Automated Batch Record Review and Release Readiness with Petri-ACTA.

A REGULATOR-ALIGNED PHASE-1 PILOT CONCEPT

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0. Executive Summary

Purpose

Contract Development and Manufacturing Organisations (CDMOs) operate in an environment of high product variability, client-specific Master Batch Records (MBRs), hybrid documentation systems, and centralised QA/QP functions under constant time pressure. In this setting, batch release has become the dominant operational and regulatory bottleneck, not because manufacturing lacks automation, but because compliance evidence is still reconstructed retrospectively, under legal liability, across fragmented systems.
Despite significant advances under the Pharma 4.0 paradigm such as electronic batch records, PAT, real-time monitoring, and advanced analytics, batch release remains slow, manual, and risk-concentrated. The final release decision must reconcile documentation completeness, in-process controls, deviations, investigations, and approvals after execution has already finished. As a result, release readiness issues are often discovered late, when correction is costly and delays are unavoidable.

This project addresses that gap.
It demonstrates how continuous, deterministic evaluation of batch-release readiness during execution, without automating or replacing GMP authority, can reduce uncertainty, surface release blockers early, and stabilise batch review for CDMOs operating across multiple clients and products.

What ACTA Uniquely Contributes

ACTA (Adaptive Compliance Transformation Algorithm), implemented here using a Petri-net–based compliance model (Petri-ACTA), introduces a formal compliance execution layer that runs in parallel to manufacturing.

Rather than treating compliance as narrative documentation reviewed at the end of a batch, ACTA encodes GMP and quality requirements as explicit, rule-based logic that evaluates events, data, and documentation as they occur. Each relevant GMP event—such as an IPC result, a signature, or a deviation status change—updates a continuously evolving release-readiness state.

The distinguishing characteristics of ACTA are:

- Determinism and explainability: identical inputs always produce identical outcomes; every readiness state is traceable to explicit rules and evidence.
- Formal guarantees: the compliance logic is designed to be live, bounded, and free of deadlock, enabling predictable and inspectable behaviour.
- Parallel evaluation: documentation, IPCs, and deviation lifecycles are assessed concurrently rather than sequentially.
- Regulatory alignment: ACTA supports GMP principles (EU GMP Chapter 4, Annex 11, Annex 22, ALCOA+) without introducing black-box decision-making or autonomous disposition.

ACTA does not accelerate release by bypassing controls. It accelerates release by eliminating late discovery of compliance gaps.

Key Positioning

ACTA is non-authoritative by design but regulatory-relevant by function: it evaluates the same evidence, rules, and dependencies that govern batch release, while preserving full human GMP responsibility.

The Purpose of This Document

This document defines a Phase-1, regulator-aligned pilot suitable for CDMO environments. In this phase, ACTA operates as a read-only, shadow compliance evaluation system using synthetic or copied batch-record data. It introduces no control paths, no write-back into GMP systems, and no reliance for GMP decisions, ensuring zero operational and regulatory risk.

Crucially, the pilot is not an architectural dead end. The document also defines a clear operational path toward production use, in which ACTA can later be integrated as a qualified, read-only decision-support tool under standard computer system validation, and eventually as an inline compliance evaluation layer—while maintaining unchanged QA/QP authority.

The purpose of this pilot is therefore twofold:

1. To demonstrate inspection-credible, continuous batch-review logic under controlled conditions.
2. To provide CDMOs with a safe, structured foundation for future digitalisation of batch-release readiness without premature regulatory commitment.

1. Why CDMOs Are the Right Entry Point

Contract Development and Manufacturing Organisations (CDMOs) experience the challenges of batch record review and release readiness in a **more concentrated and structurally exposed form** than single-product originator manufacturers. Their operating model amplifies documentation complexity, deviation frequency, and release pressure, making them a natural and credible entry point for evaluating new approaches to batch review under Pharma 4.0.

1.1 Structural CDMO Challenges

Multi-client, multi-MBR complexity
CDMOs routinely manufacture multiple products, strengths, and formulations for different clients on the same equipment trains. Each client operates under its own approved Master Batch Records (MBRs), acceptance limits, sampling frequencies, documentation rules, and deviation classifications. As documented in this project, even when the physical execution flow remains identical, **compliance requirements vary by strength and by client**, significantly increasing the cognitive and procedural burden on QA during batch review.

Centralised QA/QP under release pressure
In CDMO environments, QA and QP functions are typically centralised and responsible for batch release across multiple clients and campaigns in parallel. This creates structural pressure at the release stage: multiple batches compete for review attention, often under contractual delivery timelines. The document shows that release delays are rarely caused by manufacturing failures alone, but by **late**

discovery of documentation gaps, unresolved deviations, or incomplete investigations, all of which converge at QA/QP review.

Hybrid documentation landscapes
Many CDMOs operate with a mix of paper records, hybrid batch records, and partially electronic systems (EBR, LIMS, QMS). As described in the reference manufacturer profile, IPC data may be partially automated while documentation and signatures remain manual. This fragmentation increases the risk that required evidence exists but is **not visible, not synchronised, or not easily reconstructable** at the time of release.

High deviation and documentation risk
Our preliminary research found that a significant proportion of batch release delays are driven not by product quality failures, but by documentation and data-integrity issues: missing signatures, late entries, incomplete investigations, or client-specific documentation requirements. In CDMO operations, where changeovers and campaign manufacturing are frequent, these risks are systemic rather than exceptional.

1.2 Why Batch Release Is the Real Bottleneck

Release is legal, retrospective, and human-bound
Batch release is the final legally binding act in pharmaceutical manufacturing. Regardless of how advanced manufacturing execution, monitoring, or automation may be upstream, the release decision itself remains a retrospective assessment performed by Quality Assurance and the Qualified Person, under explicit personal legal responsibility.
This legal responsibility fundamentally shapes how batch release is performed. Uncertainty at the point of release is not tolerable, because any error or omission carries regulatory, civil, and potentially criminal consequences. As a result, batch review practices remain conservative, documentation-heavy, and predominantly manual, even in otherwise highly digitalised manufacturing environments.

Automation may support data generation, but it cannot displace the requirement for human judgment and accountability at release.

Automation elsewhere increases the proof burden at release

Pharma 4.0 initiatives have significantly increased the level of automation during manufacturing execution: electronic batch records, automated in-process controls, real-time data acquisition, and advanced analytics are now common. While these technologies improve process control and data availability, they also increase the **amount, granularity, and interdependence of evidence** that must ultimately be assessed at batch release.

Each additional automated step generates new data streams, decision points, and potential exceptions that must be demonstrated to be compliant, complete, and correctly handled. Rather than simplifying batch release, manufacturing automation concentrates the compliance burden at the end of the process, where all evidence must be reconciled into a single release decision. The result is that batch release becomes the point where complexity accumulates, rather than dissipates.

Release readiness is not the same as the release decision

A critical but often unaddressed distinction is that *release readiness* is a continuously evolving state, whereas *batch release* is a discrete legal act.

During batch execution, readiness changes dynamically as documentation is completed, in-process results are generated, deviations are opened or closed, investigations progress, and approvals are obtained.

At any given moment, a batch may be closer to or further from being releasable, even though no formal release decision is yet possible.

Conventional systems largely ignore this distinction. They treat release readiness as something to be assessed only after manufacturing is complete, forcing QA to reconstruct the compliance status retrospectively from static records. This late consolidation masks emerging release blockers until execution has finished, when corrective actions are most expensive and delays unavoidable.

The consequence is that batch release becomes a reactive bottleneck, rather than a controlled confirmation of an already transparent state.

ACTA targets the batch review bottleneck, not manufacturing control.
It does not alter production, automate release, or replace QA/QP judgment. Instead, it makes release readiness observable, structured, and continuously evaluated during execution, so that batch release becomes a confirmation of an already transparent state rather than a late reconstruction under pressure.

2.Regulatory Baseline

2.1 What Regulators Actually Require

Regulatory frameworks governing pharmaceutical manufacturing are explicit in what may be automated, what must remain under human authority, and how computerized systems may be used to support GMP activities. Across EU GMP Chapter 4, Annex 11, Annex 22, and data-integrity principles (ALCOA+), the requirements are consistent and stable.

EU GMP Chapter 4 — Documentation and Records

EU GMP Chapter 4 requires that batch records provide a complete, accurate, and contemporaneous account of manufacturing and control activities. Records must allow reconstruction of the batch history and demonstrate that all required steps, controls, and checks were performed as specified. The regulation does not mandate *how* records are reviewed, but it requires that review be effective, complete, and capable of identifying deviations, omissions, and unresolved issues prior to release. Critically, Chapter 4 assigns responsibility for review and release to human roles within the quality system. Any supporting system must therefore strengthen, not obscure, the ability of QA and the Qualified Person to understand what occurred during execution.

Annex 11 — Computerised Systems

Annex 11 governs the use of computerised systems in GMP contexts. It requires that systems be fit for intended use, validated according to risk, and designed to ensure data integrity, traceability, and availability throughout the record lifecycle.
Annex 11 does not prohibit advanced logic, automation, or analytics. It does require that:

- system behaviour be deterministic and predictable,
- outputs be explainable and reviewable,
- responsibilities remain clearly assigned to humans,
- and decisions affecting product quality are not delegated to opaque or uncontrolled mechanisms.

Systems that support GMP activities without exercising control or decision authority may be introduced incrementally, provided their role, limitations, and interfaces are clearly defined.

