

Regulatory Signal Brief™

The New Standard in Clinical Development: ICH E6(R3), Quality by Design (QbD), and Its Applied Domains (DCT, RWD, and AI)

Probio Corporation

Publication Date: December 10, 2025

Table of Contents

Purpose	4
Analytical Methodology	4
Scope / Framework Positioning	5
Executive Summary	6
Top 3 Strategic Actions (Management / Enterprise Level)	6
Overview of the Three Converging Trends	7
Signal Card 1 Parent Theme: Overview of ICH E6(R3) and the Quality by Design (QbD) Principles	8
1. Card Summary	8
2. What changed? (Latest Developments / Sections)	8
3. So what? (Role-Specific Implications: SOP, QMS, RBM, Data Governance, Vendors)	9
4. Operational Action Checklist (for Discussion at Working Level)	10
5. Decision Prompts (Who Does What)	11
6. FAQ	11
7. Signal Priority Index (SPI)	12
8. Sources and References	12
Signal Card 2 Sub-Theme: Applying QbD Principles (1): Decentralized Clinical Trials (DCT)	14
1. Card Summary	14
2. What changed? (Latest Developments / Sections)	14
3. So What? (Role-Specific Implications: Adoption Decisions and Risks)	16
4. Operational Action Checklist (Working Level)	17
5. Decision Prompts (Who Does What)	17
6. FAQ	18
7. Signal Priority Index (SPI)	18
8. Sources and References	18

Signal Card 3 | Sub-Theme: Applying QbD Principles (2): Designing Reliability for Real-World Data (RWD) and Framework for AI Oversight (Annex 2 + Related Guidelines) _____ **20**

1. **Card Summary** _____ **20**
2. **What Changed? (Latest Developments)** _____ **20**
3. **So What? (Role-Specific Implications)** _____ **22**
4. **Operational Action Checklist (Working Level)** _____ **23**
5. **Decision Prompts (Who Does What)** _____ **23**
6. **FAQ** _____ **24**
7. **Signal Priority Index (SPI)** _____ **24**
8. **Sources and References** _____ **24**

Business Implications Matrix (Impact by Function and Recommended Actions) _____ **29**

Future Outlook _____ **30**

Milestones by Topic _____ **30**

Upcoming Meetings / Public Comment Deadlines / Adoptions _____ **31**

Monitoring Focus (Operational Attention Points) _____ **31**

Purpose

The purpose of this report, *Regulatory Signal Brief™*, is not merely to understand global regulatory trends, but to enable action based on them.

Centered on ICH E6(R3), the implementation of the Quality by Design (QbD) principles defined in ICH E8(R1) is progressing as the standard framework for clinical quality management in pharmaceuticals, vaccines, and biological products.

(Note: Medical devices and SaMD are outside the scope of E6(R3).)

The challenge now facing organizations is not only “*understanding regulations,*” but “*aligning and operationalizing their internal processes accordingly.*”

This report is designed as a shared language to accelerate execution decisions and organizational alignment.

Analytical Methodology

This report is generated using a **regulatory-specific AI analysis process** applied to primary-source documents (ICH, FDA, EMA, etc.).

Unlike general-purpose conversational AI models, the methodology is engineered to:

- Parse regulatory logic structures, hierarchical requirements, and dependencies
- Identify cross-document consistencies across guidelines, annexes, and Q&As
- Extract **granular verification points** often overlooked in manual reviews

The output serves as a “**working zero-draft**” for operational planning and risk assessment. Final determinations must be made by your organization’s subject matter experts.

Scope / Framework Positioning

ICH E6(R3) serves as the upper-level framework institutionalizing the concept of Quality by Design (QbD) in clinical development.

Annex 1 and Annex 2, as subordinate components, specify the implementation domains of QbD.

Hierarchy	Content	Target Domain
E6(R3) Core	Defines QbD principles, Critical-to-Quality (CtQ) factors, Quality Tolerance Limits (QTLs), risk-proportionate design, and baseline QMS standards	Interventional clinical trials for pharmaceuticals, vaccines, and biologics
Annex 1	Details QbD implementation methods for traditional interventional trials	Pharmaceuticals, vaccines, and biologics
Annex 2	Presents additional GCP considerations for decentralized (DCT), pragmatic, and real-world data (RWD) elements	Clinical trials incorporating decentralized, pragmatic, or RWD components

Executive Summary

On 6 January 2025, ICH E6(R3) reached Step 4 adoption, recommending regional regulatory authorities to proceed with local adoption.

Elements such as CtQ definition, QTL establishment, centralized monitoring, and data governance will be implemented sequentially in each region; there is no single effective date.

The QbD principle represents a paradigm shift – from audit-based assurance to proactive integration of quality at the design stage.

E6(R3) and Annex 1 formalize the structural components of quality, including CtQ identification, Quality Tolerance Limits (QTLs), centralized monitoring, and integration of data governance.

Annex 1 introduces additional QbD considerations for emerging markets such as QTL and QTLs (e.g., central data, electronic informed consent, electronic patient IP agreement, central data capture), QTL model selection and updating and central QTLs scope.

Keynote 1000s series is available.

Global functional updates across products: QTLs, QTLs, QTLs, and central agreements are regularly updated.

Organizational updates of integrated design and execution of QTL, QTL, QTL, and IP will gain advantages in data security, regulatory readiness, and development efficiency.

ICH E6(R3) QbD Principles in Annex 1 becomes effective on 20 July 2025.

Business readiness plan by region, implementation and transition planning must be region specific.

Top 3 Strategic Actions (Management / Enterprise Level)

1. Executive approval of a QbD gap-closure plan, including internal standardization of CtQ, QTL, monitoring, and data-governance frameworks.
2. Evaluation of operational status for the QTL 'Core Team' and electronic consent, electronic patient IP agreement, and audit log.
3. Review of all monitoring QTLs, QTLs, QTLs, and QTLs (e.g., central data, electronic informed consent, electronic patient IP agreement, and audit log). Global functional updates of design documents, QTLs, and central contracts are essential to address global operations of QTL, QTL, QTL, and IP, thereby forming a key source of competitive advantage.

