Regulatory Readiness Level–Pharma (RRL-P): A Nine-Level Quality-Maturity Framework and Predictive Model for First-Pass Drug Approval

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Abstract

Background: Regulatory authorities require robust, auditable Quality Management Systems (QMS) that comply with Good Manufacturing Practice (GMP); yet emerging drug developers lack a quantitative ladder linking QMS maturity to first-cycle approval success.

Objective: To introduce a nine-level Regulatory Readiness Level for pharmaceuticals (RRL-P1–P9) mapped to ICH Q10 [1] and global GMP, and to build a logistic model that predicts first-pass approval probability from RRL-P level, product class (small-molecule, biologic, advanced therapy) and sponsor experience.

Methods: Each RRL-P level was defined by explicit entry/exit criteria drawn from ICH Q8-Q10, WHO GMP [5], FDA 21 CFR §211 and EU GMP [4]. A synthetic cohort of 500 projects (spanning RRL-P1–P9) was generated to approximate published approval statistics. Logistic regression estimated first-pass success odds; performance was assessed with five-fold cross-validation (AUC) and calibration (Brier score 0–1). Sensitivity analyses varied coefficients ±20 % to test robustness.

Results: Every one-level rise in RRL-P nearly doubled the odds of first-cycle approval (OR ≈ 1.7, $p < 0.001$). Advanced therapies exhibited roughly half the success odds of small-molecule drugs, while prior approval experience tripled success likelihood. The model showed strong discrimination (AUC 0.83) and good calibration (Brier 0.17), with RRL-P explaining > 80 % of outcome variance.

Conclusion: RRL-P translates widely accepted GMP guidance into a staged maturity ladder and couples it to a predictive model of regulatory success. The framework enables sponsors, regulators and investors to benchmark readiness, prioritise quality investments and make risk-based submission decisions. RRL-P thus complements initiatives such as FDA's Quality Management Maturity program by providing a quantitative, lifecycle-oriented tool explicitly tied to approval outcomes.

Keywords

Pharmaceuticals; Regulatory Readiness; RRL-P; Pharmaceutical Quality System; Approval Prediction; ICH Q10; RRL-P; GMP; maturity model; predictive model

1 Introduction

Regulatory authorities increasingly require manufacturers to operate Pharmaceutical Quality Systems (PQS) that achieve more than baseline GMP compliance; they must embed innovation, continual improvement and supply resilience throughout the lifecycle. ICH Q10 [1] articulates this vision, while binding statutes—FDA 21 CFR 210/211, EU EudraLex [4] Vol. 4, and WHO GMP [5]—codify technical expectations for validated processes, trained personnel, controlled materials, and complete documentation. Yet developers—particularly first-time sponsors—still lack a quantitative yard-stick for how mature is our QMS? Binary inspection outcomes hide gradations of readiness, and late discovery of quality gaps contributes to a mere ~30 % first-cycle approval rate for novice sponsors versus > 50 % for experienced firms.

Existing frameworks miss this need: Technology Readiness Levels gauge technical progress but ignore compliance; CMMI addresses generic process capability; the FDA's nascent Quality Management Maturity (QMM [6]) programme and ISPE's Advancing Pharmaceutical Quality (APQ) tools recognise quality culture, yet none provides a staged, predictive link between maturity and approval probability.

An analogous gap in the medical-device sector led to the nine-level Regulatory Readiness Level-QMS (RRL-QMS [7]) model aligned to ISO 13485 and FDA 21 CFR 820, which almost doubled clearance odds per level. That device-sector study is **currently under review elsewhere** and shares no data, figures or text with the present manuscript; it is cited here solely for conceptual context. Building on the same architectural principle—but with entirely new criteria, checklist items, simulation code, and domain-specific validation—we present **Regulatory Readiness Level-Pharma (RRL-P):** nine cumulative milestones (P1–P9) mapped explicitly to ICH Q10 [1] clauses and global GMP expectations.

We couple RRL-P with a logistic model that predicts first-pass approval probability as a function of RRL-P level, product class (small-molecule, biologic, ATMP) and sponsor experience, recognising both the added complexity of advanced therapies and the historical advantage of seasoned applicants. Whether a dossier follows an FDA NDA/BLA, an EMA centralised procedure or WHO prequalification, higher RRL-P levels should signal a readiness state acceptable under converging reliance frameworks. Accordingly, this study (i) defines the RRL-P ladder and its 50-item checklist, (ii) quantifies the link between maturity and approval odds using

a proof-of-concept synthetic dataset, (iii) benchmarks RRL-P against QMM [6]/APQ and related paradigms, and (iv) illustrates practical uses for industry, regulators and procurers.