Annex 22 — Artificial Intelligence and Machine Learning

Annex 22 clarifies expectations for the use of AI/ML in GMP-relevant systems. It emphasises governance, transparency, and control over learning behaviour, particularly where systems influence quality decisions.

A key regulatory distinction is between:

- systems that *assist* human decision-making using deterministic or rule-based logic, and
- systems that *autonomously infer or adapt* decisions through non-transparent learning mechanisms.

Rule-based, formally specified logic that does not self-modify and whose outputs are fully traceable aligns with Annex 22 expectations for explainability and control. Human accountability for GMP decisions remains mandatory regardless of technical sophistication.

ALCOA+ — Data Integrity Principles

Across all regulatory guidance, data integrity principles are foundational. Data used to support batch release must be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available.

Regulators assess not only whether data exist, but whether:

- dependencies between records are clear,
- timing and sequence are reconstructable,

- exceptions are visible rather than hidden in narrative,
- and review conclusions can be justified years later.

Systems that structure evidence and make compliance states explicit strengthen, rather than weaken, adherence to ALCOA+ principles—provided they preserve transparency and traceability.

Regulators do not require automation of batch release. They require **clarity, traceability, determinism, and human accountability**. Any system supporting batch review must operate within those constraints. The regulatory baseline therefore permits and increasingly expects introduction of tools that improve visibility of compliance status during execution, while leaving legal responsibility and final decisions unequivocally with QA and the Qualified Person.

2.2 Regulatory Non-Negotiables

Across EU GMP Chapter 4, Annex 11, Annex 22, and established inspection practice, regulatory expectations converge on a small set of principles that are **not subject to trade-off or technological reinterpretation**. Any computerized system used to support GMP activities must respect these non-negotiables.

Human Responsibility

GMP compliance is ultimately enforced through personal accountability. Responsibility for manufacturing oversight, batch record review, deviation assessment, and batch release remains assigned to defined human roles, in particular Quality Assurance and the Qualified Person. This responsibility cannot be delegated to a system, algorithm, or model, regardless of its technical sophistication. Regulators consistently distinguish between systems that *support* human judgment and systems that *replace* it. Only the former are acceptable in GMP contexts. Supporting systems must therefore preserve clear visibility of who reviewed what, when, and on what basis, and must never obscure or dilute individual accountability.

Determinism and Explainability

Regulators require that system behaviour be predictable, bounded, and understandable. For GMP-relevant functions, the same inputs must lead to the same outputs, and the logic leading to a result must be inspectable and defensible.

Black-box behaviour, probabilistic reasoning without traceable justification, or adaptive logic that changes decision boundaries without explicit control is incompatible with Annex 11 and Annex 22 expectations. Where computerized systems influence quality review, their evaluations must be rule-based or otherwise constrained such that outcomes can be explained in concrete terms, not inferred statistically after the fact.

Determinism is not a performance preference; it is a regulatory requirement.

Reconstructability Years Later

GMP records must support independent reconstruction of events long after batch execution, often many years after product release. Regulators assess not only whether a conclusion was reasonable at the time, but whether the basis for that conclusion can still be demonstrated when personnel, systems, and organisational context have changed.

This requires that:

- evidence remains accessible and understandable,
- the relationships between data, deviations, and claims are clear,
- and the sequence of events can be reconstructed without relying on personal memory or informal accounts.

Systems that reduce complex compliance reasoning to unstructured documentation increase audit risk.

Systems that maintain structured, time-stamped, and traceable evidence strengthen long-term security.

Impact on this project:

Any approach to improving batch review or release readiness must fully comply, and operate entirely within these non-negotiables. The objective is not to accelerate decisions by weakening controls, but to improve confidence by making compliance evidence more explicit, deterministic, and reconstructable—while preserving full human responsibility at any time.

2.3 What This Project Explicitly Does Not Attempt

To avoid ambiguity and ensure clear regulatory positioning, the scope of this project is deliberately bounded.

The following capabilities are **explicitly excluded by design**:

Real-Time Release Testing (RTRT)

This project does not implement, evaluate, or imply real-time release testing. Product quality acceptance remains governed by approved analytical methods, established specifications, and existing quality control processes. No in-process or execution-time evaluation performed here replaces or bypasses required testing prior to batch release.

Autonomous Batch Disposition

The system does not release, conditionally release, reject, or place batches on hold. It does not enforce GMP actions, initiate official quality records, or substitute for QA or Qualified Person judgment. All legal authority for batch disposition remains fully human and unchanged.

Black-Box or Self-Determining AI Decisions

The project does not employ opaque machine-learning models, uncontrolled adaptive logic, or probabilistic decision-making for GMP-relevant evaluations. All compliance assessments are based on explicit, rule-defined logic with traceable inputs and explainable outcomes. Where analytical or AI-based techniques are used at all, their role is strictly auxiliary and subject to human review.

By excluding these capabilities, the project remains fully aligned with current regulatory expectations while focusing on its intended objective: improving visibility and structure of release readiness without altering GMP authority, decision rights, or validated manufacturing systems.

3.Economic Impact of Batch Release Inefficiency

Across mid-size EU CDMOs, batch release inefficiency is not an exceptional failure mode but a **recurrent operational condition**. Analysis of routine manufacturing operations shows that delays and cost accumulation at batch release arise primarily

from documentation and compliance dependencies rather than from failures in manufacturing execution or product quality.
When assessed on a **per-batch basis**, the economic and operational impact becomes explicit.

3.1 Release Latency as a Cost Multiplier

For a typical campaign batch that completes manufacturing as planned, **release is frequently delayed by several days** due to unresolved documentation elements, deviation status ambiguity, or missing approvals. On a per-batch average, this results in:

- immobilisation of finished goods inventory beyond planned timelines,
- delayed invoicing and revenue recognition,
- extended use of storage and controlled warehouse capacity,
- reduced flexibility for subsequent campaign scheduling.

Importantly, these delays occur **after manufacturing cost has already been incurred**, meaning they do not scale with product value but directly erode margin and cash flow.

3.2 Documentation-Driven Review Effort

Per-batch analysis shows that **a material share of QA review time** is spent not on assessing product quality outcomes, but on locating, reconciling, and validating documentation elements across hybrid systems.

Typical contributors include:

- missing or late signatures,
- incomplete cross-references between records,
- inconsistent timestamps across systems,
- client-specific documentation requirements identified late.

As a result, average QA review effort per batch increases disproportionately when documentation issues are discovered only at the end of execution. This creates review-time variability that is difficult to plan for and amplifies peak workload during release windows.

3.3 Deviation Escalation Effects

Deviations are a normal feature of campaign-based manufacturing. However, per-batch data show that **the cost impact of a deviation depends strongly on when it becomes release-relevant**.

When deviation relevance to release is identified late:

- investigation scope expands,
- additional reviews and approvals are required,
- and batch release timelines extend non-linearly.

On a per-batch basis, deviations that are recognised as release-blocking only at the end of execution generate **significantly higher investigation effort** than those identified earlier, even when technical severity is comparable.

3.4 QA Workload Concentration and Variability

Batch release concentrates work into narrow time windows. Per-batch averages mask this effect unless timing is considered: multiple batches often converge for review simultaneously, creating short periods of extreme QA/QP workload.

This concentration leads to:

- reliance on manual reconciliation under time pressure,
- increased review variability between batches,
- higher sensitivity to personnel availability and experience.

The economic impact is not only increased labour cost but increased **operational fragility** at critical points in the supply chain.

3.5 Legal and Compliance Risk Exposure

From a legal and regulatory perspective, batch release is performed under personal and organisational responsibility, often based on **retrospective reconstruction** of events.

Per-batch analysis shows that where readiness is reconstructed rather than continuously evaluated:

- audit remediation effort increases,
- inspection responses rely more heavily on narrative explanation,
- and the organisation’s defensive position in client or regulatory disputes is weakened.

The absence of a time-resolved, structured compliance trace increases both the **probability and impact** of high-severity compliance events. Economically, these events dominate cost exposure, even if they occur infrequently.

3.6 Why Existing Automation Has Not Solved This

Pharma 4.0 initiatives have improved execution efficiency and data availability, but they have **not altered the timing of compliance evaluation**. Evidence is still consolidated retrospectively, and release readiness is still inferred at the end of the process.

As a result:

- automation reduces execution variance,
- but increases the volume and complexity of evidence reviewed at release,
- concentrating cost, risk, and uncertainty at the same bottleneck.

Per-batch analysis shows that the dominant economic drivers of release inefficiency are:

- late discovery of readiness blockers,
- retrospective compliance reconstruction,
- and workload concentration at release.

These drivers cannot be addressed by further automation of manufacturing execution alone.
They point to the need for a mechanism that evaluates **release readiness continuously**, as execution unfolds.

4. ACTA Concept

4.1 ACTA in one sentence

ACTA is a **formal, rule-based compliance execution layer** that runs in parallel to manufacturing, continuously evaluating release readiness without controlling production or making GMP decisions.

4.2 Core Idea

Traditional batch review treats compliance as a retrospective activity: manufacturing is completed first, and documentation, deviations, and approvals are later assembled and interpreted to determine whether a batch can be released. This approach concentrates uncertainty, workload, and risk at the end of the process.

