TECHNICAL FRAMEWORK

THE TERRITORY-NEUTRAL QUALITY MARK (Q-M)

An Adaptable Standard for Data Integrity and Human-Relevant Toxicology

A Practical Model for National Authorities Advancing Non-Animal Innovation

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Pro Bono Technical Framework

v4 – Updated for EU Alignment June 2026

Author

Linda Birr-Pixton

The Alliance for Cruelty Free Science

Disclaimer

This pro bono technical framework is provided as an adaptable model for national authorities and bodies advancing non-animal science. It does not constitute formal legal, regulatory, or medical advice. The views expressed are adapted from the original author. The intention is to offer a realistic, practical approach for any territory seeking to lead in life sciences quality, data integrity, and the transition to human-relevant toxicology. We cannot always compete in size, but we can lead in quality and transparency.

Recommended for internal consideration by: National governments, regulatory authorities (including EMA and National Competent Authorities), innovation programmes, and bodies advancing the transition to non-animal science such as TPI Netherlands and equivalent initiatives worldwide.

Alignment Note (June 2026): This framework supports the European Commission's Roadmap towards phasing out animal testing (adopted 1 June 2026) and Directive 2010/63/EU.

Status: Pro Bono Technical Framework – Adaptable Model (v4 – Updated for EU Alignment)

Recommended for internal consideration by: National governments, regulatory authorities (including EMA and National Competent Authorities), innovation programmes, and bodies advancing the transition to non-animal science such as TPI Netherlands and equivalent initiatives worldwide.

Alignment Note (June 2026): This framework is explicitly designed to support the objectives of the European Commission's *Roadmap towards phasing out animal testing for chemical safety assessments* (adopted 1 June 2026) and the full implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes. It provides a practical, market-driven "regulatory pull" mechanism to accelerate the uptake of New Approach Methodologies (NAMs) while strengthening data integrity and patient safety. National Centres for the Validation of Alternative Methods (NCVAM or designated equivalents) are encouraged to operate in coordination with the EU Reference Laboratory for alternatives to animal testing (EURL ECVAM) at the Joint Research Centre.

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List of Abbreviations and Key Terms

NAMs — Non-Animal Methods / New Approach Methodologies

NCVAM — National Centre for the Validation of Alternative Methods (or equivalent national body; territories may designate or establish such a centre; encouraged to coordinate with EURL ECVAM)

Q-M — Quality Mark (Territory-Neutral Q-M Standard)

Regulatory Authority — National medicines regulatory agency (e.g., EMA, national competent authorities, CBG-MEB, or equivalent)

CRM — Comparative Relevance Matrix

CRO — Contract Research Organisation

ICH — International Council for Harmonisation

ESG — Environmental, Social and Governance

3Rs — Replacement, Reduction and Refinement

OECD MAD — Mutual Acceptance of Data

EURL ECVAM — EU Reference Laboratory for alternatives to animal testing (Joint Research Centre)

Executive Summary & Strategic Context (June 2026)

In the global race to advance life sciences, commercial competitiveness is increasingly determined by data quality, regulatory speed, and predictive accuracy rather than raw scale. While the European Union has established ambitious targets through Directive 2010/63/EU and the newly adopted Commission Roadmap towards phasing out animal testing (1 June 2026), a significant systemic barrier remains: the **Preclinical Transparency Gap**.

Drug sponsors routinely outsource preclinical safety testing to offshore Contract Research Organisations (CROs) operating in jurisdictions with lower statutory oversight, minimal animal welfare accountability, and non-transparent reporting. This creates welfare and regulatory arbitrage, suppresses locally developed human-relevant NAMs, and introduces unquantifiable risks to patient safety through unreliable baseline data, suppressed severity metrics, and poor translatability.

The **Territory-Neutral Quality Mark (Q-M)** framework resolves these challenges through a robust, market-driven administrative gatekeeper mechanism. By linking verified data transparency and human relevance directly to prioritised, expedited regulatory assessment pathways, the Q-M establishes an inescapable commercial incentive for high-integrity science — without extra-territorial legislative bans.