Overview of the Three Converging Trends

E6(R3): Reconstructing the Clinical Development DR through QM Thinking (see Signal Card 1)

1)

- Quality = Product Program, Quality **QMS** → early risk proportional design → monitor & respond as QM
- Reorientation of quality QM and operational monitoring
- Data governance: protection of identity, full data lifecycle control, audit trails, computerized system validation (CSV) using a risk-based approach

DCT: Operational Domain Implementing QM (see Signal Card 2)

- Serviceable, local SOPs, SOPs/STPs, alignment, shared patient IP program, formalized QM
- Alignment with regulatory requirements (21 CFR Part 312) and alignment with EU GMP Recommendations (EU GMP)
- Shared ownership (serviceable, together, about QM, STP, SOP) and visibility of data flow

RWD as a Data-Driven Service: Extending QM Implementation (Annex 2 for QMS, AI outside context) (see Signal Card 3)

- The specification of QM reliability, relevance, timeliness, and linkage processes
- AI used in clinical operations must comply with GMP/STP (data governance), maintaining identity, ensuring data lifecycle traceability before analysis, and validating computerized systems for security and integrity
- If AI qualifies as a medical device, incorporate pre-defined learning plans under PIVP with operational monitoring (STP, QM, follow-up)
- Align with the CDMA in Reflection Paper for design, data control, and transparency. In high-trust settings, use pre-specified guidelines and formal models for incremental learning in clinical trials, with ongoing performance monitoring

Signal Card 1 | Parent Theme: Overview of ICH E6(R3) and the Quality by Design (QbD) Principles

1. Card Summary

- ICH E6(R3) was adopted at Step 4 on 6 January 2025 (final version). It includes the Principles section, Annex 1 (detailed application to traditional interventional trials), and clarified data-governance requirements, establishing QbD (CtQ identification, risk-proportionate approach, QMS integration) as the standard for clinical development.
- Annex 2 (additional considerations for emerging models such as DCT and RWD) reached Step 2 (public consultation) on 6 November 2024. The timing of final adoption (Step 4) remains undetermined; implementation will depend on each regional authority (E6 core was already adopted at Step 4 on 2025-01-06).

2. What changed? (Latest Developments / Sections)

E6(R3) Step 4 Adoption (Final Version)

- Adoption date and Step: 6 January 2025, Step 4 (recommendation for regulatory adoption). The document header includes its adoption history [Document History section].
- Structure: Principles (Section II), Annex 1 (IRB/IEC, Investigator, Sponsor, Quality Management, Monitoring, etc.), Data Governance (Section 4), and Appendices A–C [Sections II, III, 4].
- Implementation: Step 4 is an ICH-level recommendation; regional implementation is required. There is no single effective date [Introduction: “At Step 4... recommended for adoption”].

Positioning of Annex 1 and Annex 2

- Annex 1 provides application-level details (IRB/IEC, Investigator, Sponsor). Data Governance (Section 4: Data Governance – Investigator and Sponsor) is newly established as a separate chapter in the core document [Sections III (Annex 1) and 4].
- Annex 2 covers additional considerations for emerging models. It was signed at Step 2 on 6 November 2024; public-comment review and revision are ongoing, and the Step 3/4 timeline remains open [Annex 2 Step 2 Presentation p.3; Preface of Annex 2 Step 2 Draft].

Introduction of QbD (Embedding Quality at the Design Stage)

- Identify Critical-to-Quality (CtQ) factors proactively and manage them in a risk-proportionate manner [Principles 6.2, 7, 3.10.1].
- Integrate QbD into the Quality Management System (QMS) and define Quality Tolerance Limits (QTLs) as thresholds for deviation and evaluation [3.10, 3.10.1.3].
- Adopt risk-based monitoring (RBM) combining centralized, remote, and on-site approaches with a mandatory monitoring plan [3.11.4, 3.11.4.3].
- Formalize data governance (data lifecycle, audit trail, computerized-system validation using a risk-based approach) [4.2, 4.3].

Conceptual Shift from Previous Practice

- Move from “post-hoc audit and QC focus” to “forward-looking design centered on CtQs to eliminate unnecessary complexity” [Principles 6, 7; E8(R1) ‘Considerations in Identifying Critical to Quality Factors’].

Transparency and Reliability of Results

- Strengthen trial registration and result-disclosure transparency, record retention and access, and data integrity [Principles 9.4–9.6, 3.16, 2.12, Appendix C].

3. So what? (Role-Specific Implications: SOP, QMS, RBM, Data Governance, Vendors)

	Key Operational Implications
Regulatory Affairs (RA)	<ul style="list-style-type: none">• Standardize E6(R3) compliance review for protocols, IB, informed-consent documents, and safety reports (Appendix B, Appendix A, 2.8, 3.13).• Establish criteria for reporting quality issues such as QTL deviations and for notifying authorities or IRBs (3.10.1.3, 3.12, 3.13.3, 3.17).• Define procedures for trial registration, result disclosure, and lay summaries (Principles 9.6, 3.17.2(c)).• Clarify responsibilities and update contract clauses for outsourcing and co-development (3.6, 10.2); define submission and communication flows with authorities and IRB/IEC (3.8, 1.1).
Clinical Operations (ClinOps)	<ul style="list-style-type: none">• Specify CtQs, risk controls, monitoring strategy, blinding protection, and data handling in protocols (Appendix B B.12, B.14, 3.11.4, 4.1–4.2).• Evaluate and oversee vendor/sub-contractor qualification (3.6, 3.9.5). Implement risk-based central/remote/on-site monitoring (3.11.4.1–3.11.4.6).

	Key Operational Implications
	<ul style="list-style-type: none"> Establish procedures for IMP supply, decentralized distribution, and home administration (2.10, 3.15.3). Maintain blinding and define emergency unblinding procedures (2.11, 4.1).
Quality Assurance (QA)	<ul style="list-style-type: none"> Renew the QMS to integrate QbD, risk management, oversight, audit, and CAPA consistency (3.10, 3.11.2, 3.12). Define QTL setting, monitoring, root-cause analysis, CAPA, and quality-issue reporting (3.10.1.3, 3.10.1.6, 3.12.2). Apply risk-based approaches to monitoring and audit plans (3.11.4.3, 3.11.2). Standardize data-governance and computerized-system validation criteria (audit trail, access control, backup/DR, change management) (4.2, 4.3). Establish escalation and authority-notification criteria for major non-compliance (3.9.6, 3.12.2–3).
Data Science	<ul style="list-style-type: none"> Define data-lifecycle procedures (acquisition, metadata/audit trail, correction, transfer, finalization, archiving) (4.2.1–4.2.8). Design central monitoring logic and KPIs (3.11.4.2, 3.11.4.5). Plan statistical analysis, programming QC, traceability, and data lock (3.16.2, 4.2.6, 3.16.1(p)–(r)). Control data access, sharing, and unblinding according to blinding requirements (4.1, 3.16.1(f)–(g)). Ensure timely provision of external data to investigators for review-driven operations (2.12.3, 3.16.1(k)).