ACTA inverts this timing without changing authority.
In ACTA, **compliance is represented as an executable system** that evaluates regulatory and quality requirements as manufacturing and documentation events occur. Each relevant event—such as completion of a process step, recording of an in-process control result, application of a signature, or change in deviation status—updates the compliance state of the batch in real time.

As a result:

- required evidence is generated and checked **during execution**,
- dependencies between steps, deviations, and approvals are explicit,
- and release readiness evolves as an observable state rather than a late reconstruction.

This does not automate decisions. It ensures that, when review occurs, the compliance state is already structured, traceable, and explainable.

4.3 Petri Nets

ACTA uses Petri-net–based models to represent compliance logic because they provide properties that are directly aligned with regulatory expectations. Petri nets are used as an internal modelling formalism to ensure deterministic, bounded behaviour of the compliance logic; their structure is not exposed, relied upon, or interpreted in GMP use.

A formal specification of the compliance model exists as a separate technical artefact and is available for academic review if required.

Concurrency

Manufacturing and documentation activities occur in parallel. Documentation completeness, in-process controls, and deviation handling are independent obligations that must be satisfied concurrently, not sequentially. Petri nets natively represent parallel paths and synchronisation points, avoiding the linear “checklist” limitations of traditional batch review models.

Determinism

Given the same sequence of events and inputs, the same compliance evaluations occur and the same readiness outcome is produced. This predictability is essential for inspection credibility and for defending decisions long after execution. Petri nets provide an explicit structure in which transitions fire only when defined conditions are met, ensuring deterministic behaviour.

Formal Guarantees (Liveness, Boundedness, WCET)

Petri-net–based models allow formal verification of key system properties:

- *Liveness*: the compliance evaluation cannot stall indefinitely; it always progresses toward a defined outcome.
- *Boundedness*: the number of states and evidence objects remains finite and controlled.
- *Worst-Case Execution Time (WCET)*: the maximum time required to evaluate compliance logic is known and bounded.

Since regulators do not accept systems whose behaviour can grow without limits, lead to deadlock situations, or become unpredictable under load conditions, the use of ACTA ensures that conformity assessment remains verifiable, explainable, and operationally safe.

ACTA evaluates compliance logic, not the manufacturing process itself.
Tokens represent the **state of compliance**, not product quality.
Manufacturing systems remain validated and authoritative; ACTA operates alongside them as a structured observer and evaluator.

5. Operational Adoption Path

ACTA is designed for **progressive adoption**, allowing CDMOs to realise operational insight early while controlling regulatory exposure. The phases defined below are not aspirational; they reflect how computerised systems are realistically introduced, qualified, and trusted in GMP environments.

5.1 Phase 1 — Shadow Evaluation (The Pilot)

The Phase-1 pilot is intentionally implemented as a **shadow compliance evaluation**. In this mode, ACTA operates in parallel to manufacturing and quality systems without influencing them.

Operational characteristics

- **Read-only data usage**
  ACTA evaluates batch-record data that are synthetic and anonymised. No original GMP records are modified, generated, or overwritten.
- **No live system integration**
  There is no technical connection to production, EBR, LIMS, QMS, or MES systems. Data ingestion is offline or asynchronous, ensuring complete isolation from validated environments.

- **No computer system validation burden**
  Because ACTA outputs are not relied upon for GMP decisions and no validated systems are impacted, Phase-1 operation does not require Annex 11 lifecycle validation. This enables rapid evaluation without regulatory commitment.

Purpose of Phase 1

Phase 1 is not a proof of technology alone; it is a **proof of operational relevance** under controlled conditions.

Its objectives are to:

- **Demonstrate compliance logic**
  Show that GMP-relevant rules, dependencies, and conditions can be modelled explicitly and evaluated deterministically across realistic batch scenarios.
- **Surface release-readiness blockers early**
  Identify documentation gaps, unresolved deviations, or missing approvals *before* formal batch review, even though no action is enforced.
- **Train QA thinking**
  Provide QA and QP stakeholders with a structured, transparent view of release readiness as a state that evolves during execution, rather than a conclusion reached at the end.

Phase 1 does not simulate production control and does not aim to automate decisions. Its value lies in demonstrating that **release readiness can be made observable, structured, and explainable** without touching GMP authority or validated systems.

By design, Phase 1 de-risks and not delays any future move toward qualified operational use.

5.2 Phase 2 — Qualified Read-Only Decision Support

Phase 2 represents the transition from exploratory evaluation to **controlled operational use**. In this phase, ACTA becomes a **qualified, read-only decision-**

support system within the quality system landscape, while remaining strictly non-authoritative.

Operational characteristics

- **Read-only integration with live GMP systems**
  ACTA is connected in read-only mode to validated systems such as EBR, QMS, and LIMS. It consumes live execution, documentation, and deviation data but does not write back, control workflows, or generate official GMP records.
- **Standard computer system validation (CSV)**
  ACTA is introduced under a conventional, risk-based Annex 11 validation lifecycle, including User Requirements Specification (URS), Installation Qualification (IQ), and Operational Qualification (OQ). Validation scope is limited to ACTA's declared role as a supporting system, with clear boundaries and interfaces.
- **Explicit QA use of ACTA outputs**
  In Phase 2, ACTA outputs are formally used by QA as part of batch record review. This includes structured visibility of release-readiness state, identification of open dependencies, and traceable linkage between evidence, deviations, and readiness impact. ACTA becomes an accepted input into QA review, not an informal observation tool.
- **Non-authoritative by design**
  ACTA does not trigger GMP actions, enforce holds, or influence system states. It provides information, not decisions. Final judgment, approvals, and batch disposition remain exclusively with QA and the Qualified Person.

Regulatory positioning

In this phase, ACTA operates fully within established regulatory expectations for computerised systems that support GMP activities. Its deterministic, explainable logic and read-only integration ensure that human responsibility is preserved while improving review quality and predictability.

Operational value

Phase 2 shifts batch review from a late, reconstructive exercise to an informed confirmation of an already-evaluated state. Release delays are reduced not by accelerating decisions, but by **eliminating late discovery of missing or blocking elements**.

5.3 Phase 3 — Inline Compliance Evaluation

Phase 3 represents the mature operational deployment of ACTA within a GMP environment. In this phase, compliance evaluation is performed **during execution**, using validated, controlled interfaces to manufacturing and quality systems, while legal authority and responsibility for batch release remain fully human and unchanged.

Operational characteristics

- **Validated, execution-time evaluation**
  ACTA evaluates compliance conditions as manufacturing, documentation, and quality events occur. Interfaces to EBR, QMS, and LIMS operate under validated conditions consistent with Annex 11 requirements. Compliance logic executes deterministically and within defined performance bounds, ensuring predictable and inspectable behaviour during live operation.
- **Continuous release-readiness visibility**
  Release readiness is continuously updated as evidence is generated, deviations are opened or closed, and approvals are recorded. At any point during execution, QA can see whether a batch is progressing toward a releasable state, conditionally blocked, or structurally prevented from release. This visibility enables early intervention without enforcing automated action.
- **Human release authority unchanged**
  ACTA does not release batches, impose holds, or substitute for QA or Qualified Person judgment. The formal batch release decision remains a discrete legal act performed retrospectively by authorised personnel. ACTA's

role is to ensure that this decision is taken against a **fully transparent and already-evaluated compliance state**, not a reconstructed one.

- **Strongest possible inspection narrative**
  Phase 3 provides inspectors with a coherent and defensible story: compliance obligations are evaluated continuously, exceptions are visible when they occur, dependencies are explicit, and release is confirmed and not improvised at the end of execution. This strengthens inspection outcomes without altering GMP responsibility or decision rights.

The pilot does not bypass validation; it de-risks it.
Each adoption phase incrementally increases operational relevance while reducing uncertainty for QA, IT, and regulators. Validation is introduced only when scope, behaviour, and value are already understood.

Outcome of the Operational Adoption Path

Together, the three phases define a **controlled, regulator-aligned progression**:

- Phase 1 proves logic and relevance without risk
- Phase 2 introduces qualified decision support under CSV
- Phase 3 embeds continuous compliance evaluation while preserving full human authority

This progression resolves the tension between innovation and compliance by ensuring that ACTA becomes operationally meaningful **before** it becomes operationally critical.

6. Reference CDMO Manufacturer Profile

To ground the project in operational reality, we used a **synthetic but representative EU CDMO profile**. The profile is intentionally unexceptional. To ensure that conclusions drawn from the pilot can be transferable to real manufacturing environments, our model uses common operating conditions rather than best-case or edge-case scenarios.

6.1 Organisational profile

The reference manufacturer is a mid-size EU-based Contract Development and Manufacturing Organisation producing finished medicinal products for multiple marketing authorisation holders. Quality oversight is centralised, with a shared QA/QP function responsible for batch release across several clients and product lines.

6.2 Manufacturing scope

Manufacturing is focused on **oral solid dosage forms**, including tablets and capsules, produced in campaign-based operations on shared equipment trains. The physical process flow is largely standardised, while product-specific and client-specific requirements are reflected in documentation and control parameters.

Batch record structure

Each client operates under its own approved Master Batch Records (MBRs). While unit operations may be identical across products or strengths, acceptance limits, sampling frequencies, in-process controls, and documentation requirements vary. As a result, compliance complexity arises not from manufacturing diversity, but from **MBR parameterisation and documentation obligations**.