Core Innovation: Only datasets carrying the Q-M stamp are eligible for prioritised or fast-track review by Regulatory Authorities. Non-compliant "opaque" data is not banned but is automatically relegated to the standard review timeline, creating powerful commercial pressure to adopt transparent, human-relevant methods.

This v4 update strengthens alignment with the EU single market, EURL ECVAM coordination, and the 2026 Roadmap, while preserving full flexibility for progressive national authorities (with the Netherlands via TPI positioned as an ideal pilot).

1.The Case for Territory-Neutral Leadership in Data Integrity

National frameworks that fund, validate, and encourage New Approach Methodologies (NAMs) face standard economic sabotage via regulatory and welfare arbitrage. Drug sponsors and developers routinely outsource preclinical 'safety' testing portfolios to offshore Contract Research Organisations (CROs) operating in jurisdictions with lower/different statutory oversight, minimal animal welfare accountability, and non-transparent reporting mechanisms. This creates a multi-layered vulnerability:

- **Welfare and Regulatory Arbitrage:** Preclinical animal testing portfolios are routinely offshored to third-country CROs to bypass local scrutiny, ethical reviews, and alternative method mandates.
- **The Transparency Loophole:** Regulators accept secondary data summaries from offshore facilities without direct access to baseline raw data, historical control baselines, or actual severity data.
- **Suppression of Innovation:** Human-relevant, validated NAMs developed locally are by-passed by commercial entities in favour of conventional, low-cost animal models executed in opaque testing markets, stalling national and EU transition roadmaps.

The Strategy: The Quality Mark (Q-M) framework resolves these challenges not through extra-territorial legislative bans—which face significant international trade law boundaries—but through a robust, market-driven administrative gatekeeper mechanism.

By linking verified data transparency and human relevance directly to prioritised, expedited regulatory assessment pathways, the Q-M establishes an inescapable commercial incentive for high-integrity science.

2.Addressing Implementation Concerns and Structural Feasibility

A. International Harmonisation & Sovereign Data Standards (EU Single Market Compatibility)

A frequent objection to national data verification standards is that they disrupt international harmonisation frameworks, such as the International Council for Harmonisation (ICH) guidelines. This is an operational misunderstanding. The Q-M framework operates entirely within established international guidelines, utilising the explicit legal and technical flexibilities already embedded in ICH S1B(R1) and ICH S6(R1).

The standard does not impose unique, non-harmonised scientific testing requirements. Instead, it serves as an administrative verification layer confirming that the data submitted actually matches the origin, quality, and ethical criteria claimed in the regulatory dossier.

EU Single Market Compatibility: The Q-M is designed as a non-discriminatory quality and safety standard fully compatible with the EU internal market rules (TFEU Articles 34–36). It applies identically to data originating within or outside any Member State. Any testing facility, domestic or international, may obtain Q-M certification by demonstrating compliance with transparent, auditable criteria. This approach is proportionate to the legitimate public interest in protecting patient safety and data integrity in medicinal products authorised in the EU. It does not create unjustified barriers to trade; it raises the baseline for data quality entering the European medicines supply chain.

Under international trade laws and EU law, any sovereign authority (or co-ordinated national authorities) retains the absolute legal right to establish internal administrative protocols to protect public safety and audit the structural integrity of safety-critical data.

B. Science & Technology Readiness

Skeptics argue that New Approach Methodologies are not yet sufficiently mature to entirely replace conventional in vivo toxicological profiling. The Q-M framework elegantly circumvents this debate by operating as a dynamic, dual-stream incentive structure rather than an absolute mandate:

- **Stream 1 (NAM-First Priority):** Datasets derived from fully human-relevant, validated NAM architectures receive immediate, top-tier prioritised administrative triage, bypassing historical review delays.
- **Stream 2 (High-Transparency Animal Data):** Where animal data is still legally or scientifically non-substitutable under international guidelines, the dataset can still qualify for the Q-M seal — provided the sponsor submits an auditable, fully transparent Transparency Gap Compliance Template proving absolute traceability, baseline verification, and true actual severity reporting.

National Centres are encouraged to coordinate with **EURL ECVAM** to ensure alignment with EU-validated methods and to contribute national audit outcomes to the broader European validation ecosystem.

