Regulatory Evolution & Regional Harmonization

The New Era of GCP : Navigating ICH-E6 (R3) Implementation Across Asian Regulatory Landscapes

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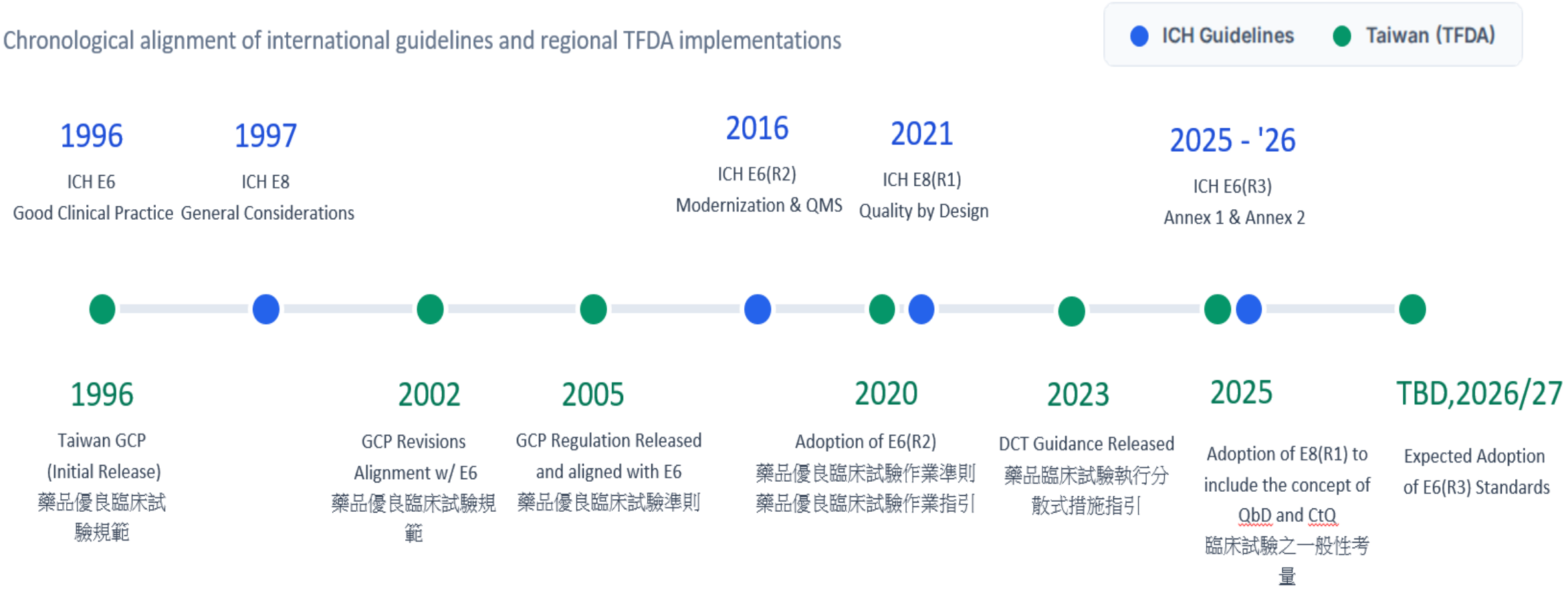
Evolution of GCP : ICH vs. Taiwan (1990s - Present)

Chronological alignment of international guidelines and regional TFDA implementations



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ICH E6(R3) Global Implementation Landscape

2019	2021	2023	Jan 2025	✓ Jun 2026
Concept Paper	Draft Principles	Step 2 (Draft)	Step 4 (Principles & Annex 1)	Step 4 (Annex 2)