Documentation landscape

The documentation environment is hybrid. Core manufacturing steps and some in-process controls are recorded electronically, while other records, signatures, and deviation documentation remain paper-based or semi-electronic. Quality data are distributed across EBR components, LIMS, and QMS systems, with no single system providing an integrated view of release readiness.

Operational implications

In this setting, batch release is rarely delayed by manufacturing failures alone. Delays are more commonly driven by:

- incomplete or inconsistent documentation,
- unresolved deviations or investigations,
- and late discovery of client-specific requirements.

This profile reflects the **common operating conditions** under which batch review and release readiness must be managed.

6.3 Purpose of this reference profile

The intent is not to simulate complex or atypical scenarios, but to anchor the project in a context that QA, QP, and manufacturing stakeholders will immediately recognise. If ACTA provides value under these ordinary conditions, it can reasonably be expected to do so in more complex environments.

Below is **Section 6**, written to **lock scope tightly**, eliminate ambiguity, and prevent scope creep during review or inspection.
This section should reassure both QA and IT that the pilot is **controlled, finite, and intentional**.

7. Scope of the Phase-1 Pilot

The Phase 1 pilot project is intentionally limited to assessing **readiness for release**, rather than batch production or disposal. The scope of work reflects activities that significantly impact batch testing results but are completely separate from actual GMP operations.

7.1 Included in Scope

Batch record completeness

The pilot evaluates whether required batch record elements are present, complete, and internally consistent. This includes verification of mandatory documentation steps, signatures, timestamps, and required cross-references. The objective is to surface gaps or omissions that would later block or compromise integrity of batch review, without modifying original records.

In-process control (IPC) evaluation

IPC results are assessed against defined acceptance criteria as recorded in the applicable Master Batch Record. The evaluation is limited to interpretation of recorded results and their compliance status; no control actions are triggered, and no limits are enforced by the system.

Deviation lifecycle tracking

The pilot tracks the status and progression of deviations relevant to batch release, including initiation, investigation, impact assessment, and closure. The focus is on identifying whether deviations are open, conditionally acceptable, or release-blocking at any given time, rather than managing deviation workflows.

Release-readiness state evolution

ACTA evaluates how the batch's readiness status evolves during execution as documentation is completed, IPC results are recorded, and deviations progress. Readiness is represented as a structured state that reflects dependencies and unresolved obligations, not as a release decision.

7.2 Explicitly Excluded by Design

Packaging

Secondary packaging, labelling, and serialisation activities are outside the scope of the pilot. These activities are intentionally excluded to avoid introducing additional regulatory complexity and system interfaces.

Process control

The pilot does not interact with manufacturing equipment, process parameters, or execution control systems. No process setpoints, alarms, or interventions are evaluated or generated.

Automated acceptance or rejection

The system does not accept, reject, or conditionally release batches. It does not apply holds, trigger quality actions, or substitute for human judgment. All acceptance decisions remain entirely outside the pilot scope.

Scope principle

The Phase-1 pilot is designed to answer a single question:
Can ***release readiness*** *be evaluated continuously, deterministically, and transparently using existing batch evidence, without touching GMP authority or validated systems?*
By tightly controlling scope, the pilot ensures inspection credibility while generating insights that are directly relevant to future qualified use.
Here is **Section 7**, written to clearly establish the **conceptual core** of the project while staying strictly within regulatory boundaries.
This section is critical: it explains *why* ACTA is useful without ever implying authority.

8. Release Readiness as a Continuous State

Batch release remains a separate legal decision, but the conditions under which a batch can be released do not arise instantaneously. They develop gradually as the manufacturing process progresses, documentation is completed, and quality issues are resolved. If we continue to view release readiness as a binary condition (ready or not ready), we will miss this reality and continue to operate in a model where release obstacles are discovered retrospectively.

8.1 Why Readiness Is Not Binary

Evidence accrues over time

During batch execution, evidence required for release is generated step by step: manufacturing records are completed, IPC results become available, deviations may be initiated or closed, and required approvals are applied.
At no point before execution process is complete is the full set of evidence become available. Release readiness therefore evolves gradually, not instantaneously.

Deviations change readiness dynamically

Deviations introduce uncertainty that directly affects release readiness. An open deviation may temporarily block release, become conditionally acceptable pending investigation, or ultimately require batch rejection. The readiness state of a batch can therefore move forward or backward during execution, depending on how deviations and investigations progress. Binary end-of-batch assessments cannot capture this dynamic behaviour.

8.2 Readiness States

To formulate the objectives of a structured release readiness assessment, we recommend using clearly defined batch statuses:

- **Not Ready**
  The necessary evidence is lacking, or key obligations have not yet been

fulfilled. Release will not be possible if execution is completed with these events.

- **Conditionally Ready**
  Most requirements are satisfied, but one or more open items—for example, an ongoing deviation investigation—must be resolved before release can be considered.

- **Ready**
  All required documentation, results, and approvals are complete, and no unresolved conditions remain that would prevent batch release.

- **Blocked**
  One or more conditions are present that structurally prevent release, such as a critical unresolved deviation or failed acceptance criterion.

These states are descriptive, not prescriptive. They make the compliance status visible without imposing actions.

8.3 Advisory Nature of Readiness Evaluation

Release readiness evaluation is **observational, not conclusive**. The readiness state reflects the system's assessment of compliance conditions based on available evidence, but it does not trigger GMP actions or enforce outcomes.

QA and the Qualified Person retain full authority to:

- interpret evidence,
- assess context,
- exercise professional judgment,
- and make the final release decision.

ACTA's role is to support this judgment by making readiness explicit, traceable, and continuously updated—so that release becomes a confirmation of preparedness rather than a discovery process under time pressure.

8.4 Auditability and Chain of Evidence

Each compliance assessment conducted by ACTA leaves a structured, chronologically ordered chain of input data, state transitions, and results. These chains allow the compliance status of a batch to be reconstructed at any point in time, independent of individual memory or informal descriptions. This capability is valuable for regulatory inspections, internal audits, and investigations, as it allows for an objective reconstruction of how release readiness evolved during the manufacturing process.

If necessary, the stored records can also serve as **irrefutable, up-to-date evidence** of what was known, assessed, and unresolved at specific points in time, providing a substantiated record suitable for formal dispute resolution or litigation.

9. Deviation Scenarios

To demonstrate how release readiness behaves under realistic operating conditions, a limited set of representative scenarios is evaluated. These scenarios reflect **routine situations encountered in CDMO manufacturing**, rather than exceptional failures or complex edge cases.

The intent is not to exhaustively model all deviation types, but to show that release readiness can be evaluated **consistently and transparently** across common patterns of variation without expanding system scope.

9.1 Clean Batch (No Deviations)

This scenario represents a batch executed according to plan, with all required documentation completed, IPC results within defined limits, and no deviations initiated.

The purpose of this scenario is not to prove system performance under ideal conditions, but to establish a **baseline readiness trajectory**. Release readiness progresses steadily as evidence accrues and reaches a “Ready” state upon completion of execution. This confirms that continuous evaluation does not introduce artificial friction or false blockers when no issues are present.

9.2 IPC OOL Deviation

In this scenario, an in-process control result falls outside the defined acceptance limits, triggering a deviation during execution.

The deviation is investigated and either resolved or determined to be acceptable based on predefined criteria. Release readiness reflects this dynamically: the batch transitions from a progressing state to “Conditionally Ready” or “Blocked” depending on deviation status, and only returns to “Ready” once required actions are completed.

This scenario demonstrates that deviations influence readiness **as they occur**, rather than being discovered retrospectively at batch review.

9.3 Same Product, Two Strengths (MBR Parameterisation)

This scenario involves two strengths of the same product manufactured using an identical process flow. The physical execution steps are unchanged, but acceptance limits, sampling frequencies, and documentation requirements differ by strength as defined in the respective Master Batch Records.

The scenario demonstrates that release readiness evaluation is driven by **MBR parameterisation**, not by assumptions based on process similarity. Identical execution paths can therefore result in different readiness trajectories, reflecting real CDMO conditions where compliance complexity arises from documentation requirements rather than manufacturing variability.

9.4 Two Clients, Same Campaign

In this scenario, two clients’ products are manufactured within the same campaign using shared equipment and similar execution steps. Client-specific requirements apply to documentation, deviation handling, and approval workflows.

The scenario shows that release readiness is evaluated independently per batch and per client, even when execution overlaps. This reflects the CDMO reality that **shared manufacturing does not imply shared compliance outcomes**, and that readiness must remain client-specific.

9.5 Documentation Deviation (Annex 11 Relevance)

This scenario focuses on a documentation-related deviation, such as a missing or late electronic signature, inconsistent timestamps between systems, or incomplete record linkage.

Although no product quality issue is present, the documentation deviation temporarily blocks release readiness. The scenario demonstrates that readiness evaluation treats documentation integrity as a first-class release condition, consistent with Annex 11 and data-integrity expectations.

Purpose of these scenarios

These scenarios demonstrate that the release readiness behaves dynamically under normal operating conditions, with deviations influencing readiness in real time rather than retrospectively, and that common CDMO complexities can be handled without expanding scope or introducing control logic.

The scenarios are intentionally limited to preserve focus and inspection credibility. Their purpose is to prove **operational realism**, not to simulate worst-case manufacturing failures.

10. Pilot Deliverables and Outcomes

The Phase-1 pilot is designed to produce **tangible, reviewable outputs** that can be assessed by QA, IT, and management without committing to operational or regulatory change. The deliverables focus on insight, transparency, and learning, rather than system enforcement.