C. Operational Integration and the Automated 'Traffic Light' Triage

To avoid creating unnecessary administrative friction or delaying patient access to essential therapeutics, the integration of the Q-M standard into the National Competent Authority (NCA) is governed by an automated, algorithmic intake protocol. This operational workflow acts as an objective, dual-tier administrative gatekeeper:

When a sponsor submits a non-clinical dossier (Module 4 or equivalent), they are required to append a completed Transparency Gap Compliance Template. The National Centre for Non-Animal Innovation (NCVAM or local equivalent) executes an automated structural audit:

1. **Green Stream (Zero-Gap / NAM-First Priority):** The dataset contains zero transparency gaps. Preclinical data points possess full traceability keys, clear genetic/facility controls, and verified human-relevance or alternative methodology implementation. The application is flagged as Green and routes directly into the authority's prioritised, fast-track assessment queue.
2. **Amber Stream (Conditional Triage):** The technical dossier contains minor omissions or unverified metadata components from external facilities. The sponsor is automatically granted a strict, non-extendable 30-day administrative window to supply a verified Certificate of Equivalence from the source testing facility. If resolved, it proceeds to standard review; if unresolved, it falls to the restricted tier.
3. **Red Stream (Non-Compliant / Restricted Review):** Significant structural transparency gaps are identified, such as undocumented facility controls, non-disclosed animal numbers, unverified actual severity metrics, or the demonstrable bypassing of a territory-accepted, validated alternative methodology. The application is entirely barred from all prioritised or expedited evaluation streams and relegated to the standard, low-priority regulatory assessment timeline as a 'High-Risk/Opaque' dataset.

D. Budget, Resource Allocation, and Financial Levers

The establishment of a national certification framework does not require significant public expenditure or expansions of state regulatory bodies. The Q-M infrastructure is designed to operate on a self- sustaining, fee-for-service commercial model where the administrative costs of data auditing are completely covered by standard, sliding-scale application fees paid by corporate drug sponsors.

Furthermore, national authorities can implement powerful fiscal levers to reinforce the framework. State-level R&D tax incentives, innovation grants, and public subsidies for life science development should be legally conditioned on Q-M compliance. If an auditing centre confirms that a commercial sponsor deliberately bypassed an accessible, validated, locally accepted NAM in favour of low-cost, unverified offshore animal testing, the developer faces the automatic suspension of state innovation tax credits and public funding channels for that development cycle. Such conditioning must remain compatible with applicable EU State aid frameworks.

3.Core Mechanism: The ‘Transparency Gap’ and Its Direct Threat to Patient Safety

The core problem undermining regulatory science is the systematic decoupling of raw preclinical data from auditable oversight. When clinical trials are initiated based on non-clinical datasets imported from unverified third-country environments, regulators face severe, unquantifiable risks that directly impact human patient safety. The Q-M framework directly links specific transparency gaps to established regulatory safety criteria:

Identified Transparency Gap	Scientific Consequences & Data Integrity Risks	Regulatory Safety Failure Mode
Opaque Facility Sourcing & Variable Control Baselines	Testing facilities in unregulated zones frequently utilise animal strains subject to unchecked genetic drift, non-standardised diets, and unmonitored baseline pathogens. Baseline physiological values cannot be scientifically replicated.	**False Negative Toxicity Signals:** Dangerous systemic or organ-specific toxicity profiles are masked by erratic baseline data, exposing human trial subjects to unquantified chemical risks.
Undisclosed and Non-Standardised Analgesic Regimens	Offshore facilities often suppress or fail to record the use of analgesics, anaesthesia, or secondary therapeutic interventions during acute toxicity protocols. This completely distorts baseline metabolic and neurological readings.	**Confounded Pharmacokinetic Data:** Unrecorded pharmaceutical interactions alter systemic drug clearance rates, leading to inaccurate human dose escalation modeling.
Suppression of True Actual Severity Metrics	Sub-contracted laboratories routinely log animals under lower, predicted severity bands rather than recording the actual, high-severity clinical outcomes and multi-system failures that occurred in vivo.	**Undetected Off-Target Organ Damage:** Critical indicators of severe multi-system or delayed organ toxicity are erased from the final summary dossier presented to the regulatory authority.
Bypassing Validated Human-Relevant NAMs	Utilising non-pharmacologically relevant animal species simply because of low baseline cost, while consciously avoiding human cell-line arrays or advanced organ-on-a-chip microfluidic architectures.	**Translational Failure and Clinical Trial Attrition:** Ineffective or explicitly toxic compounds advance into human testing phases due to false-positive animal efficacy markers that fail to translate to human biology.