Regulatory Authority	E6(R3) Principles & Annex 1 Interventional Clinical Trials	Annex 2 Non-traditional/Decentralized Trials
EU European Union (EMA) Founding Member (1990)	Implemented Effective July 23, 2025	Adopted Effective Jan 15, 2027
US United States (FDA) Founding Member (1990)	Implemented Final Guidance Sept 9, 2025	Pending TBD post-Step 4
GB United Kingdom (MHRA) Member (2022)	Implemented Effective Apr 28, 2026	Pending TBD post-Step 4
JP Japan (MHLW/PMDA) Founding Member (1990)	Pending Translation Historically adopts within 6-12 mos of Step 4	Pending TBD post-Step 4
TW Taiwan (TFDA) Regulatory Member (2018)	Expected 2026-2027 Drafting local translation	Pending TBD post-Step 4
KR South Korea (MFDS) Regulatory Member (2016)	Pending Notification Awaiting official MFDS update	Pending TBD post-Step 4
AU Australia (TGA) Observer (2015)	Implemented Effective Jan 16, 2026	Pending TBD post-Step 4
CN China (NMPA) Regulatory Member (2017)	Pending Notification Historically adopts swiftly post-Step 4	Pending TBD post-Step 4

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Key Differences : R2 versus R3

Aspect	ICH E6 (R2)	ICH E6 (R3)
Structure	Single guideline	Overarching Principles document plus Annex 1 (interventional trials) and Annex 2 (non-traditional trials); separate Glossary and Appendices
Focus	Compliance checklist; all errors flagged	Principles-led **quality by design**; focus on **critical-to-quality elements (CtQ)** rather than perfection, Define Critical-to-Quality (CtQ) factors before first patient enrolled. For example, Informed Consent, Eligibility, Safety Reporting, IMP Management, Primary Endpoint.
Risk Management	Introduced Risk-based monitoring	**Proactive** Quality Risk Management throughout trial lifecycle; encourages Quality by Design and **continuous** quality improvement
Quality Tolerance Limits	Strict QTLs per protocol; deviations require detailed justification	Broader concept of "acceptable ranges"; deviations handled via continuous adjustment and contextual judgment
Terminology	Uses "subjects," "source documents/data", "essential documents " and etc	Updates terms: "trial participant" (replacing subject); "source records" (documents including electronic data), "essential records" and etc New terms: : "metadata", "service provider" and etc
Technology and Data	Basic mentions; compliance-centered (e.g. Part 11 fulfillment)	Explicit guidance on eConsent, eCRFs, wearables, EHR integration and data governance; media-neutral language for digital tools
Trial Designs	Primarily interventional trials	Recognizes adaptive, platform, pragmatic, and decentralized designs via Annex 2; encourages innovative models
Roles & Responsibilities	Defined for sponsor, investigator, IRB broadly; mostly static	Clarified and expanded descriptions: **each stakeholder's duties are detailed** (e.g. informed consent process, data integrity, quality systems)
Ethics & Consent	Standard informed consent and IRB review	Additional guidance on consent (e.g. eConsent, multi-lingual ICFs, assents for minors) and transparency; emphasizes participant welfare, equity, privacy

Taiwan in Focus

Strengths ✓

Strong MRCT track record; TFDA review widely regarded as competitive
Sites experienced with sponsor-driven RBQM requirements
TACTC (33-hospital alliance) — built for coordinated implementation

Current gaps △

TFDA formal adoption timeline for E6(R3)/Annex 2: TBD (2026-2027)
IRB fragmentation = real operational bottleneck for multi-site trials
DCT/remote monitoring readiness varies significantly across institutions

Opportunity: Collaboration to streamline the process and aligns with R3's harmonization goals

E6(R3): Action Plan for Taiwan Site

Institution

→ Update SOPs: embed CtQ review at study activation stage

→ Invest in DCT infrastructure: eConsent, telemedicine, home health SOPs

→ Assign documented decision rights in quality governance

PI (Principal Investigator)

→ Ask sponsors: "What risk level drove your monitoring approach?"
→ Ask: "What are THIS study's CtQ factors?" — not just "what must I document?"
→ Review sponsor QTLs and escalation triggers at startup meeting
→ Champion digital audit trail discipline in your team