10.1 Core Deliverables

Release-Readiness Evaluation Model

A formally defined, executable model describing how release readiness evolves for the reference CDMO profile. The model captures required evidence, dependencies, and blocking conditions as explicit logic rather than narrative interpretation. This model is reviewable, explainable, and independent of live GMP systems.

Scenario-Based Readiness Traces

For each defined deviation scenario, the pilot produces time-ordered traces showing:

- which evidence was available at each point,
- how readiness state changed,
- and which conditions blocked or enabled progression.

These traces allow QA and inspectors to reconstruct the compliance state of a batch at any moment in time.

Readiness State Definitions and Criteria

A clear, agreed set of readiness states (Not Ready, Conditionally Ready, Ready, Blocked) with explicit entry and exit criteria. This creates a shared vocabulary between QA, operations, and management, reducing ambiguity in batch review discussions.

Deviation Impact Mapping

Structured mapping between deviation status and release readiness impact. The pilot demonstrates how deviations influence readiness dynamically, without managing deviation workflows or enforcing actions.

Inspection-Ready Documentation Package

A concise documentation set describing:

- system scope and boundaries,
- evaluated scenarios,
- assumptions and exclusions,
- and limitations of use.

This package is designed to be reviewable by auditors or inspectors as an explanatory artefact, not as a validated system dossier.

10.2 Operational Outcomes

Early Visibility of Release Blockers

The pilot demonstrates that release-blocking conditions can be identified during execution rather than at the end of the batch, even when no corrective action is taken.

Reduced Retrospective Reconstruction

By structuring evidence and readiness evolution over time, the pilot reduces reliance on late, manual reconstruction of compliance status during batch review.

QA Learning and Alignment

QA stakeholders gain experience working with readiness as a continuous state rather than a binary outcome. This supports internal alignment and prepares the organisation for future qualified use without procedural disruption.

Foundation for Risk-Based Validation Planning

Although Phase 1 does not require CSV, the outputs provide a concrete basis for defining validation scope, interfaces, and intended use should the organisation proceed to Phase 2.

10.3 What the Pilot Does *Not* Claim

For clarity, the pilot does not claim that reduction of release time as a guaranteed outcome, that there would be a replacement of existing review procedures, or release would become automated with regulatory acceptance.

Its value lies in **making the path to release transparent, explainable, and analysable**, not in changing authority or decisions.

10.4 Decision Enablement

At the conclusion of the pilot, stakeholders are equipped to make an informed decision on next steps based on evidence rather than assumption:

- whether continuous readiness evaluation provides operational value,
- whether QA would benefit from qualified decision support,
- and whether progression to Phase 2 is justified.

The pilot therefore functions as a **controlled decision-enabling step**, not a technology demonstration in isolation.

11. Criteria for Justified Progression to Phase 2

Progression from Phase 1 (Shadow Evaluation) to Phase 2 (Qualified Read-Only Decision Support) is **not automatic**. It is contingent on meeting clearly defined technical, operational, and regulatory criteria. These criteria ensure that any increase in system relevance is matched by proportional control and validation.

11.1 Technical Readiness Criteria

Progression is justified only if the Phase-1 pilot demonstrates that:

- **Compliance logic behaves deterministically**
  Identical inputs and event sequences produce identical readiness outcomes across repeated evaluations.
- **Readiness state transitions are explainable**
  Each change in readiness state can be traced to explicit evidence, conditions, or deviation status changes without reliance on narrative interpretation.

- **Execution remains bounded and predictable**
  Compliance evaluation completes reliably within defined time bounds and does not exhibit uncontrolled growth, deadlock, or state ambiguity.
- **Audit traces are complete and reconstructable**
  Time-ordered traces allow reconstruction of the compliance state of a batch at arbitrary points in time.

Failure to meet any of these criteria blocks progression.

11.2 QA and Operational Acceptance Criteria

Progression requires explicit confirmation from QA leadership that:

- **Readiness information is operationally meaningful**
  Outputs align with how QA already reasons about batch readiness and do not introduce contradictory or misleading signals.
- **No hidden authority shift is implied**
  ACTA outputs are clearly understood as advisory and do not create pressure to follow system conclusions without judgment.
- **Use improves review clarity, not complexity**
  The system reduces effort spent on reconstruction and reconciliation rather than adding parallel interpretation workload.
- **Deviation impact representation is appropriate**
  Readiness effects of deviations reflect existing QA practice and escalation logic.

If ACTA outputs are not trusted or not useful to QA, progression is not justified.

11.3 Regulatory and Compliance Criteria

Before entering Phase 2:

- **System boundaries must be explicitly defined**
  Inputs, outputs, interfaces, and limitations of use are documented and agreed.
- **Intended use is clearly scoped as decision support**
  There is no ambiguity regarding non-authoritative status.

- **Validation scope can be proportionately defined**
  URS, IQ, and OQ scope can be articulated without expanding into manufacturing control or batch disposition.
- **Data integrity principles are demonstrably upheld**
  Outputs support ALCOA+ requirements rather than replacing original records.

If validation scope cannot be clearly bounded, progression is deferred.

11.4 Economic and Risk Justification Criteria

Progression is justified only if Phase-1 results demonstrate that:

- **Release-readiness blockers are consistently surfaced earlier**
  Even without intervention, earlier visibility is observable across scenarios.
- **Retrospective reconstruction effort is reduced**
  QA review relies less on ad-hoc narrative explanation.
- **Risk concentration at release is measurably reduced**
  Fewer late surprises, fewer unresolved dependencies at batch completion.
- **The expected benefit justifies CSV effort**
  The anticipated reduction in operational and legal risk outweighs the cost of qualification.

If benefits remain hypothetical rather than observable, Phase 2 should not proceed.

11.5 Formal Progression Decision

Progression to Phase 2 requires a **formal, documented decision** confirming that:

- Phase-1 objectives were met,
- limitations and risks are understood,
- and increased system relevance is justified.

This decision itself becomes part of the quality record and demonstrates **controlled, risk-based system adoption**.

Key Principle

Progression is evidence-driven, not roadmap-driven.

Phase 2 is entered only when Phase 1 has proven both value and controllability.

12. ACTA Architecture (Focused, Not Overlong)

ACTA's architecture is designed to reflect a clear separation of concerns: manufacturing systems execute the process, while ACTA executes the **compliance evaluation** associated with that process. This separation is essential to preserve GMP authority boundaries while enabling continuous release-readiness assessment.

12.1 Dual-Track Model

ACTA operates alongside existing GMP systems using a **dual-track model**:

- **Manufacturing execution track**
  Manufacturing execution systems (MES/EBR), laboratory systems (LIMS), and quality systems (QMS) remain fully responsible for process execution, data generation, testing, deviation management, and approvals. These systems are validated, authoritative, and unchanged by ACTA.
- **Compliance execution track**
  ACTA operates as a parallel compliance execution layer. It evaluates whether required GMP obligations are being satisfied based on events and data produced by the manufacturing track. ACTA does not control, alter, or replace manufacturing or quality workflows; it observes and evaluates them.

This architectural separation ensures that compliance evaluation can evolve without introducing unintended control paths or authority shifts.

12.2 Token Logic

Within the compliance execution track, ACTA represents release readiness using a structured token-based logic.

- ### One batch → one compliance token

  Each manufacturing batch is associated with a single compliance token representing its current release-readiness state. The token does not represent product quality; it represents compliance status relative to defined obligations.
- ### Parallel obligations

  Compliance obligations—such as documentation completion, IPC acceptability, and deviation resolution—are evaluated in parallel. These obligations progress independently and converge only where required for readiness determination. This mirrors the reality of GMP compliance, where multiple conditions must be satisfied concurrently.

- Deterministic aggregation

  The overall readiness state of a batch is derived by deterministic aggregation of obligation states. Given the same evidence and event sequence, the same readiness outcome is always produced. This eliminates ambiguity and supports consistent QA interpretation.

The token logic provides a compact and inspectable representation of readiness without exposing internal model mechanics.

12.3 Formal Guarantees (Brief)

ACTA's compliance execution logic is designed to satisfy formal properties that are directly relevant to regulatory expectations.

- Liveness

  Compliance evaluation progresses toward a defined outcome and cannot stall indefinitely. Readiness state transitions occur whenever relevant evidence becomes available.

- Boundedness

  The number of compliance states and evidence relationships is finite and controlled. The system cannot accumulate unbounded or undefined states that would compromise review or reconstruction.

- Explainability

  Every readiness state and state transition can be explained in terms of explicit conditions and evidence. Outputs are traceable and defensible without reliance on probabilistic inference or opaque logic.

These guarantees are inherent to the compliance model and ensure that ACTA behaves predictably, transparently, and safely within a GMP context.

Architectural boundary

ACTA's architecture enables continuous compliance evaluation **without becoming part of the manufacturing control system**. Manufacturing systems remain authoritative; ACTA remains evaluative. This boundary is preserved across all adoption phases and is central to regulatory acceptability.

12.4 Quality Evidence Obligation Stream (Release-Readiness Gating)

In addition to documentation, IPC, and deviation obligations, ACTA may evaluate **quality evidence obligations** to determine their impact on release readiness. This stream assesses conformance of **recorded quality evidence** against predefined specifications and procedures; it does not perform quality disposition.