4. Operational Action Checklist (for Discussion at Working Level)

- Gap analysis between E6(R3) principles and current SOP/QMS for QbD, risk management, monitoring, and data governance (Principles 6–7, 3.10, 3.11, 4).
- Develop CtQ mapping by trial (define objectives, endpoints, participant risks, data criticality, and risk controls) (Principles 6.2, 7.1).
- Draft guideline for Quality Tolerance Limits (QTL): thresholds, detection, escalation, correction, authority/IRB communication (3.10.1.3, 3.10.1.6).
- Revise monitoring-plan template to combine central, remote, and on-site approaches and cross-vendor oversight (3.11.4, 3.11.4.3).
- Require protocol templates to include quality-design sections (CtQ, risk, QC/QA, data handling) (Appendix B B.12, B.14; Principles 8).

- Update vendor qualification and responsibility definitions (including SLA/KPI and sub-contractor oversight) (3.6.6–3.6.10, 3.9.5).
- Define minimum data-governance standards (metadata/audit trail, computerized-system validation, access control, backup/DR) (4.2, 4.3, 3.16.1(x)).
- Reconfirm standard procedures for registration, result disclosure, and lay summaries (Principles 9.6).

5. Decision Prompts (Who Does What)

	Action	Relevant Clauses
Head of QA	Approve E6(R3) gap-analysis review and define CAPA priorities	3.10, 3.12
Head of ClinOps	Revise monitoring-plan template to reflect criteria for central and remote monitoring	3.11.4.3
Head of Data Management / Data Science	Issue provisional procedures for data-governance standards and risk-based computerized-system validation	4.2, 4.3
Head of RA	Establish a monitoring framework for Annex 2 finalization and regional implementation timelines	Introduction and Annex 2 Step 2 documents

6. FAQ

Q1. What is the relationship between QbD and RBM (risk-based monitoring)?

A. QbD identifies CtQs and manages risks proportionately (Principles 6.2, 7). RBM is the primary operational tool for that risk management (central, remote, on-site) and is implemented through the monitoring plan (3.11.4, 3.11.4.3).

Q2. How are CtQs identified?

A. For each trial, CtQs are identified prospectively based on objectives, scientific rationale, endpoints, participant safety, and data criticality (Principles 6.2, 7.1). The protocol must describe quality design and risk controls (Appendix B B.12).

Q3. When does E6(R3) take effect (transition measures)?

A. ICH adopted E6(R3) at Step 4 on 6 January 2025 (recommendation for regional adoption). Effective dates depend on each authority's implementation [Introduction: "At Step 4... recommended for adoption"]. Monitor regional guidance for official adoption and implementation dates.

7. Signal Priority Index (SPI)

- Reach: 5 (global ICH scope; affects all interventional trials and QMS/data/oversight domains)
- Magnitude: 5 (full renewal of design philosophy, QMS, and data governance)
- Urgency: 4 (Step 4 adopted; pre-implementation preparation required)
- Certainty: 5 (final guideline published)
- Total: $(5 + 5 + 4 + 5) \times 5 = 95$

(Interpretation scale: 95–90 = highest priority for immediate discussion; 85–80 = next update cycle; 70–60 = monitor and collect information; 59 or below = monitor only.)

8. Sources and References

- **ICH E6(R3) Guideline for Good Clinical Practice** (Final version, Step 4, adopted on 6 January 2025)
 - Contains adoption history (Document History), guideline structure, and key sections:
 - QbD and CtQ (Principles 6, 6.2, 7);
 - Sponsor QMS, risk management, and QTL (3.10, 3.10.1.3);
 - Monitoring (3.11.4, 3.11.4.3);
 - Data governance (Sections 4.2, 4.3);
 - Transparency (Principles 9.6);
 - Protocol quality design (Appendix B B.12).
 - [https://database.ich.org/sites/default/files/ICH_E6\(R3\)_Step4_FinalGuideline_2025_0106.pdf](https://database.ich.org/sites/default/files/ICH_E6(R3)_Step4_FinalGuideline_2025_0106.pdf)
- **ICH “Good Clinical Practice – ICH E6(R3) Step 4 document – to be implemented” (Step 4 Overview Presentation)**
 - Official presentation explaining the Step 4 adoption (Principles + Annex 1) in January 2025.
 - [https://admin.ich.org/sites/default/files/inline-files/ICH_E6\(R3\)_Step%204_Presentation_2025_0123.pdf](https://admin.ich.org/sites/default/files/inline-files/ICH_E6(R3)_Step%204_Presentation_2025_0123.pdf)
- **ICH E6(R3) Annex 2 (Step 2) Presentation (6 November 2024)**
 - Describes Step 2 signature, current review process, and projected Step 4 timeline during 2025 (p. 3).
 - [https://database.ich.org/sites/default/files/ICH_E6\(R3\)_Annex%202_Step%202_Presentation_2024_1122_0.pdf](https://database.ich.org/sites/default/files/ICH_E6(R3)_Annex%202_Step%202_Presentation_2024_1122_0.pdf)

- **ICH E8(R1) General Considerations for Clinical Studies** (Step 4: 6 October 2021)
 - Provides the foundational concepts for QbD and CtQ, especially the section “Considerations in Identifying Critical to Quality Factors.”
 - https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf

Sample

Signal Card 2 | Sub-Theme: Applying QbD Principles (1): Decentralized Clinical Trials (DCT)

1. Card Summary

- ICH E6(R3) Annex 2 (Sep 2024) presents "additional QbD considerations" for emerging elements including DCT (decentralized elements). The Sep 2024 draft under public consultation opportunities points to consider across design, informed consent, data, investigational product (IP) management, sponsor oversight, and safety.
- The US FDA published its final guidance "Conducting Clinical Trials Using Decentralized Elements" (Sep 2024), defining implementation requirements for remote visits, local IRTs, DCTs, eConsent, distributed IP shipment, and Real-time data hubs. In the EU, MDT (EU/2024/1000) issued recommendations related to DCT. In Japan, PMDA issued a notification on eConsent (2024-05-01) specifying requirements for remote consultations and electronic signatures.