SC (Site Coordinator)

→ Know your audit trail end-to-end: source data, timestamps, metadata
→ Complete DCT / eConsent / remote data collection training proactively
→ Understand the sponsor RBQM plan for each active study
→ Flag data quality risks to PI BEFORE monitor visits — not after

IRB

→ Build capacity to review Annex 2 decentralized trial designs
→ Update consent templates for remote / digital consent processes
→ Align review timelines with R3-compliant sponsor submissions

Key Takeaways for Site

Start now — sponsors already expect R3-aligned practices regardless of local adoption

- **Embed CtQ thinking from Day 1 — quality is a plan, not a monitoring afterthought**
- **Digitize & trace everything — audit trails, e-consent, source records under new scrutiny**
- **Taiwan sites: MRCT experience is the R3 bridge; watch for HA update on adoption**

Ask ourself: "If this became a decentralized trial tomorrow — would we be ready?"

Asia Ambassador Symposium

Aug 15, 9:00 AM - 12:30 PM (Taipei)

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ICH GCP E6(R3)

Practical challenges investigators face

R3 changes the site question from ‘Did we follow the process?’ to ‘Can we show control of the critical risks?’

Two examples to anchor the discussion

Autologous CAR-T
Chain of identity, acute safety, long follow-up

AI at the trial site
Eligibility support, source data, oversight

R3 shifts the operating question

From "did we complete the checklist?" to "can we show evidence of control over the risks that matter?"

1 Quality by design

- Build quality before enrollment

2 Risk-proportionate controls

- Focus controls on what matters

3 Investigator oversight

- Delegation does not dilute PI accountability

4 Data governance

- Data must be traceable across systems

Practical implication
Make three proof points visible

What is critical? Safety, endpoint reliability, eligibility, blinding, product integrity

Who controls it? Site, sponsor, CRO, lab, vendor, algorithm, EHR

What proves it? Training, delegation, source, audit trail, reconciliation, escalation

Takeaway message: Less ritual. More visible control of clinical judgment, delegation and technology.

Autologous CAR-T: when clinical care, manufacturing and trial conduct collide

The practical challenge is not one task—it is the chain across tasks.

1 Before infusion

Apheresis slot, product release, eligibility windows and bridging therapy can move faster than protocol paperwork.

2 At treatment

Conditioning, ICU transfer, CRS/ICANS management and unplanned rescue actions generate deviations and safety data fast.

3 After infusion

Long-term safety, re-consent, secondary malignancy vigilance and records retention extend beyond the acute trial visit.

Eligibility is not a one-time decision; it may need reassessment before infusion.

R3 lens: Delegation is not abdication — the PI should be able to show qualified teams, documented handoffs, protocol deviation logic, IP controls, source/metadata traceability and timely safety escalation.

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AI at the trial site: useful only if the use case is governed

Scenario: an AI tool pre-screens EHR records, drafts query responses, and prioritises data review.

Intended use – Is it administrative support, eligibility support, endpoint assessment, or safety signal triage?

Human review – Who has authority to accept, override or reject AI output and where is that decision captured?

Traceability – Can we reconstruct input data, prompt, model version, output, reviewer and audit trail?

Change control – What happens when the model, EHR feed or performance changes mid-trial?

R3 lens – If AI influences eligibility, safety, endpoints or critical data review, treat it as a governed trial process—not a convenience tool.