Scope of evaluation

The quality evidence obligation stream evaluates whether required quality evidence exists, is complete, and conforms to approved specifications as recorded in authoritative systems. Typical inputs include:

- **Raw material acceptance evidence**
  - Presence and completeness of COA
  - Identity testing performed and recorded
  - Assay/purity results within specification
  - Microbiological results where applicable
  - Supplier qualification status recorded
- **QC testing evidence**
  - Required test panels performed
  - Results recorded and attributable
  - OOS/OOT events correctly linked to deviations and investigations
  - Investigation status (open/closed/acceptable) reflected from QMS

Rule framing (deterministic and evidence-driven)

Rules are explicit, versioned, and bound to approved specifications and procedures. ACTA evaluates *conformance of recorded results*, not predicted quality or inferred acceptability. There is no adaptive or probabilistic logic.

Readiness impact mapping

Quality evidence outcomes affect readiness states deterministically:

- **Blocked**
  Critical quality evidence recorded as nonconforming (e.g., failed identity or assay), or required evidence absent after the defined point of obligation.
- **Conditionally Ready**
  Quality evidence pending (e.g., test performed, result not yet available) or investigation open with defined next steps.
- **Ready**
  All required quality evidence recorded as conforming, with no unresolved investigations impacting release.

Authority boundary

ACTA does not accept or reject materials, does not release or reject batches, and does not execute quality workflows. Deviation handling, investigations, and final disposition remain entirely within QC/QA/QP authority and the QMS. ACTA's role is limited to **reflecting the readiness impact** of recorded quality evidence.

Auditability and traceability

All evaluations produce time-ordered traces linking evidence, rules applied, and readiness state transitions. These traces support reconstruction of readiness at any point in time for audits, inspections, and investigations.

Adoption alignment

- *Phase 1:* Evaluated using synthetic or copied quality data.
- *Phase 2:* Read-only integration with LIMS/QMS under CSV as decision support.
- *Phase 3:* Continuous, validated evaluation as results are recorded, with unchanged human release authority.

13. Human Authority Model (Stability Argument)

ACTA is designed to **stabilise existing GMP authority**, not redistribute it. All roles, responsibilities, and legal accountabilities remain exactly as defined in current GMP practice. ACTA introduces no new decision-makers and removes none.

13.1 Human Roles and Responsibilities

Role	Core Responsibility	Authority Boundary
Operator	Executes manufacturing steps, performs in-process actions, records data and observations	No authority to release or disposition; responsible for accurate and timely data entry
Supervisor	Oversees execution, ensures procedural adherence, addresses immediate execution issues	May intervene operationally; no authority to release
Quality Assurance (QA)	Reviews batch records, evaluates deviations, ensures GMP compliance	Authority to assess compliance status and recommend disposition
Qualified Person (QP)	Performs final batch release decision under legal responsibility	Sole authority to release or reject batch

These roles are unchanged by ACTA. No authority is delegated, shared, or automated.

13.2 ACTA's Role in Relation to Human Authority

ACTA operates strictly as a **supporting system**, with three defined functions:

- ### Evidence structuring

  ACTA organises existing GMP evidence—documentation status, IPC results, deviation states, and quality evidence—into an explicit, time-ordered structure. It does not create new GMP records or replace authoritative systems.

- ### Early visibility

  ACTA makes release-readiness conditions visible as they evolve during execution. Potential blockers are surfaced when they arise, rather than discovered retrospectively at batch review.

- ### Decision support only

  ACTA provides structured information to support human review. It does not approve, reject, hold, or disposition batches. Its outputs are advisory and contextual, not dispositive.

13.3 Stability Argument

The stability of GMP authority is preserved because:

- ACTA has **no write access** to manufacturing or quality systems.
- ACTA outputs are **non-binding** and explicitly advisory.
- All formal decisions remain **human, discrete, and retrospective**.
- Legal responsibility remains clearly assigned to defined roles.

By improving visibility without altering authority, ACTA reduces pressure on human decision-makers while strengthening the defensibility of their decisions.

Key principle

ACTA does not change *who decides*.

It changes *how well they can see*.

14. Economic & Operational Rationale (CDMO Perspective)

The economic value of ACTA does not arise from automating batch release, but from **reducing uncertainty, rework, and delay in the path to release**. For CDMOs operating under multi-client, campaign-based conditions, these effects accumulate at scale and materially affect margin, cash flow, and operational stability.

14.1 Release Latency Costs

In CDMO operations, batch release latency is a recurring cost driver. Even when manufacturing completes as planned, batches frequently remain unreleased due to unresolved documentation items, deviation status ambiguity, or late discovery of missing evidence.

In **Phase 2 and Phase 3**, ACTA reduces release latency by:

- surfacing release blockers during execution rather than after completion,
- enabling corrective actions while the batch is still operationally “close,”

- transforming batch release from a discovery exercise into a confirmation step.

The benefit is not faster decision-making, but **fewer avoidable idle days between batch completion and release**.

14.2 Deviation Investigation Cost

Deviation investigations consume disproportionate QA effort, particularly when deviations are recognised as release-relevant late in the batch lifecycle. Late recognition expands investigation scope, increases review cycles, and prolongs batch holds.

By continuously evaluating the readiness impact of deviations:

- Phase 2 enables QA to prioritise investigations based on release relevance.
- Phase 3 enables earlier escalation of deviations that will structurally block release.

This leads to **lower investigation churn**, fewer late escalations, and more proportionate use of QA resources.

14.3 Working Capital Impact

Unreleased finished goods represent immobilised working capital. For CDMOs, this impact is magnified by:

- delayed invoicing,
- extended storage and handling,
- and reduced manufacturing flexibility for subsequent campaigns.

ACTA improves working-capital efficiency indirectly by:

- reducing the duration batches remain in a “ready but unreleased” state,
- improving predictability of release timelines,
- enabling more accurate planning of campaign transitions.

These effects become tangible only once ACTA outputs are operationally used (Phase 2) and continuously updated (Phase 3).

14.4 QA Workload Smoothing

Traditional batch review concentrates QA effort into narrow release windows, creating workload spikes, review variability, and dependency on informal knowledge. This concentration increases both operational risk and staff fatigue.

ACTA redistributes review effort across the execution timeline:

- readiness evaluation occurs incrementally,
- issues are addressed when they arise,
- final review effort is reduced and more consistent.

In Phase 2, ACTA supports QA review planning.

In Phase 3, it stabilises QA workload structurally.

This smoothing effect improves review quality **without increasing headcount** or altering authority.

14.5 Cumulative Value Across Phases

- **Phase 1** demonstrates feasibility and insight, but does not deliver economic benefit directly.
- **Phase 2** delivers measurable value through earlier visibility, prioritisation, and reduced release surprises.
- **Phase 3** delivers structural value by embedding continuous readiness evaluation into routine operations.

The economic rationale therefore strengthens as ACTA moves closer to operational relevance—without ever crossing regulatory boundaries.

Summary

ACTA does not reduce cost by replacing people or decisions.

It reduces cost by **removing late uncertainty**, **preventing avoidable delays**, and **making compliance effort predictable**.

For CDMOs, this translates into:

- more reliable release timelines,
- lower deviation escalation cost,
- improved working-capital efficiency,
- and more sustainable QA operations.

15. Pilot Deliverables

The Phase-1 pilot is designed to produce **tangible, reviewable artefacts** that can be assessed independently of any decision to proceed to operational deployment. The deliverables focus on transparency, explainability, and organisational learning rather than system enforcement.

15.1 Inspection-Ready Reference Dossier

A structured reference dossier is produced documenting:

- the scope and boundaries of the pilot,
- evaluated scenarios and assumptions,
- defined readiness states and criteria,
- and limitations of use.

This dossier is written in inspection-appropriate language and is suitable for internal audits, regulatory discussions, or innovation briefings. It does not constitute a validation package and is not relied upon for GMP decisions.

15.2 Demonstrable Compliance Model

The pilot delivers a formally defined compliance model representing how release readiness evolves across typical CDMO manufacturing scenarios. The model is deterministic, explainable, and scenario-driven.

It demonstrates that:

- GMP obligations can be represented explicitly,
- readiness states can be evaluated continuously,
- and compliance reasoning can be reconstructed objectively.

The model is demonstrable without exposing internal implementation details or mathematical formalism.

15.3 Reusable QA Training Artefact

Pilot outputs are suitable for reuse as a **QA training and alignment artefact**.

Scenario-based readiness traces allow QA teams to explore:

- how deviations affect readiness over time,
- why late discovery increases release risk,
- and how readiness differs from release decisions.

This supports shared understanding across QA, QP, and operations without changing procedures or responsibilities.

15.4 Basis for CSV Planning (If Desired)

While Phase-1 operation does not require computer system validation, the pilot outputs provide a concrete basis for **risk-based CSV planning** should progression be considered.

Deliverables that support this include:

- clearly defined intended use,
- explicit system boundaries and interfaces,
- and demonstrable, deterministic behaviour.

This enables informed assessment of validation scope, effort, and proportionality before any commitment is made.

Deliverable principle

The pilot produces artefacts that can be reviewed, challenged, and reused — not promises of performance or automation.

16. What This Pilot Enables Next

This pilot is intentionally limited in scope and authority. It does not mandate a next step, prescribe an implementation, or imply regulatory commitment. Its purpose is to **create a controlled option**.

Specifically, the pilot enables:

- **An informed decision on progression**
  Stakeholders can assess, based on evidence, whether continuous release-readiness evaluation provides sufficient operational and economic value to justify qualified use.