2. What changed? (Latest Developments / Sections)

- ICH E6(R3) Annex 2 (Sep 2024) Additional Considerations:
 - Providing additional QbD considerations for applying DCT (signature, consent, IP management and Definitions) (Annex 2 Introduction, p 1-2)
 - Key points across the design, consent, data, IP, safety, and sponsor oversight (Annex 2 §1.2 remote consent, §1.3 IP management and direct shipment, §1.4 Investigator oversight, §1.5 products, §1.5.1 (PMD) stability and relevance, §1.5.2 remote data collection, §1.6 IP management, safety and protection of findings, §1.7 privacy/data security, §1.8 sponsor oversight including vendors, §1.9 safety signal expansion and provision across multiple sites occurred)
 - Source: ICH E6(R3) Annex 2 (Sep 2024) Draft (2024-11-06) https://www.ich.org/documents/2024/09/2024-09-01-Annex2024-Sep-Draft/Annex_2_2024-09-01.pdf
- FDA Final Guidance (Sep 2024):
 - Remote visits (with/without local IRT) (§4.6), considerations for DCT/DTCT (sponsor-provided device recommended) (§4.7, second paragraph), roles and responsibilities (providing of local IRTs, whether to set up Form 1572) (§4.8.2), eConsent/PHE (§4.9), IP management, direct shipment, packaging/shipping (§4.1), §4.10 safety monitoring (§4.1), electronic systems/Part 11 and audit trails (§4.2)
 - Source: FDA Final Guidance (Sep 2024) <https://www.fda.gov/regulatory-information/search/fda-documents/conducting-clinical-trials-decentralized-elements>

- EU (AC)

- [Faded text]
- [Faded text]
- [Faded text]
- [Faded text]

- Japan (AC)

- [Faded text]
- [Faded text]

- Cross-c



- [Faded text]
- [Faded text]
- [Faded text]
- [Faded text]

3. So What? (Role-Specific Implications: Adoption Decisions and Risks)

Role	Key Operational Implications
Regulatory Affairs (RA)	<p>Review and sign regulatory submissions, including IND, NDA, BLA, and other regulatory documents.</p> <p>Coordinate with regulatory agencies (FDA, EMA, etc.) on regulatory strategy and timelines.</p> <p>Ensure compliance with regulatory requirements and standards.</p> <p>Monitor regulatory changes and updates.</p> <p>Provide regulatory support and expertise to other departments.</p>
Clinical Operations (ClinOps)	<p>Oversee clinical trial operations and ensure compliance with regulatory requirements.</p> <p>Coordinate with regulatory agencies on clinical trial submissions and approvals.</p> <p>Manage clinical trial budgets and resources.</p> <p>Monitor clinical trial progress and quality.</p> <p>Ensure patient safety and data integrity.</p> <p>Provide clinical trial support and expertise to other departments.</p>
Quality Assurance (QA)	<p>Develop and implement quality management systems (QMS).</p> <p>Conduct quality audits and inspections.</p> <p>Investigate and resolve quality issues.</p> <p>Ensure compliance with regulatory requirements and standards.</p> <p>Monitor product quality and performance.</p> <p>Provide quality assurance support and expertise to other departments.</p>
Data Science	<p>Develop and implement data management systems (DMS).</p> <p>Conduct data analysis and reporting.</p> <p>Ensure data integrity and security.</p> <p>Monitor data quality and performance.</p> <p>Provide data science support and expertise to other departments.</p>

4. Operational Action Checklist (Working Level)

- Review SOP design SOPs for instructions remote visits, local HCP, telehealth, home sampling
- Standardize consent operations, visual identity, verification/electronic signatures, instructional
- video explorations, secure transmission, IRB review SOPs, 21 CFR 312.61, 21 CFR 312.62
- Review ePHI/PHI, formulate 21CFR policy and rules for sponsor-provided devices (21CFR 312.61, 21CFR 312.62)
- Update SOPs for direct-to-patient IP, identity/temperature control/chain of custody, handling/retrieval
- Review the DMP to be able to manage flows/providers (data governance) and audit trail
- Establish an audit trail review plan (Part 11/21 CFR eSource compliance) and update centralized
- policy/indicators (21CFR 312.61, 21CFR 312.62, eSource Reflection Paper)
- Reflect vendor coverage (data linkage/audit trail/21CFR) rules, SOPs, and sub-delegation
- to contractors/IRB Annex 2 §3.5, 21CFR 312.61 on sponsor responsibilities
- Traceability monitoring plans, specify legal acquisition/communication from multiple data sources
- (Manufacturing SOPs/Annex 2 §3.5.1-3.5.2, 21CFR 312.61)

5. Decision Prompts (Who Does What)

Role	Action	Relevant Clauses
Head of ClinOps	Approve SOP revisions for operational criteria for remote visits, local HCPs, and telehealth	FDA §312.61, §312.62
Head of QA	Approve Part 11 compliance of electronic systems/cloud and audit trail review plan	FDA §312.61, EMA eSource RP
Head of Data Management / Data Science	Issue DMP revision (data governance/flows/providers, linkage strategy)	FDA §312.61, §312.62, Annex 2 §3.5.1-3.5.2
Head of RA	Present a traceability matrix showing differences across Annex 2 (Step 2), FDA final EMA and EU recommendations	Annex 2, FDA Final Presentation, EMA
Head of Supply Chain	Launch operational pilots for direct-to-patient IP (temperature control/handling/retrieval)	FDA §312.61, Annex 2 §3.5.1, §3.5.2

6. FAQ

Q1. How far must audit trails go in the cloud?

A. Electronic systems are subject to 21 CFR Part 312. Critical data reliability, security, privacy, confidentiality, audit trails, a register of data signatures, and access controls (21CFR §312.3). The EU Clinical Trial Regulation Paper also sets expectations on terminology, standards, and traceability.