- **Is the AI output used for a critical decision?**
- **Can we reconstruct input, output, human review and final decision?**

AI can recommend; investigator decides

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A comparative analysis of evolving requirements for eSource, Audit Trails, and System Validation

Dimension	ICH E6(R2)	ICH E6(R3)
eSource Definition	Primarily focused on Sponsor-controlled systems (e.g., EDC, eCRF).	**Expanded to include Site-level systems (e.g., EMR, ePRO, wearables).**
Audit Trail Requirements	Mentioned but lacked specific enforcement. Under most circumstances, regulatory authorities accepted hospital EMRs as the institution's responsibility; Investigators only ensured the CRF matched the EMR.	Explicitly requires tracking **"Who, When, What, and Why"** with full reviewability. Must ensure complete data traceability via audit trails or other verification methods. Any modifications/corrections (e.g., EMR record updates) must be tracked [who, when, what kind of change]. **Both Sponsor and Investigator** share responsibility for ensuring EMR systems support GCP audit trail standards. If a hospital EMR lacks sufficient audit trails, remedial measures (e.g., certified copies, data export with integrity verification) are required. Emphasizes a **risk-based approach**: complete, reviewable audit trails are mandatory for EMR data directly impacting patient safety and critical endpoints.
Review Frequency	No explicit frequency defined; typically performed as pre-audit preparation.	Requires regular, **risk-directed** reviews.
Focus on Critical Data	No specific classification.	Intense focus on monitoring changes and anomalies within **"Critical Data"**.
System Validation	Emphasis largely on Sponsor system validation.	**All** eSource systems require validation, including Site-level systems.
Data Governance	No dedicated section.	Annex 1 introduces a new **Data Governance** chapter, heavily emphasizing ALCOA+ principles.

eSource Readiness Assessment tool for site self-assessment

- **eClinical Forum**

- Founded in 2000 as a global non-profit, non-commercial organization.
- Members include pharmaceutical companies, CROs, investigator sites, and regulators.
- **Provides a neutral platform for sharing best practices in eClinical technologies.**
- Developed the **eSRA (eSource Readiness Assessment) tool for site self-assessment**.
- Supports GCP compliance and ICH E6(R3) implementation for electronic source systems.
- Resources are publicly available and regularly updated based on global regulations.

- eSource Readiness Assessment is a structured evaluation to determine whether electronic systems used in clinical trials—such as EMR, ePRO, or wearable devices—are compliant with Good Clinical Practice (GCP) and ICH E6(R3) requirements.

  - ✅ Purpose: Ensure data reliability, traceability, and regulatory compliance.
  - 👥 Users: Investigator Sites, Sponsors, CROs, Auditors.
  - 📋 Key Checklist Items:
    - - Audit Trail (who/when/what/why)
    - - System Validation (CSV)
    - - Data Integrity (ALCOA+)
    - - Metadata and Source Records
    - - IRB/IEC Notification Mechanisms

Hurdles to implement eCosent

- The e-consent is multimedia components such as images, audio, video, diagrams, call out check boxes that will provide interaction with patients. But this is difficult to fit for IRB ICF format for header or footer.
- It is difficult to customize ICF formats (e.g., extra check boxes, watermarks).
- Even minor changes (animation, layout…etc.) or final screenshot require IRB review, which may cause delays in practice.
- low adoption rate due to lack of SOPs, limited experience,, and concerns about usability for elderly participants.

AI Readiness Starts with R3: The 4-Layer Foundation

4-Layer AI Readiness Stack

(Dhody, 2026 — kushdhody.com)

Layer 1 · QbD Operating Model ← Start here

CtQ factors, RBQM, QTLs, decision rights — defined BEFORE protocol is written

Enabled by: ICH E8(R1) + E6(R3) Principles + Annex 1 & 2

Layer 2 · Structured Protocol & Standards

Protocol as machine-readable asset (ICH M11 + CDISC USDM)

One change reconfigures downstream systems — no manual re-keying

Layer 3 · Governed, Interoperable Data

Every value has a source, lineage, owner, and use policy

Enabled by: CDISC SDTM/ADaM · Dataset-JSON · FAIR principles

Layer 4 · AI-Enabled Execution ← Only works on solid L1–3

Protocol authoring copilots · RBQM triage · Safety signal monitoring

"A deliberate portfolio, not a procurement"

Local implication

"Your readiness is defined by your weakest foundational layer."

R3 adoption = building Layer 1. It is not just compliance — it is the foundation for AI-enabled clinical development.