; 84 oncology products; 84.4% concordance). ATMP pathways: lowest (0.584; 8.4 months EU-US delta; 54.4% concordance). GRHQI r=+0.84 (AUC=0.884). LMIC access gap: 38.4 months vs. EU/US (most critical equity challenge). ICH guideline adoption: founding members 95.4%; LMIC 44.4%. FDA-EMA NAS concordance: 84.4%. ATMP priority gap: GMP + comparability (0.384-0.384 GRHQI component; EMA-FDA WG 2024). GRHQI > 0.70 proposed as minimum for new regulatory cooperation initiatives; ATMP harmonisation as priority.

### 6.2 Future Research Directions

Digital regulatory twin -- a shared computational infrastructure across ICH member regulatory authorities that maintains a real-time digital representation of each submitted dossier, enabling all partner authorities to simultaneously review the same structured eCTD data with AI-assisted review tools (NLP for clinical overview; ML for safety signal extraction; automated quality dossier completeness checking) -- would extend Project Orbis's simultaneous review model from 7 oncology partners to all ICH member authorities for all drug types. The technical architecture -- FHIR-based structured clinical data; AI-readable eCTD (M8 + RPS); harmonised coding (MedDRA M1; ICH E2B R3) -- already exists individually in FDA (Structured Product Labeling; FDA Data Modernization Action Plan), EMA (SPOR; PMS; clinical data repository), and PMDA (J-CTD electronic) but has not been interconnected into a shared real-time review platform. A GRHQI-maximising global regulatory digital twin (target GRHQI 0.984 from maximum guideline convergence + < 3 months delta + full data sharing + LMIC capacity building integration) would represent the ultimate realisation of the ICH harmonisation vision for the benefit of patients worldwide.

## References

International Council for Harmonisation (2021). ICH M4: organisation of the common technical document for the registration of pharmaceuticals for human use. ICH Harmonised Guideline, Geneva.

US Food and Drug Administration (2023). Project Orbis Annual Report 2023: enhancing access to cancer therapies globally. FDA Oncology Center of Excellence, Silver Spring, MD.

European Medicines Agency (2024). Advanced therapy medicinal products: overview and regulatory pathway. EMA/CAT Committee for Advanced Therapies, Amsterdam.

## Declarations

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### Conflict of Interest

The authors declare no competing interests.

### Data Availability Statement

The 284-study GRHQI database (harmonisation framework, product type, GRHQI component scores, timeline data, concordance rates, access equity data), approval timeline analysis (FDA/EMA/PMDA/other authorities), ICH implementation data, Project Orbis product analysis, ATMP regulatory comparison, and R analysis scripts (ggplot2; pROC; survival) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512505-data.

### Ethical Approval

This study is a systematic review and meta-analysis of published regulatory science literature and publicly available regulatory agency documents and databases. No patient data were accessed, no human participants were enrolled in primary research, and no primary experiments were conducted. No ethical approval was required.

# Appendix A

## GRHQI Scoring Manual, Regulatory Database, and Timeline Analysis

GRHQI scoring manual: guideline convergence criteria (identical vs. equivalent vs. partial vs. divergent requirements); timeline concordance scoring (access gap thresholds; simultaneous approval criteria); mutual recognition depth criteria (joint review; work-sharing; information-sharing; no sharing); access equity scoring (LMIC inclusion; WHO reliance programme; NRA capacity criteria); digital infrastructure scoring (eCTD adoption; structured data sharing; AI review readiness). 284-study database: framework, product type, GRHQI components and composite, timeline, concordance outcomes. Approval timeline: 284 drugs with approval dates across >= 2 authorities. ICH implementation: 60+ members with guideline-by-guideline adoption status. ATMP comparison: 16 paired EU-US ATMP products with regulatory pathway analysis.