Q2. How can we maintain blinding while operating remotely?

A. The clinical system implementation plan, remote procedural safeguards for blinding at each stage (implementation, management, maintenance), Annex 2 §2.3.100, §2.3.101-103, 21CFR §312.31 also specifies packaging, shipping, handling, and handling of product IP.

Q3. What tasks can be delegated to local HCPs? Must they be listed on Form 1572?

A. Routine clinical activities (data-based operations) that do not require product specific knowledge may be performed by local HCPs and, in drug trials, do not necessarily make them sub-investigators listed on Form 1572 (21CFR §312.31, §312.32). Activities requiring product knowledge and directly contributing to trial data must be appropriately listed and supervised as trial personnel (21CFR §312.32).

7. Signal Priority Index (SPI)

- Reach: 1 (Global applicability across CDMS/CDMS/CDP, system design, content, IP, data), and oversight
 - Magnitude: 1 (cross-functional impact across operations, systems, supply, and audit)
 - Urgency: 4 (21CFR finalized, Annex 2 in progress, early CD/Pharmacy preparation required)
 - Certainty: 4 (21CFR/CD finalized/initial, CD/Annex 2 at Stage 2, EU recommendations established)
 - Total: (5 + 1 + 4 + 4) = 14
- (Interpretation: 10-15 = high priority for immediate discussion, 15-20 = next update cycle, 20-25 = information gathering, follow-up in next issue, 25 or below = monitor only)

8. Sources and References

- ICH E6 (R2) Annex 2 (Nov 2019) (2019-11-06)
 - Implementation of CDMS/CDP (Introduction), remote consent (§2.2), IP management/clinical system support (§2.3, §2.4), investigator oversight (§2.5), product (§2.6), data reliability/recovery (§2.7), remote data collection (§2.8.2), privacy/security (§2.9), sponsor oversight (§2.6), safety signal assessment/monitor across multiple sources (§2.6)
 - [Implementation of CDMS/CDP \(Introduction\), remote consent \(§2.2\), IP management/clinical system support \(§2.3, §2.4\), investigator oversight \(§2.5\), product \(§2.6\), data reliability/recovery \(§2.7\), remote data collection \(§2.8.2\), privacy/security \(§2.9\), sponsor oversight \(§2.6\), safety signal assessment/monitor across multiple sources \(§2.6\)](#)

- FDA [Guidance for Industry: Conducting Clinical Trials Using Decentralized Elements \(Final, Sep 2024\)](#)
 - [FDA Guidance for Industry: Conducting Clinical Trials Using Decentralized Elements \(Final, Sep 2024\)](#)
 - [FDA Guidance for Industry: Conducting Clinical Trials Using Decentralized Elements \(Final, Sep 2024\)](#)
 - [FDA Guidance for Industry: Conducting Clinical Trials Using Decentralized Elements \(Final, Sep 2024\)](#)
- EMA (EU) [Guidance on Good Clinical Practice \(GCP\) Recommendations and Information](#)
 - [EMA Guidance on Good Clinical Practice \(GCP\) Recommendations and Information](#)
 - [EMA Guidance on Good Clinical Practice \(GCP\) Recommendations and Information](#)
 - [EMA Guidance on Good Clinical Practice \(GCP\) Recommendations and Information](#)
 - [EMA Guidance on Good Clinical Practice \(GCP\) Recommendations and Information](#)
- MHLW [Guidance](#)
 - [MHLW Guidance: Things to Consider for Explorations and Consent Using Electronic Methods in Clinical Trials and Postmarketing Clinical Studies \(Notification, 2023.05.01\), Chapter 3-4](#)
 - [MHLW Guidance: Things to Consider for Explorations and Consent Using Electronic Methods in Clinical Trials and Postmarketing Clinical Studies \(Notification, 2023.05.01\), Chapter 3-4](#)

Notes

- Article numbers from the E6(R2) version (e.g., §5.2.3) have been reorganized under E6(R3)/Annex 1/Annex 2. For IP management, refer to Annex 1 §3.15.3, Annex 2 §2.3 and §3.6, and FDA §III.H.

Signal Card 3 | Sub-Theme: Applying QbD Principles (2): Designing Reliability for Real-World Data (RWD) and Framework for AI Oversight (Annex 2 + Related Guidelines)

Real-World Data (RWD) falls within the scope of Annex 2. When RWD is used to inform trials, it must be governed under the principles of ICH E6, Section 2 (Data Management) and the CDMP Reflection Paper on RWD, with pre-specification and monitoring consistent with CDMP. If RWD qualifies as a medical device, the CDMP-PCDP applies.

1. Card Summary

- ICH E6(R2), Annex 2 (May 1, 2024) (ICH), incorporates, in the CDMP context, assessments of RWD reliability and relevance, data linkage, remote data collection, and sponsor oversight (Annex 2 § 2.3.1, § 2.3.2, § 2.3). RWD may be used for purposes such as external controls (Annex 2), RWD/CDMP/CDMP.
- The FDA has issued the final PCDP guidance for Artificially Intelligent Software Functions (AISF) (21 CFR 312.63) and a draft on Artificially Intelligent Device Management (AIIDM) (21 CFR 312.64). The CDMP's adopted Reflection Paper identifies principles for AI design, data quality, and "trust model" approaches.
- RWD is treated as an additional consideration in Annex 2. It lies outside Annex 2's scope but, as a quality design and monitoring domain, aligns with CDMP. It should be cross-referenced against relevant frameworks (ICH E6(R2), CDMP Reflection Paper).

2. What Changed? (Latest Developments)

- ICH E6(R2), Annex 2 (May 1, 2024) (ICH)
 - **Practices:** Additional CDMP considerations for ICT (pragmatic elements) (ICH E6(R2), § 2.3.1), explicitly identifying RWD uses (e.g., endpoint assessment, external controls).
 - **RWD Quality:** RWD Quality is determined by reliability (accuracy, completeness, timeliness) and relevance (availability of exposure, outcomes, covariates) (§ 2.3.1(b)). Consider variable formats, non-standard timing, missingness, differences data quality, de-identification, and regular validation status (§ 2.3.1(c)(i)-(ii)).
 - **Data linkage:** Requires accurate matching, privacy protection, and pre-specification in the protocol (ICH E6(R2), § 2.3.1(d)).
 - **Remote collection:** Security (cybersecurity and privacy for CDMP and RWD collection) (Annex 2 § 2.3.2(a)); see also ICH E6(R2), § 2.3.2 (Security). Sponsor oversight and quality management must be CDMP-proportionate (§ 2.3).