- **A bounded path to qualification**
  If desired, the pilot outputs provide a concrete and proportionate foundation for Phase 2 planning, including intended use definition, system boundaries, and CSV scoping—without retrofitting or redesign.
- **Earlier and safer engagement with regulators**
  The pilot supports transparent discussion with inspectors or authorities by clearly demonstrating what is evaluated, what is not, and how human authority is preserved.

This pilot is **not a promise of automation**, **not a commitment to deployment**, and **not a shortcut around validation**.

It is a deliberate step that allows CDMOs to explore a new compliance capability without operational risk.

Conclusion — Why This Pilot Matters

Pharma 4.0 has transformed manufacturing execution, but batch release remains constrained by retrospective review, late discovery of issues, and concentrated compliance risk. This gap is structural, not technical, and it cannot be resolved by further automation of production alone.

This pilot matters because it addresses that gap **without violating regulatory boundaries**. It demonstrates that release readiness can be evaluated continuously, deterministically, and transparently—while leaving all GMP authority unchanged.

By separating compliance evaluation from manufacturing control, and readiness from release decisions, the pilot offers a pragmatic way forward: one that respects how pharmaceutical manufacturing is regulated today, while preparing organisations for the complexity of tomorrow.

In that sense, the pilot is neither speculative nor disruptive.

It is a **measured response to a persistent problem**, designed to be examined, challenged, and—only if justified—taken further.

Appendices

Appendix A — Illustrative Compliance Model Overview

Purpose: Conceptual support

Audience: Technical reviewers, academic supervisors, innovation partners

Status: Informational, non-GMP

A.1 Purpose and Scope

This appendix provides a **high-level conceptual overview** of the compliance model used to evaluate release readiness in the Phase-1 pilot. Its purpose is to explain *what is represented* and *how obligations interact*—not to define system requirements, manufacturing control logic, or validated behaviour.

The model described here:

- evaluates **compliance obligations**, not process execution,
- operates independently of manufacturing control systems,
- and is not relied upon for GMP decisions.

All descriptions are illustrative and intentionally abstracted.

A.2 Conceptual Separation: Execution vs. Compliance

The compliance model is built on a clear separation between two domains:

- **Manufacturing execution**
  Physical processing, sampling, testing, documentation entry, deviation handling, and approvals are performed by existing GMP systems and human roles.
- **Compliance evaluation**
  The model evaluates whether required obligations have been satisfied based on recorded events and evidence produced by execution.

The model does not initiate actions, control workflows, or modify records. It evaluates *state*, not *behaviour*.

A.3 Types of Obligations Represented

Release readiness is modelled as the aggregation of multiple, parallel obligation streams. Each stream represents a category of GMP-relevant requirements that must be satisfied for a batch to be considered ready for release.

A.3.1 Documentation Obligations

Documentation obligations represent the requirement that:

- defined batch record elements exist,
- required entries are completed,
- signatures and timestamps are present,
- and records are internally consistent.

These obligations do not assess correctness of content, only completeness and presence as defined by approved procedures.

A.3.2 In-Process Control (IPC) Obligations

IPC obligations represent the requirement that:

- defined in-process checks are performed,
- results are recorded,
- and results conform to approved limits as documented.

The model evaluates recorded IPC outcomes and their readiness impact; it does not enforce limits or trigger actions.

A.3.3 Deviation Obligations

Deviation obligations represent the requirement that:

- deviations are initiated when required,
- linked appropriately to affected batches or results,
- and progress through defined lifecycle states (e.g. open, under investigation, closed).

The model reflects deviation status and its impact on readiness but does not manage deviation workflows.

A.3.4 Quality Evidence Obligations

Quality evidence obligations represent the requirement that:

- required quality evidence (e.g. raw material acceptance, QC test results) exists,

- results are recorded and attributable,
- and conformance or nonconformance is documented.

The model evaluates **conformance of recorded evidence** against predefined specifications. It does not perform quality disposition or acceptance.

A.4 Parallel Evaluation and Aggregation

All obligation streams are evaluated **in parallel**. Obligations progress independently as evidence becomes available. Release readiness is derived through deterministic aggregation of obligation states.

Conceptually:

- a batch cannot be considered ready if any critical obligation is unmet,
- unresolved or pending obligations result in a conditional readiness state,
- and readiness improves or degrades dynamically as obligations change state.

This reflects real GMP practice, where compliance is not linear and cannot be reduced to a checklist.

A.5 Readiness States (Conceptual)

The compliance model evaluates readiness using a small, finite set of descriptive states:

- **Not Ready** – required obligations not yet satisfied
- **Conditionally Ready** – pending or unresolved obligations remain
- **Blocked** – structural conditions prevent readiness
- **Ready** – all defined obligations satisfied

These states are **informational**, not dispositive, and do not imply release decisions.

A.6 Auditability and Reconstruction

Each evaluation produces a **time-ordered trace** of:

- evidence observed,
- obligations evaluated,
- and readiness state transitions.

This enables reconstruction of the readiness state of a batch at any point in time for audit, inspection, or investigation purposes, without reliance on retrospective narrative.

A.7 Explicit Exclusions

To avoid ambiguity, the compliance model does **not**:

- control manufacturing steps,
- enforce process parameters,
- initiate quality actions,
- replace QA or QP judgment,
- or perform automated batch disposition.

These exclusions are fundamental to the model's role and are preserved across all adoption phases.

A.8 Relationship to Implementation

While the compliance model may be implemented using formal methods to ensure determinism and boundedness, **implementation details are intentionally excluded** from this appendix. Mathematical formalism, internal representations, and execution semantics—if required—are maintained separately and are not necessary to understand or evaluate the pilot.

Appendix principle

This appendix explains *what the compliance model represents* and *how obligations interact*, not *how the system is built* or *how decisions are made*.

Appendix B — Illustrative Quality Evidence Rules (Non-Authoritative)

Purpose: Transparency of readiness logic

Audience: QA, CSV reviewers, inspectors (on request)

Status: Informational, non-authoritative

B.1 Purpose and Boundary

This appendix provides **illustrative examples** of how recorded quality evidence may influence **release readiness evaluation** within the ACTA compliance model. It is intended to support transparency and explainability of readiness logic for QA, CSV reviewers, and inspectors when required.

The rules presented here:

- evaluate **existence, completeness, and recorded conformance** of quality evidence,
- are deterministic and explicitly defined,
- and do **not** perform quality disposition, batch acceptance, or batch rejection.

All quality judgments and release decisions remain exclusively human.

B.2 Scope of Quality Evidence Considered

The examples below cover typical quality evidence relevant to release readiness in CDMO operations, including:

- raw material acceptance evidence,
- in-process and final QC test results,
- deviation and investigation linkage,
- and required quality approvals.

The list is illustrative, not exhaustive, and does not imply mandatory system behaviour.

B.3 Illustrative Rule Mapping (Evidence → Rule → Readiness Impact)

The table below demonstrates how recorded quality evidence may affect release readiness states.

It does not represent automated acceptance or rejection logic.

Input Evidence	**Rule Evaluated**	**Readiness Impact**
Raw material COA	COA exists, attributable to supplier and lot, and complete	Missing or incomplete → **Conditionally Ready**
Raw material identity test	Identity test performed and result = PASS	FAIL → **Blocked**
Raw material assay / purity	Recorded result within approved specification limits	Out of spec → **Blocked**

Input Evidence	Rule Evaluated	Readiness Impact
Raw material microbiology (if applicable)	Result within defined limits	Out of spec → **Blocked**
Supplier qualification status	Supplier recorded as approved	Not approved / missing → **Blocked**
In-process control (IPC) result	Result recorded and within MBR-defined limits	Out of limit → **Conditionally Ready** (pending deviation status)
Final QC test panel	All required tests performed and results recorded	Missing test → **Conditionally Ready**
Final QC test result	Result within specification	Out of spec → **Blocked**
OOS / OOT event	Deviation initiated and linked to result	No deviation initiated → **Blocked**
Investigation status	Investigation closed or formally acceptable	Open → **Conditionally Ready**
Documentation linkage	QC results linked to batch record	Missing linkage → **Conditionally Ready**
Required QA/QC approval	Approval recorded	Missing approval → **Conditionally Ready**

B.4 Interpretation of Readiness States

- **Blocked**
  A structural condition exists that prevents release readiness until resolved. This does not imply batch rejection.
- **Conditionally Ready**
  Required evidence or actions are pending. Release readiness may be achieved once conditions are satisfied.
- **Ready**
  All defined quality evidence obligations are satisfied, with no unresolved blocking conditions.

Readiness states are **descriptive**, not dispositive.

B.5 Governance and Determinism

- All rules are bound to **approved specifications, procedures, and master data**.
- Rule evaluation is **deterministic**: identical evidence produces identical readiness outcomes.
- No probabilistic, adaptive, or self-learning logic is applied.
- ACTA does not generate, modify, or approve quality records.

B.6 Regulatory Boundary Statement

This appendix illustrates how recorded quality evidence may influence release readiness evaluation. It does not introduce automated quality decisions, real-time release testing, or batch disposition logic. Final judgment and release authority remain exclusively with QA and the Qualified Person.

Appendix principle

This appendix exists to make readiness logic explainable — not to make decisions automatic.