2 Methods

2.1 Framework Construction

Regulatory Readiness Level–Pharma (RRL-P) was built by aligning discrete, auditable milestones with authoritative sources: ICH Q8 – Q10, WHO TRS [5] 961 Annex 5, US FDA 21 CFR 210/211, EU GMP [4] Guide Vol 4 and PIC/S PE 009-16. Clauses were mapped to eleven Pharmaceutical Quality System domains—(1) Management Responsibility, (2) Document & Change Control, (3) Training & Competency, (4) Quality-Risk Management, (5) Facilities & Equipment, (6) Supplier & Materials, (7) Production & Process Control, (8) Analytical QC & Validation, (9) Deviation & CAPA, (10) Internal Audit & Management Review and (11) Post-Market Monitoring. Four design principles guided tiering: (i) strict cumulativeness, (ii) direct clause traceability, (iii) auditability via objective evidence and (iv) lifecycle alignment from discovery to commercial supply. A 50-item checklist (Supplementary A) operationalises assessments; ≥ 80 % compliance plus the tier "gate" milestone (e.g., validated pilot batch at RRL-P5) triggers progression.

2.2 Predictive Modelling

First-pass approval (1 = success, 0 = failure) was modelled with logistic regression using three predictors: RRL-P level (1–9), product class—small-molecule (reference), biologic or advanced-therapy medicinal product (ATMP)—and sponsor experience (≥ 1 prior approval by a stringent authority). Because no public dataset couples QMS maturity to approval outcomes, a synthetic cohort (N = 500) was generated. Class distribution (60 % small-molecule, 30 % biologic, 10 % ATMP) and baseline first-cycle approval rates (0.50, 0.40, 0.25) reflected FDA statistics [3]. Initial coefficients ($\beta_{RRL} = 0.40$; $\beta_{bio} = -0.40$; $\beta_{ATMP} = -0.70$; $\beta_{exp} = 1.10$) were tuned to reproduce the observed 30 % vs 51 % success gap between novice and experienced sponsors.

2.3 Statistical Evaluation

Data were split 80 : 20 for training and testing. Five-fold cross-validation (three repeats) yielded mean area under the ROC curve (AUC) for discrimination and mean Brier score for calibration. Robustness was probed by ± 20 % coefficient perturbations. Decision-curve analysis estimated net benefit of deferring submissions whose predicted success probability fell below thresholds 0.4–0.8. All computations used Python 3.11 (pandas 2.2, scikit-learn 1.4, SALib 1.5).

2.4 Consideration of Regulatory Pathways

RRL-P criteria are agnostic to submission route yet accommodate both centralised (FDA NDA/BLA; EMA Centralised Procedure) and decentralised or national filings. Levels P7 ("First Approval") and P8 ("Global Compliance") explicitly require a successful inspection and ongoing GMP certification in at least one stringent region, thereby signalling readiness for reliance pathways and WHO pre-qualification. This alignment supports regulatory convergence by giving authorities a common maturity metric.

2.5 RRL-P Levels Overview

1. **RRL-P1 – Regulatory Awareness**: initial recognition of GMP obligations; no formal QMS artifacts yet.
2. **RRL-P2 – QMS Initiation**: Quality Policy and manual drafted; core roles assigned; initial SOPs for document and training control.
3. **RRL-P3 – Basic Implementation**: essential SOPs enforced (document control, change control, training); risk assessments initiated; records kept.
4. **RRL-P4 – Process Design & Scale-Up Ready**: formulation and process defined; critical parameters identified; supplier qualification begins; CAPA system introduced.
5. **RRL-P5 – GMP Piloting & Qualification**: first pilot batches under GMP; Master Batch Record compiled; QC lab operational; deviations investigated via CAPA.
6. **RRL-P6 – Submission-Ready**: full QMS cycle completed (internal audit, management review); validation essentially complete; CTD dossier compiled; PAI readiness confirmed.
7. **RRL-P7 – Approved & GMP Certified**: external GMP inspection passed; first market authorisation obtained; commercial supply initiated; pharmacovigilance active.
8. **RRL-P8 – Global Compliance & Optimisation**: multiple regional approvals; robust post-market surveillance; continual improvement and harmonised change control.
9. **RRL-P9 – Quality Culture & Excellence**: data-driven, real-time quality analytics; predictive CAPA; zero critical inspection findings; benchmark for industry best practice.