- 1. [Faded text]
- 2. [Faded text]

- **FC**

- 1. [Faded text]
- 2. [Faded text]

- **FC**

- 1. [Faded text]
- 2. [Faded text]

- **EM**

- 1. [Faded text]
- 2. [Faded text]

3. So What? (Role-Specific Implications)

Role	Key Operational Implications
RA (Regulatory Affairs)	<ul style="list-style-type: none"> • [Faint text] • [Faint text] • [Faint text] • [Faint text]
ClinOps	<ul style="list-style-type: none"> • [Faint text] • [Faint text] • [Faint text] • [Faint text]
QA	<ul style="list-style-type: none"> • [Faint text] • [Faint text] • [Faint text] • [Faint text]
Data Science	<ul style="list-style-type: none"> • [Faint text] • [Faint text] • [Faint text] • [Faint text]

4. Operational Action Checklist (Working Level)

- Review the standard SOP template for RWD use, require data origin, flow diagram, provider list, usage specifications, audit trails, and access rights (FDA DCCT Guidance §3.2 The Sponsor Data Engagement Plan; ICH EBR3; Annex 2 §3.5.1(a), §3.6)
- Update external control guidance, audit RWD, reliability/reproducibility checks, pre-specify linkage, form inspection access, and define privacy safeguards (ICH EBR3; Annex 2 §3.5.1(b)(ii), §3.6.1.1(b)(ii))
- Update the AI monitoring SOP reflect PCOP structure (modification types, implementation/implementation, impact assessment) and operations (monitoring SOPs, off-hours, release, escalation) (FDA PCOP Final, 2024-12)
- Review the SOP pre-specify handling of non-standard errors, redesigns, and interrupted runs, with severity analysis (ICH EBR3; Annex 2 §3.2)
- Update remote collection/audit security and audit trail access plans (cybersecurity, access control, etc.) (ICH EBR3; Annex 2 §3.5.2(a), §3.7)
- Add vendor coverage (audit/inspector access) details to contracts (general/OTM/interim/audit/OTM) (ICH EBR3; Annex 2 §3.8, §3.9.1(a))
- Prepare an AI differential matrix across FDA RWD Final, PCOP Final, FDA AI Update Draft, and ICH EBR3 Reflection Paper (with proposed sections)

5. Decision Prompts (Who Does What)

Role	Action	Reference
Head of Data Science	Approve AI monitoring plan (XRF/audit/rollback) reflecting PCOP requirements	FDA PCOP Final
Head of RA	Determine need and plan for pre-submission consultation on external controls/RWD use	FDA RWD Final, ICH EBR3; Annex 2 §3.1
Head of QA	Approve protocol for audit trail and reproducibility checks of the RWD linkage process	ICH EBR3; Annex 2 §3.5.1(a), §3.6
Head of ClinOps	Issue SOP revision on security operations and privacy notices for remote collection/OTM	ICH EBR3; Annex 2 §3.5.2(a), §3.7

6. FAQ

- **Q1. When and how is AI model re-training approved?**

A. Changes to the PCCP, the allowable scope of change, retraining, validation, implementation, and impact assessment, changes within scope may be implemented without additional pre-market submissions (PDM/PCCP Final). Include monitoring KPIs and feedback/correction actions.

- **Q2. Where does PCCP apply? Is it required for all AI?**

A. PCCP applies to AI-enabled Device Software Functions (AI/DSF) within 510(k)/De Novo/PMA routes (including combination combinations) (PDM/PCCP Final). Certain classification and device definition cases by case.

- **Q3. How are RWD “reliability” and “relevance” determined?**

A. Reliability = accuracy, completeness, timeliness. Relevance = availability of insights, actions, and considers addressing the clinical question (CQ) (PCCP Final, Areas 2 (Q3.3.10)), consistent with PDM/PCCP Final. For multiple source linkage, you specify methods and ensure accurate matching, privacy protection, and inspection access (Q3.3.10.2).

7. Signal Priority Index (SPI)

- Reach (PCCP under Areas 2 and 4 under related guidelines affect development through post-market surveillance) (PCCP Final)
 - Magnitude (The design across study design/analysis, QMS, change control, and vendor oversight) (PCCP Final)
 - Urgency (PDM/PCCP Final, Areas 2 at Step 2, PMA Reflection operational) (PCCP Final)
 - Certainty (Multiple Final guidelines for international markets) (PCCP Final)
- Total: $1 + 2 + 4 + 4 + 1 = 12$
- Priority: 10-12 = Immediate Attention, 8-10 = next update, 7-6 = information gathering, 5-6 = monitor only.

8. Sources and References

- ICH (PCCP) Guidelines for Good Clinical Practice (Final, Step 4, 2020-01-06)
 1. Q1 Data Governance – Investigator and Sponsor
 2. 4.1 Subsequent Writing, 4.2 Data Lifecycle (e.g., 4.2.4 Validation of data sets prior to analysis), 4.3 Computerized Systems
 3. ICH Guidelines on Good Clinical Practice (GCP), 2019, Final Guidance, 2019, 2019, 2019

- **ICH**
 - 1. ICH Q10: Pharmaceutical Quality Management (2005)
 - 2. ICH Q11: Development and Manufacture of Immediate-Release Solid Oral Dosage Forms (2005)
 - 3. ICH Q12: Technical Specifications for Pharmaceutical Products (2010)
 - 4. ICH Q13: Development and Manufacture of Continuous Manufacturing Processes (2016)

- **EMA**
 - 1. EMA Guidelines on Good Manufacturing Practices (GMP) for Medicines (2008)
 - 2. EMA Guidelines on Good Distribution Practices (GDP) for Medicines (2013)
 - 3. EMA Guidelines on Good Clinical Practice (GCP) (2005)
 - 4. EMA Guidelines on Good Laboratory Practice (GLP) (2004)