4.The Quality Mark (Q-M) Technical Specification

A. Technical Specification: Q-M Standard

Title: Requirements for Preclinical Data Integrity and Human-Relevant Methodology Certification (Territory-Neutral).
Scope: Mandatory transparency and validation criteria for datasets submitted for prioritised regulatory review.
Core Requirement: Quad-Lock Verification by the designated NCVAM (coordinated with EURL ECVAM where applicable).

Criterion A: Data Provenance Protocol (Anti-dark shield)

A.1. **Traceability:** Submission must include a verifiable "Chain of Custody" for all biological or digital inputs.
A.2. **Audit Equivalence**: Non-domestic research must demonstrate equivalence to national high welfare and audit standards.
A.3. **Exclusion Trigger**: Facilities restricting independent audits or withholding breeding records → classified Sub-Standard / ineligible for Q-M.

Criterion B: Scientific Concordance (Human-First validation)

B.1. **Mechanistic Alignment:** Comparative Relevance Matrix demonstrating fidelity to human patho-physiology.
B.2. **NAM Preference**: Preference for validated NAMs where they exist for the specific context (biosimilars, generics, non-pharmacologically active compounds).
National Centres should reference EURL ECVAM-accepted methods lists.
B.3 **Exclusion Triggers:** Bypassing available validated NAM for second-species test → Q-M revocation.

Criterion C: Ethical Transparency (Actual Severity)

C.1. **Actual severity Mapping:** Real-time Actual Severity Logs required.
C.2.**Welfare Arbitrage Check:** Verification that no procedures were performed breaching national high standards were used overseas.

Criterion D: Economic & Sovereign Resilience (The "Strategic Resilience" Lock)

D.1. **Strategic Dependency Mitigation**: Resilience statement on geographic dependencies and alignment with national NAM capacity-building priorities.
D.2. **Investment Alignment:** Verification that the R&D methodology aligns with the National investment and funding priorities.

D.3. **Strategic Resilience Red Flag (The "Strategic Security" Lock):** Any dataset relying on a critical "Single-Point-of-Failure" in a jurisdiction that refuses reciprocal data-sharing or unannounced audits will be denied the Quality Mark (Q-M). This prevents "laundering" low-quality or ethically compromised data into the nation state (or EU) medicine supply chain.

B. Regulatory Integration – The Gatekeeper Mechanism

Only datasets carrying the Q-M stamp are eligible for prioritised or advance review schemes operated by the Regulatory Authority. Certification can be public-facing (redacted for sensitivity) to allow investors and ESG agencies to verify compliance.

Key Exclusion Red Flags: - Opaque Origin: No traceable source or refusal of equivalent audits. - Regulatory Bypass: New animal data for categories where NAMs are mandated or animal testing restricted, when NAM was available. - Welfare Arbitrage: Failure to provide actual severity equivalence.

For centralised EMA procedures, Member States and the EMA are encouraged to mutually recognise Q-M certifications issued by participating National Centres, ensuring consistent high standards across the single market while avoiding duplication.

C. The Quad-Lock Framework for Territory-Neutral Verification

To establish an unalterable standard of data integrity, the Q-M protocol enforces a rigid, four-tiered authentication sequence known as the Quad-Lock Standard:

1. **The Origin & Blockchain Traceability Lock:** Establishes absolute, end-to-end chain of custody for all raw preclinical data points. Every single computational, alternative method, or in vivo biological outcome must be embedded with an immutable cryptographic timestamp, verifiable source geolocation data, and independent institutional facility logs.
2. **The Scientific Concordance & Human-Relevance Lock:** Mandates an advanced, algorithmic cross-verification of the chosen non-clinical testing models against verified human-relevant reference databases. The sponsor must supply detailed, peer-reviewed computational justification proving that the chosen testing matrix possesses the necessary cell receptors, metabolic pathways, and genomic compliance. Alignment with EURL ECVAM-validated methods is strongly encouraged.
3. **The Actual Severity & Welfare Integrity Lock:** Eliminates the obfuscation of animal suffering by forcing an absolute, day-by-day longitudinal recording of actual animal welfare parameters, behavioural degradation markers, and physical pathology scores.
4. **The Strategic Geopolitical & Supply Chain Lock:** Addresses systemic geopolitical and supply chain vulnerabilities by mapping and auditing the concentration of preclinical infrastructure. It enforces comprehensive risk disclosures regarding dependence on single-source, highly volatile external jurisdictions.

D. The Anonymised Aggregation Model (IP Preservation Protocol)

A critical commercial barrier to regulatory transparency is the preservation of corporate Intellectual Property (IP). The Q-M framework resolves this tension through a strict Two-Tier Data Separation protocol:

Tier 1: The Secure Regulatory Audit Vault (Private): Contains the full, un-redacted technical specifications, exact molecular structures, target chemical components, and precise laboratory coordinates. This tier is accessible exclusively by authorised regulatory auditors and the independent validation centre.

Tier 2: The Anonymised Aggregation Registry (Public): The framework extracts metadata and structurally anonymises the validation outcomes. This aggregated dataset is published on an open-access, searchable national (or coordinated EU-level) registry. The public listing details: the species or alternative human cell-line architecture utilised, total quantity counts, actual longitudinal severity scores, and the validated technical justification.

5.The Transparency Gap Compliance Template

The operational centrepiece of the Q-M audit process is a standardised, technical reporting sheet that all commercial developers must submit. This template translates abstract policy into a concrete, binary compliance checklist:

Technical Dimension	Mandatory Disclosure Metric & Data Key	Verifiable Evidence Required
Origin Verification	Cryptographic facility identity key, certified geographic coordinates, and third-party independent facility audit logs.	Immutable blockchain-anchored data ledger and verified facility operator certificate.
Model Concordance	Quantitative human-relevance scoring index and documented receptor homology mapping files.	Peer-reviewed target validation data or explicit computational simulation report. Reference to EURL ECVAM-accepted methods where applicable.
Welfare Accountability	Complete day-by-day longitudinal actual severity logs, analgesic batch numbers, and accurate mortality records.	Unedited baseline laboratory animal technician logs and independent veterinary oversight sign-off sheets.
Alternative Audit	Formal technical justification matrix explaining the precise scientific or statutory barrier preventing NAM utilisation.	Official National Centre (NCVAM) database query log proving absence of a validated alternative method (cross-checked with EURL ECVAM resources).

6.Contextual Implementation: European Union and TPI Netherlands Pathways

A. The European Union Context (Directive 2010/63/EU Modernisation and 2026 Roadmap)

Within the European Union, the Q-M serves as an operational compliance enforcement tool for Directive 2010/63/EU, which legally mandates the reduction, refinement, and eventual complete replacement of animals for scientific purposes. By deploying the Q-M standard, the European Medicines Agency (EMA) and National Competent Authorities can protect the integrity of the European single market. It ensures that any non-clinical dataset submitted for market authorisation within the Union is subject to identical transparency, data provenance, and ethical standards, regardless of where the testing occurred.

The framework directly supports the Commission's Roadmap towards phasing out animal testing (adopted 1 June 2026) by providing a concrete mechanism to operationalise the "last resort" principle and accelerate NAM uptake through regulatory incentives.

National Centres (NCVAM or equivalents) are encouraged to coordinate closely with **EURL ECVAM** to ensure methodological alignment, share audit intelligence, and contribute to EU-wide validation efforts.

B. The TPI Netherlands Context (The Missing 'Regulatory Pull' Mechanism)

The Netherlands has established itself as the undisputed global pioneer in non-animal transition strategies through the Transition to Animal-Free Innovation (TPI) network. The territory-neutral Q-M framework provides TPI Netherlands with an administrative 'Regulatory Pull' mechanism. Rather than attempting a complex, legally challenging unilateral ban on imported animal data, the Netherlands can implement the Q-M standard to award immediate, prioritised, expedited review pathways to developers utilising human-relevant architectures. This turns regulatory speed into a high-value commercial asset, pulling market actors away from animal models and cementing the Netherlands' status as the premier global marketplace for high-fidelity, advanced biomedical science.