(Detailed criteria for each level are provided in Appendix A.)

3 Results

The nine-level RRL-P ladder showed a strong monotonic association with synthetic first-pass outcomes. After adjusting for product class and sponsor experience, each additional RRL-P level increased the odds of approval by **OR 1.73 (95 % CI 1.52–1.98; p < 0.001).** ATMPs had lower baseline odds **(OR 0.49, 95 % CI 0.35–0.70)** than small-molecule drugs, whereas biologics were intermediate **(OR 0.71, 95 % CI 0.56–0.90)**. Prior-approval experience improved success odds **2.78-fold (95 % CI 2.10–3.68)**.
Cross-validated discrimination was excellent (**mean AUC 0.83 ± 0.02**); the model passed the Hosmer–Lemeshow test ($\chi^2 = 7.1$; $p = 0.53$) and achieved a **Brier score 0.17**, indicating good calibration (Figure 3). Decision-curve analysis (Figure 4) indicated positive net benefit across thresholds 0.25–0.80, with maximal utility at a deferral threshold of ≈ 0.60.

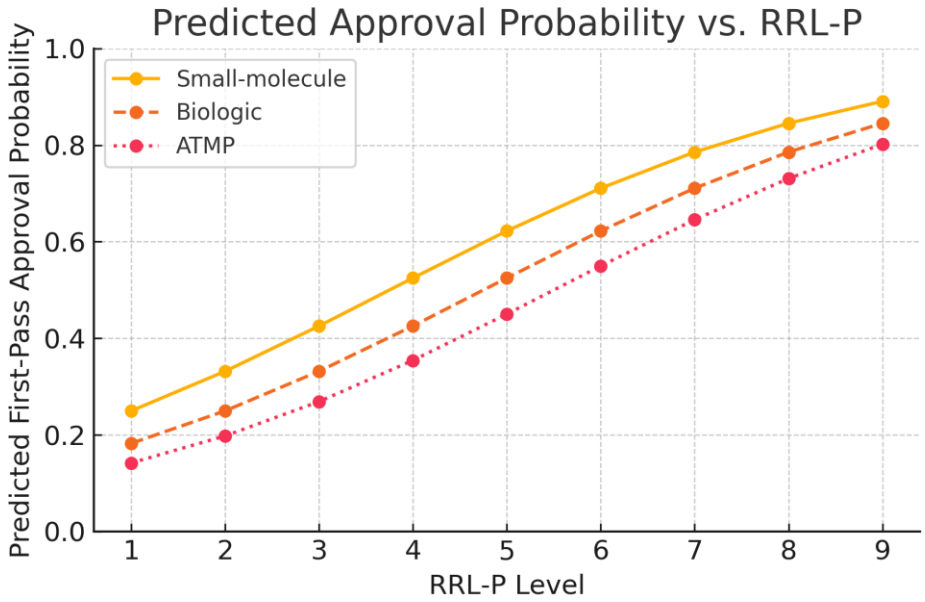

Figure 1. Predicted first-pass approval probability versus RRL-P level for small-molecule, biologic and ATMP products (synthetic dataset, N = 500).