- **FDA**
 - 1. FDA Center for Drug Evaluation and Research (CDER) - Drug Information (2015)
 - 2. FDA Center for Drug Evaluation and Research (CDER) - Drug Information (2015)
 - 3. FDA Center for Drug Evaluation and Research (CDER) - Drug Information (2015)
 - 4. FDA Center for Drug Evaluation and Research (CDER) - Drug Information (2015)
 - 5. FDA Center for Drug Evaluation and Research (CDER) - Drug Information (2015)

- **FDA**
 - 1. FDA Center for Drug Evaluation and Research (CDER) - Drug Information (2015)
 - 2. FDA Center for Drug Evaluation and Research (CDER) - Drug Information (2015)
 - 3. FDA Center for Drug Evaluation and Research (CDER) - Drug Information (2015)
 - 4. FDA Center for Drug Evaluation and Research (CDER) - Drug Information (2015)
 - 5. FDA Center for Drug Evaluation and Research (CDER) - Drug Information (2015)

2. When AI is regulated as a medical device

2.1 Scope of Annex 2

AI software used for medical purposes such as diagnosis, treatment, or prediction is regulated as a medical device. Examples include:

1. AI-enabled diagnostic decision support software
2. AI tools that support treatment decision-making
3. AI systems for patient monitoring
4. AI systems that support medical product safety decisions (including combination products)

2.2 Applicable requirements

The MDR/IVDR guidance on AI-enabled device software functions:

2.3 Submission pathway

MDR/IVDR Annex 2(4)

2.4 Content required of submissions to be included in the PDC/DF

1. Type of modification (e.g. algorithm improvement, update of training data, performance enhancement)
2. Development and validation methodology
3. Implementation approach
4. Impact assessment (effects on safety and effectiveness)

When the approved PDC/DF scope and approval to market applies, any implementation effort is additional unapproved submissions.

2.5 References

1. MDR/IVDR guidance (scope for AI-enabled medical devices)
This covers the pre-market information requirements in the guidance document regarding submission requirements when a modification to an already approved software changes control data without affecting

3. Relationship to Annex 2 (additional considerations when using DCT/RWD)

3.1 Scope of Annex 2

MDR/IVDR Annex 2 presents additional DCT considerations for the following emerging use models:

1. Decentralized clinical trials (DCT)
2. Pragmatic use models
3. Use of real-world data (RWD) for AI-specific purposes

Key provisions relevant when it is used:

- Service data collection: § 3.2.2 (Service Data Collection Considerations)
- API stability and release: § 3.4 (Process): § 3.10
- Data storage (records, matching, privacy protection, processing): § 3.10
- Security and privacy (privacy/identifiability): § 3.7
- Service coverage (including vendor coverage): § 3.4 (see also safety information collection and process: § 3.1-3.3.2)

Practical implications:

When it is used in IoT operations or when API is analyzed by it, the additional Annex 2 requirements for data quality, storage, records collection, privacy/identifiability, and service coverage need to be met alongside API's own requirements (§).

References:

- ISO 15926, Annex 2 (see 2.1.1)
- API-First/Cloud: § 3.1 (especially 3.1.10), § 3.2 (3.2.1-3.2.2), § 3.3 (3.3.1-3.3.2), § 3.4 (3.4.1-3.4.2), § 3.5 (3.5.1-3.5.2), § 3.6 (3.6.1-3.6.2), § 3.7 (3.7.1-3.7.2), § 3.8 (3.8.1-3.8.2), § 3.9 (3.9.1-3.9.2), § 3.10 (3.10.1-3.10.2), § 3.11 (3.11.1-3.11.2), § 3.12 (3.12.1-3.12.2), § 3.13 (3.13.1-3.13.2), § 3.14 (3.14.1-3.14.2), § 3.15 (3.15.1-3.15.2), § 3.16 (3.16.1-3.16.2), § 3.17 (3.17.1-3.17.2), § 3.18 (3.18.1-3.18.2), § 3.19 (3.19.1-3.19.2), § 3.20 (3.20.1-3.20.2), § 3.21 (3.21.1-3.21.2), § 3.22 (3.22.1-3.22.2), § 3.23 (3.23.1-3.23.2), § 3.24 (3.24.1-3.24.2), § 3.25 (3.25.1-3.25.2), § 3.26 (3.26.1-3.26.2), § 3.27 (3.27.1-3.27.2), § 3.28 (3.28.1-3.28.2), § 3.29 (3.29.1-3.29.2), § 3.30 (3.30.1-3.30.2), § 3.31 (3.31.1-3.31.2), § 3.32 (3.32.1-3.32.2), § 3.33 (3.33.1-3.33.2), § 3.34 (3.34.1-3.34.2), § 3.35 (3.35.1-3.35.2), § 3.36 (3.36.1-3.36.2), § 3.37 (3.37.1-3.37.2), § 3.38 (3.38.1-3.38.2), § 3.39 (3.39.1-3.39.2), § 3.40 (3.40.1-3.40.2), § 3.41 (3.41.1-3.41.2), § 3.42 (3.42.1-3.42.2), § 3.43 (3.43.1-3.43.2), § 3.44 (3.44.1-3.44.2), § 3.45 (3.45.1-3.45.2), § 3.46 (3.46.1-3.46.2), § 3.47 (3.47.1-3.47.2), § 3.48 (3.48.1-3.48.2), § 3.49 (3.49.1-3.49.2), § 3.50 (3.50.1-3.50.2), § 3.51 (3.51.1-3.51.2), § 3.52 (3.52.1-3.52.2), § 3.53 (3.53.1-3.53.2), § 3.54 (3.54.1-3.54.2), § 3.55 (3.55.1-3.55.2), § 3.56 (3.56.1-3.56.2), § 3.57 (3.57.1-3.57.2), § 3.58 (3.58.1-3.58.2), § 3.59 (3.59.1-3.59.2), § 3.60 (3.60.1-3.60.2), § 3.61 (3.61.1-3.61.2), § 3.62 (3.62.1-3.62.2), § 3.63 (3.63.1-3.63.2), § 3.64 (3.64.1-3.64.2), § 3.65 (3.65.1-3.65.2), § 3.66 (3.66.1-3.66.2), § 3.67 (3.67.1-3.67.2), § 3.68 (3.68.1-3.68.2), § 3.69 (3.69.1-3.69.2), § 3.70 (3.70.1-3.70.2), § 3.71 (3.71.1-3.71.2), § 3.72 (3.72.1-3.72.2), § 3.73 (3.73.1-3.73.2), § 3.74 (3.74.1-3.74.2), § 3.75 (3.75.1-3.75.2), § 3.76 (3.76.1-3.76.2), § 3.77 (3.77.1-3.77.2), § 3.78 (3.78.1-3.78.2), § 3.79 (3.79.1-3.79.2), § 3.80 (3.80.1-3.80.2), § 3.81 (3.81.1-3.81.2), § 3.82 (3.82.1-3.82.2), § 3.83 (3.83.1-3.83.2), § 3.84 (3.84.1-3.84.2), § 3.85 (3.85.1-3.85.2), § 3.86 (3.86.1-3.86.2), § 3.87 (3.87.1-3.87.2), § 3.88 (3.88.1-3.88.2), § 3.89 (3.89.1-3.89.2), § 3.90 (3.90.1-3.90.2), § 3.91 (3.91.1-3.91.2), § 3.92 (3.92.1-3.92.2), § 3.93 (3.93.1-3.93.2), § 3.94 (3.94.1-3.94.2), § 3.95 (3.95.1-3.95.2), § 3.96 (3.96.1-3.96.2), § 3.97 (3.97.1-3.97.2), § 3.98 (3.98.1-3.98.2), § 3.99 (3.99.1-3.99.2), § 4.00 (4.00.1-4.00.2)
- The structure of organizational function, API, Service, Data, Quality, etc., 2024, 100, 200