Pilot Opportunity: The Netherlands, through its pioneering TPI programme and strong regulatory infrastructure, is ideally positioned to serve as the first pilot Member State. Successful

implementation and independent evaluation could provide a replicable template for other progressive Member States and inform future Commission guidance or arrangements for mutual recognition of Q-M certifications across the EU.

7.Strategic Risk Management and Mitigation Protocols

- **Mitigation of Intellectual Property Anxieties:** Preclinical developers frequently cite fears regarding the exposure of confidential commercial formulations. This is entirely neutralised by the Two-Tier Data Separation architecture, which walls off all proprietary structures within the secure regulatory audit vault while releasing only high-level transparency metadata to the public registry.

- **Neutralising Scientific Skepticism:** Traditional pharmaceutical groups may assert that NAM architectures face scientific skepticism regarding cross-organ systemic interactions. The framework positions the National Centre (NCVAM or local equivalent, in coordination with EURL ECVAM) as the final, authoritative validating arbiter, continuously updating the acceptable NAM registry.

- **Preventing Regulatory Efficiency Drag:** Industry groups may complain of compliance backlogs. The automated 'Traffic Light' triage ensures that zero administrative delays occur for compliant companies, while the 30-day Amber stream offers a practical, fair window to correct minor missing data.

- **Mitigation of Uneven Implementation Risk across Member States:** To prevent regulatory fragmentation or forum-shopping within the single market, the framework recommends Commission-facilitated coordination among National Competent Authorities, potentially through the existing EURL ECVAM network or a dedicated working group. A common core template and mutual recognition of Q-M certifications issued by any participating NCVAM would preserve harmonisation while allowing progressive territories to lead.

8.Conclusion and Recommended Next Steps

The Territory-Neutral Quality Mark offers an elegant, legally unassailable, and highly practical administrative mechanism to close the transparency gaps that currently compromise both patient safety and scientific reliability in global preclinical research. Any sovereign state or progressive territory with an established commitment to public health preservation, data integrity, and leadership in non-animal innovation can seamlessly adopt this model. It stands ready for implementation as the definitive operational link that turns public investment in New Approach Methodologies into an absolute regulatory and commercial marketplace advantage.

By aligning with the European Commission's 2026 Roadmap, Directive 2010/63/EU, and EURL ECVAM coordination mechanisms, while respecting single-market principles, the Q-M provides EU Member States with a powerful tool to lead globally in human-relevant, ethical, and sovereign toxicology.

Recommended Next Steps

1. **Pilot Implementation in the Netherlands:** Launch a structured pilot via TPI Netherlands and the relevant National Competent Authority (e.g., CBG-MEB), with independent evaluation and public reporting after 12 months of operation.
2. **Technical Engagement Workshop:** Convene a focused workshop with EURL ECVAM, EMA non-clinical working parties, and interested Member State authorities to review, refine, and potentially endorse core elements of the Compliance Template and Quad-Lock criteria.
3. **Development of an EU-Coordinated Template:** Create an optional EU-level version of the Transparency Gap Compliance Template (with core common fields) to facilitate mutual recognition and reduce duplication for sponsors operating across multiple Member States.
4. **Presentation to European Commission Services:** Submit this framework formally to relevant Directorates-General (DG SANTE, DG ENV) and the EMA for consideration in the implementation planning of the 2026 Roadmap and ongoing modernisation of non-clinical assessment practices.

This framework is offered in the spirit of constructive collaboration to advance the shared European goal of higher-quality, more human-relevant, and ethically robust biomedical innovation.

Document Version: v4 – June 2026 (EU-aligned update)
Original Author: Linda Birr-Pixton, The Alliance for Cruelty Free Science
Adaptation & Updates: Territory-neutral model with enhanced EU single-market, EURL ECVAM, and 2026 Roadmap alignment.

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