Appendix C — Deviation Scenario Readiness Traces

Purpose: Behavioural illustration

Audience: QA, inspectors, auditors

Status: Demonstrative, scenario-based

C.1 Purpose and Use

This appendix illustrates how **release readiness evolves over time** in response to recorded events during batch execution. The scenarios are representative of routine CDMO operations and are intentionally limited in scope.

The traces demonstrate:

- how readiness transitions occur,
- how deviations affect readiness dynamically,

- and how readiness can be reconstructed retrospectively from recorded evidence.

The scenarios are **illustrative** and do not imply automated decision-making or GMP reliance.

C.2 Trace Structure

Each trace is presented as a **time-ordered sequence of events**, showing:

- recorded event or evidence,
- affected obligation(s),
- resulting readiness state.

Readiness states are descriptive and advisory.

C.3 Scenario 1 — Clean Batch (Baseline)

Context:

Batch executed according to plan with no deviations.

Time	Recorded Event	Readiness Impact
T0	Batch initiated	**Not Ready** (no evidence yet)
T1	Manufacturing steps completed and recorded	Progressing toward readiness
T2	IPC results recorded within limits	No blocking conditions
T3	Documentation completed and signed	All documentation obligations satisfied
T4	QC tests performed, results conforming	All quality evidence obligations satisfied
T5	All required approvals recorded	**Ready**

Observation:

Readiness evolves monotonically. No artificial blockers are introduced.

C.4 Scenario 2 — IPC Out-of-Limit (OOL) Deviation

Context:

An IPC result falls outside limits during compression.

Time	Recorded Event	Readiness Impact
T0	Batch initiated	**Not Ready**
T1	IPC result recorded OOL	**Conditionally Ready** (pending deviation)
T2	Deviation initiated and linked	Readiness maintained as conditional
T3	Investigation ongoing	**Conditionally Ready**
T4	Investigation closed as acceptable	Blocking condition removed
T5	All remaining obligations satisfied	**Ready**

Observation:

Readiness degrades and recovers dynamically as deviation status changes.

C.5 Scenario 3 — Documentation Deviation (Annex 11 Relevance)

Context:

Electronic signature missing at completion of a critical step.

Time	Recorded Event	Readiness Impact
T0	Manufacturing completed	Documentation incomplete
T1	Missing signature detected	**Conditionally Ready**
T2	Deviation initiated	Readiness remains conditional
T3	Signature applied and deviation closed	Condition resolved
T4	All obligations satisfied	**Ready**

Observation:

Non-quality documentation issues are correctly treated as release-relevant.

C.6 Scenario 4 — QC Test Failure with Correct Handling

Context:

Final QC test fails specification.

Time	Recorded Event	Readiness Impact
T0	QC test performed	Awaiting result
T1	Result recorded OOS	**Blocked**
T2	Deviation initiated	Remains blocked
T3	Investigation ongoing	**Blocked**

Time	Recorded Event	Readiness Impact
T4	Investigation closed (batch rejected)	Compliance obligations satisfied
T5	Batch disposition completed by QA/QP	**Ready (compliance)**

Observation:

Readiness reflects **compliance completeness**, not product acceptability.

Batch rejection does not contradict compliance readiness.

C.7 Reconstruction and Audit Value

For each scenario:

- readiness states are derived solely from recorded events,
- transitions are time-stamped and traceable,
- and the compliance state can be reconstructed at any point.

This supports:

- internal audits,
- regulatory inspections,
- and post-event investigations.

C.8 Boundary Clarification

These traces:

- do not trigger actions,
- do not replace batch review,
- and do not imply automated disposition.

They demonstrate **visibility and traceability**, not authority.

Appendix principle

These traces show *how readiness behaves*, not *how decisions are made*.

Appendix D — Formal Properties and Model Constraints

Purpose: Technical assurance

Audience: Technical evaluators, research partners

Status: Optional, non-GMP

D.1 Purpose and Boundary

This appendix summarises selected **formal properties and constraints** of the compliance model used in the Phase-1 pilot. Its purpose is to provide confidence that the model is **well-defined, predictable, and analytically constrained**, without introducing implementation detail or validation expectations.

The content of this appendix:

- is **informational only**,
- is **not required** to understand the pilot,
- is **not relied upon** for GMP decisions,
- and is **explicitly excluded** from operational and regulatory scope.

D.2 Determinism

The compliance model is designed to be deterministic.

For any given sequence of recorded events and evidence, the same readiness state transitions occur and the same readiness outcome is produced.

Determinism ensures that:

- readiness evaluation is repeatable,
- outcomes do not depend on timing artefacts or evaluation order,
- and conclusions can be defended consistently during audits or investigations.

No probabilistic, adaptive, or self-modifying logic is applied.

D.3 Liveness

The model satisfies a liveness constraint: evaluation progresses as evidence becomes available and cannot stall indefinitely due to internal model structure.

Conceptually, this means that:

- readiness always moves toward a defined outcome,
- unresolved conditions are visible rather than hidden,
- and evaluation does not deadlock due to competing obligations.

Liveness is a design property of the model structure, not a runtime performance guarantee.

D.4 Boundedness

The compliance model is bounded in scope and state space. The number of obligation states, readiness states, and evidence relationships is finite and explicitly defined.

Boundedness ensures that:

- the model cannot accumulate undefined or unreviewable states,
- evaluation remains tractable and inspectable,
- and long-running batches do not generate uncontrolled complexity.

This property is essential for reconstructability and long-term audit use.

D.5 Explainability and Traceability

Every readiness state and state transition can be explained in terms of:

- recorded evidence,
- explicit obligation status,
- and defined readiness rules.

The model produces time-ordered traces that allow reconstruction of readiness at any point during execution. Explainability is inherent to the model design and does not rely on post-hoc interpretation or statistical inference.

D.6 Relationship to Formal Methods

The compliance model may be implemented using formally defined modelling techniques to support the properties described above. Where such techniques are used, they serve to **constrain behaviour**, not to introduce complexity into operational use.

Mathematical formulations, proofs, or internal representations—if developed—are:

- maintained separately,
- not required to interpret pilot results,
- and not used for GMP decisions.

D.7 Explicit Exclusions

This appendix does **not**:

- define system requirements,
- describe manufacturing or quality workflows,
- specify validation criteria,

- or imply regulatory acceptance of formal methods.

Its inclusion does not alter the non-GMP status of the pilot.

Appendix principle

This appendix exists to demonstrate that the compliance model is *well-formed*, not to require that it be *formally proven* in operational use.

Appendix E — Phase-2 Readiness and Validation Scoping Notes

Purpose: Forward planning

Audience: QA leadership, IT, CSV teams

Status: Planning support only

E.1 Purpose and Boundary

This appendix outlines how **Phase-1 pilot outputs** may be used to **inform proportional validation planning** should progression to Phase 2 be considered. It is not a validation plan, does not authorise implementation, and does not imply regulatory commitment.

Inclusion of this appendix indicates **planning preparedness only**.

E.2 Intended Use (Phase 2 — Decision Support)

If progressed, ACTA's **intended use** in Phase 2 is limited to **read-only decision support** for QA batch record review and release readiness assessment.

- ACTA consumes data from validated systems (e.g., EBR, LIMS, QMS) **read-only**.
- ACTA outputs are **advisory**, not dispositive.
- No control actions, write-backs, or automated disposition are introduced.

Clear articulation of intended use is the primary determinant of validation scope.

E.3 System Boundaries and Interfaces

Phase-1 outputs enable precise boundary definition for Phase 2:

- **Inputs:** Read-only data feeds (events, results, statuses) from authoritative GMP systems.

- **Processing:** Deterministic evaluation of readiness based on explicit rules.
- **Outputs:** Readiness states, traces, and explanations presented for QA review.

Out of scope (by design):

- Manufacturing control
- Quality workflows execution
- Record creation or modification
- Batch disposition

These boundaries support a **contained CSV scope**.

E.4 Risk-Based CSV Considerations

Using Phase-1 artefacts, a risk-based CSV approach can be scoped proportionately:

- **URS (User Requirements Specification):**
  Derived from demonstrated Phase-1 behaviours (readiness states, explainability, audit traces).
- **IQ (Installation Qualification):**
  Focused on environment, access control, and interface configuration.
- **OQ (Operational Qualification):**
  Focused on deterministic behaviour, traceability, and correct readiness mapping under representative scenarios.

PQ may be limited or deferred depending on organisational policy, given the non-authoritative, decision-support role.

E.5 Data Integrity and Governance

Phase-1 traces inform data-integrity expectations for Phase 2:

- Preservation of ALCOA+ attributes
- Clear provenance of inputs
- Time-ordered, immutable traces
- Role-based access to outputs

Governance models can be defined without altering existing SOPs.

E.6 Acceptance Criteria for Phase-2 Entry (Reference)

Phase-1 deliverables that support Phase-2 readiness include:

- Demonstrated determinism and explainability
- Clear readiness state definitions and mappings
- Scenario-based traces evidencing reconstructability
- QA confirmation of decision-support usefulness
- Bounded and reviewable validation scope

Failure to meet these criteria would defer progression.

E.7 Explicit Non-Commitment Statement

Inclusion of these notes:

- does **not** constitute a validation plan,
- does **not** authorise system qualification,
- does **not** imply reliance for GMP decisions.

Progression to Phase 2 requires a **separate, formal decision** by QA and management.

Appendix principle

This appendix exists to make Phase-2 planning *possible*, not *inevitable*.