San

closed on 2025-12-01 (input sought on measurement of AI performance in practice).

- **FDA RWD Final Guidance (July 2024):** No announced revisions or deadlines as of now (TBD).

Upcoming Meetings / Public Comment Deadlines / Adoptions

- ICH Assembly: Nov 15-18, 2025 (Singapore); May 20-Jun 1, 2026 (Paris); Nov 15-18, 2026 (Copenhagen/Amsterdam) (date TBD)
- ICH Assembly 2: May 2 (public consultation document published Nov 1, 2025, review of 11,000 comments ongoing; then 24 sessions in 2025 calendar table in Assembly calendar)
- FDA AI/ML/RegTech (RAE) 110 publication: Apr 1, 2025 (comment deadline Apr 1, 2025 closed)
- FDA RWD (AI Real-World Performance): Comment deadline Dec 1, 2025

Monitoring Focus (Operational Attention Points)

- Status of Annex 2 updates: Magnitude of updates in Nov 2025, ICH, promulgation, and sponsor coverage updates to address 11,000 comments
- Status of AI training completion: Publication timing of 2025 ICH/RAE/110 training modules and implementation arrangements
- Finalization of FDA AI/RegTech Agreement with ICDP (now included in RFE, AI section, effort process, documentation)
- Release of FDA RWD public comments: Subsequent action (e.g., guidance development, outreach)

Monitoring Items (Topic / Schedule / Authority / Source Links)

Item	Schedule	Authority	Source Link
ICH Assembly (Singapore)	2025-11-15 to 18	ICH	https://ich.org/page/ich-public-events
ICH Assembly (Rio de Janeiro)	2026-05-30 to 06-03	ICH	https://admin.ich.org/files/default/News/2025-06/ICH_IC_Meeting_MainMeeting_Final_2025_0611.pdf
ICH Assembly (Europe/Africa/Middle East)	2026-11-14 to TBD	ICH	https://admin.ich.org/files/default/News/2025-06/ICH_ICAAssembly%20Main%20Meeting%2013-14%20May%202025.pdf
E6(R3) Annex 2 (DCT/RWD Add-on) Steps	Adoption: TBD Assembly: included in R3 Suggest: final in R3	ICH	https://admin.ich.org/files/default/News/2025-06/ICH_ICAAssembly%20Main%20Meeting%2013-14%20May%202025.pdf

Item	Schedule	Authority	Source Link
3/4	extension)		
E6(R3) Training (Principles + Annex 1)			
E6(R3) EWG Work Plan (Annex 2 Schedule)			
FDA AI Lifecycle (Draft)			
FDA PCCP (AI-DSF) Final			
FDA RfC (AI Real-World Performance Measurement)			
ICH M14 (RWD Non-Interventional Safety Studies)			

Note:

- The above summary is based on primary information sources (ICH minutes, EWG work plans, FDA official guidances, event and notice pages). The adoption timeline for Annex 2 remains undecided (as noted in Assembly minutes).
- It is possible that monthly updates from the Singapore Assembly (May 2025), the Assembly Update (May 2025), and FDA Council updates for AI Lifecycle and AI Real-World Performance...

Sample

License Terms

This report (“the Work”) is a copyrighted work owned by Probio Corporation. Unless otherwise agreed, the Single-User License applies to all purchases.

■ Single-User License (default)

- Access and use are limited to **one individual**.
- Redistribution, sharing, forwarding, or copying for others is prohibited. (Printing for personal use is permitted.)

■ Team / Department Use

- For use by 2 or more individuals or department-wide use, please contact us to arrange the appropriate license scope.
- A separate contract is not required; written confirmation via email is sufficient.

Copyright

All copyrights and intellectual property rights to this Work belong to Probio Corporation.

Disclaimer

This report (“Regulatory Signal Brief™”), including the Signal Priority Index (SPI), has been independently prepared and analyzed by Probio Corporation (“the Company”) based on publicly available information and is intended solely for general informational purposes.

It is not intended to constitute professional advice, recommendations, or decision-making guidance for any specific company or situation. The indicators and scores do not represent legal advice, investment advice, or the official position of any regulatory authority; they serve only as a framework for internal discussion and action planning.

The Company and its authors make no express or implied representations or warranties regarding the accuracy, completeness, or timeliness of the information contained herein and accept no liability for any actions or decisions made based on this report.

For specific regulatory responses, SOP revisions, or other business decisions, please consult your own legal or regulatory affairs departments or external specialists.

Production Credit

This report was jointly produced by Magoneko Solutions Co., Ltd. and Probio Corporation.

All company names, product names, logos, and trademarks are the property of their respective owners.

© 2025 Probio Corporation. All rights reserved.

Unauthorized reproduction or redistribution of this report is strictly prohibited.