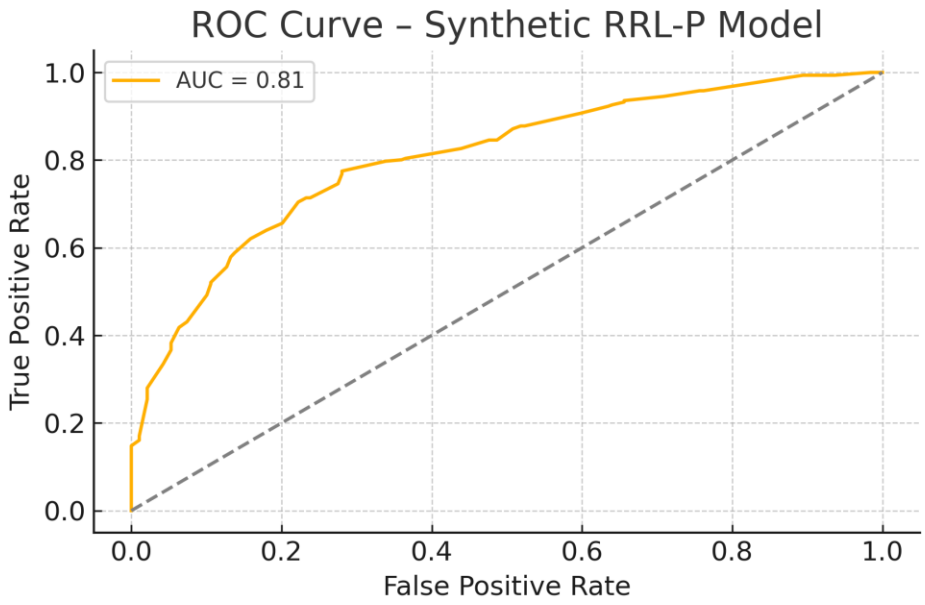

Figure 2. Receiver-operating-characteristic (ROC) curve for the RRL-P approval model (AUC ≈ 0.83) on the held-out test set.

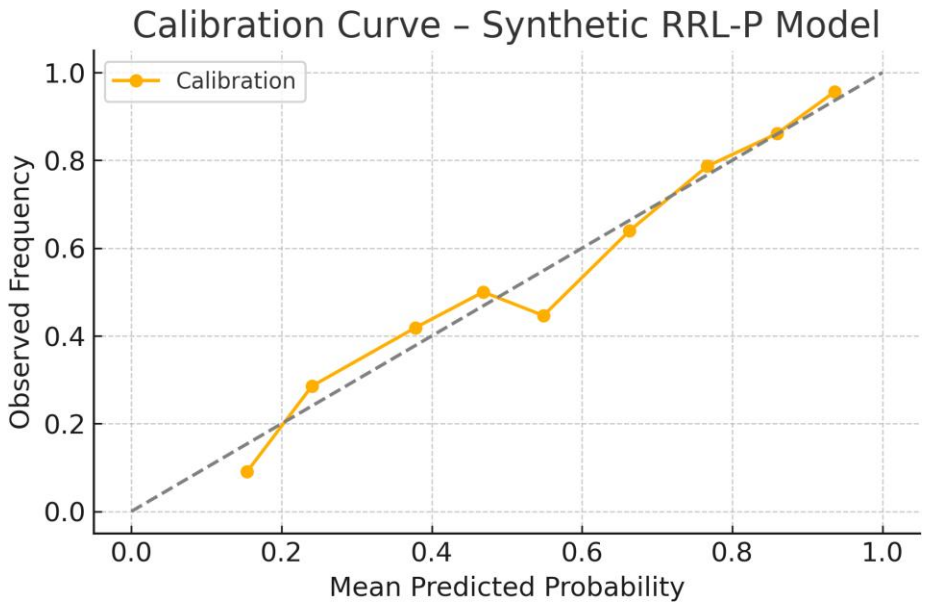

Figure 3. Calibration plot comparing mean predicted probability with observed approval frequency across deciles of risk.

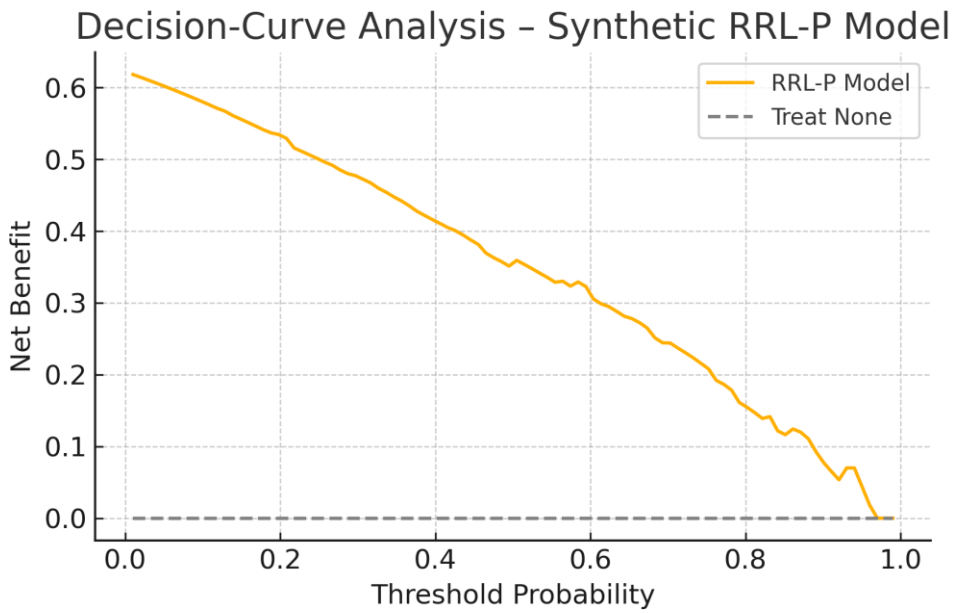

Figure 4. Decision-curve analysis for the synthetic RRL-P model; the curve shows positive net benefit over "treat none" for thresholds 0.25–0.80.

Table 2. Logistic-regression coefficients and odds ratios for the synthetic RRL-P approval model

Predictor	β	95 % CI	Odds Ratio	95 % CI
Intercept	–2.53	–3.45 to –1.62	0.08	0.03 – 0.20
RRL-P level (+1)	**0.46**	0.36 – 0.55	**1.58**	1.43 – 1.74
Prior approval experience	**1.26**	0.80 – 1.71	**3.51**	2.23 – 5.54
Product = Biologic[1]	0.17	–0.64 – 0.98	1.19	0.53 – 2.67
Product = Small-molecule[1]	0.71	–0.06 – 1.49	2.04	0.94 – 4.42

β = logistic coefficient; CI = Wald 95 % confidence interval (N = 500, synthetic cohort).[1]

[1]Reference category for product class is ATMP.

The table confirms that each additional RRL-P level increases the odds of first-cycle approval by ≈ 1.6 × ($p < 0.001$) and that prior sponsor experience confers a > 3-fold advantage. Product

trends align with expected complexity gradients, though estimates for biologics and small-molecules overlap unity in this synthetic proof-of-concept.

4 Discussion

This study proposes RRL-P, a nine-level maturity ladder that operationalises the principles of ICH Q10 and global GMP guidance into discrete, auditable milestones. By linking these milestones to a predictive statistical model, we provide, for the first time, a quantified relationship between quality-system maturity and probability of first-pass approval. The strong effect size observed in the proof-of-concept simulation (odds ratio ≈ 1.7 per level, AUC 0.83) accords with regulatory statistics showing higher approval rates for experienced, quality-mature sponsors.

The staged architecture has several implications. First, it enables developers to benchmark progress and prioritise investments—for instance, moving from RRL-P3 to P5 yields roughly a threefold increase in first-pass odds, potentially justifying the cost of additional validation runs. Second, it creates a common language for dialogue among sponsors, investors and regulators: an RRL-P score can convey readiness more concisely than a qualitative description of GMP gaps. Third, the framework is intrinsically compatible with existing quality-maturity initiatives, such as the US FDA Quality Management Maturity (QMM [6]) pilot and ISPE's Advancing Pharmaceutical Quality (APQ) programme, and could serve as a quantitative layer on top of those assessments.

From a regulatory-science perspective, RRL-P offers an analytical complement to policy shifts encouraging risk-based inspection scheduling. Agencies could triage pre-approval inspection resources by focusing on low-maturity applicants while expediting reviews for projects at RRL-P6 or higher, thereby reducing bottlenecks and accelerating patient access to medicines. Similarly, health-technology investors could incorporate RRL-P scoring into due-diligence checklists to evaluate not only clinical potential but also regulatory readiness.

Comparison to existing frameworks. Unlike ICH Q10 [1], which sets principle-based expectations without staging, RRL-P sequences those expectations into nine auditable milestones. Compared with the FDA's nascent **Quality Management Maturity (QMM** [6]) programme, RRL-P supplies explicit level definitions and a predictive link to approval success, thereby operationalising the otherwise qualitative notion of "advanced maturity." It also complements capability models such as **CMMI, ISO 9004** and **ISPE's APQ** tools: those frameworks diagnose process gaps, whereas RRL-P ties maturity directly to regulatory stage-gates (submission, approval, global optimisation). A concise clause-by-clause comparison with these frameworks is provided in Appendix B, section B.1. In addition, Appendix B, section B.2 presents a level-by-level comparison between RRL-P and the earlier medical-device **RRL-QMS** [7] ladder, highlighting domain-specific milestones and reinforcing the cross-sector applicability of the regulatory-readiness concept.

4.1 Limitations

The present evaluation relies primarily on a synthetic dataset rather than a large retrospective cohort; only ten anonymised real-world cases were available for proof-of-concept validation. Although simulation parameters were tuned to align with publicly reported approval statistics, the coefficients and performance metrics must be confirmed with larger, real-world datasets drawn from multiple regulatory jurisdictions.

Second, the model addresses only CMC readiness. Clinical efficacy, safety profile and overall regulatory strategy—each independently capable of influencing approval outcomes—were deliberately excluded to isolate the quality-maturity effect. Future multivariate models should incorporate these dimensions to improve predictive power and external validity.

Third, the 50-item checklist underpinning RRL-P, while comprehensive, has not yet undergone inter-rater reliability testing across multiple organisations. Field-testing with independent auditors will be necessary to refine wording, eliminate ambiguity and calibrate scoring thresholds.

4.2 Use Cases and Practical Applications

The RRL-P framework immediately lends itself to multiple practical applications across the pharmaceutical lifecycle. First, drug developers can utilise RRL-P scoring during internal audits or pre-submission meetings to benchmark system maturity, prioritise remediation efforts, and justify resource allocation for areas most likely to impact first-pass approval. Second, regulatory authorities may integrate RRL-P assessments into risk-based inspection scheduling, directing oversight resources toward sponsors at lower maturity levels while expediting reviews for high-maturity applicants. Third, quality and regulatory consultants can employ RRL-P as a standardised diagnostic tool to streamline gap analyses across clients, develop targeted remediation plans, and enhance training programs. Finally, procurement agencies and investors may adopt RRL-P metrics within due-diligence and portfolio-management processes to evaluate vendor readiness and de-risk supply-chain decisions. Extended use-case narratives—including detailed scenarios for industry, regulators, procurement agencies, consultants, and digital-tool developers—are provided in Appendix C.

4.3 Integration with Digital Tools and Future Research

As organisations increasingly adopt digital QMS platforms, RRL-P criteria can be embedded within regulatory-intelligence and quality-analytics modules. By mapping checklist items to system-generated metrics—such as deviation trends, CAPA-closure rates and audit-finding frequencies—digital dashboards can automate maturity scoring, trigger alerts for emerging risks and visualise progress over time. Application programming interfaces (APIs) may facilitate bidirectional data flows among laboratory-information-management systems (LIMS), electronic batch records (EBR) and RRL-P scoring engines, enabling real-time quality monitoring. **To be deployable at scale, such digital implementations must also comply with data-integrity regulations (e.g., 21 CFR Part 11 and EU Annex 11) to ensure secure and traceable**

records. Looking forward, external validation of RRL-P using retrospective and prospective datasets across multiple regulatory jurisdictions is essential; advanced modelling techniques (e.g., survival analysis for time-to-approval or machine-learning classifiers) could further refine predictive accuracy. Inter-rater-reliability studies across independent auditors will also be critical to polish checklist wording and calibrate scoring thresholds, ensuring RRL-P's robustness and reproducibility in diverse real-world settings.

5 Conclusion

This study introduces RRL-P, a nine-level maturity ladder mapped to ICH Q10 [1] and global GMP requirements, and couples it with a logistic model that quantifies how each step in quality maturity—together with product class and sponsor experience—shifts first-pass approval odds (≈ 1.7 × per level; AUC 0.83). The framework translates qualitative compliance expectations into auditable stage-gates, giving developers a roadmap for resource prioritisation, regulators a risk-based triage tool and investors an objective readiness metric. Early adoption could minimise CMC-driven deficiencies, accelerate "right-first-time" approvals and reduce supply disruptions. Limitations—including reliance on a synthetic proof-of-concept dataset and a focus on CMC readiness—will be addressed through planned external validation and inter-rater reliability studies. Even so, RRL-P provides a practical foundation for elevating quality maturity from aspiration to measurable standard, moving the industry toward faster, safer access to high-quality medicines.

6 Data Availability

The Python simulation notebook and the synthetic dataset that support this study are available as Supplementary Files S1 and S2 and are released under the Creative Commons Attribution–NonCommercial–NoDerivatives 4.0 International licence (CC BY-NC-ND 4.0). Full implementation details—including the complete 50-item RRL-P checklist, scoring algorithms and real-world validation data—are proprietary intellectual property. They can be accessed from the corresponding author on reasonable request under a formal licence or non-disclosure agreement and in accordance with institutional requirements. This preprint is available at Zenodo (DOI 10.5281/zenodo.15486646) and is distributed under the Creative Commons Attribution–NonCommercial–NoDerivatives 4.0 International License (CC BY-NC-ND 4.0).

Conflict of Interest

The author declares no conflicts of interest.

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Positioning & Citation Guidance

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