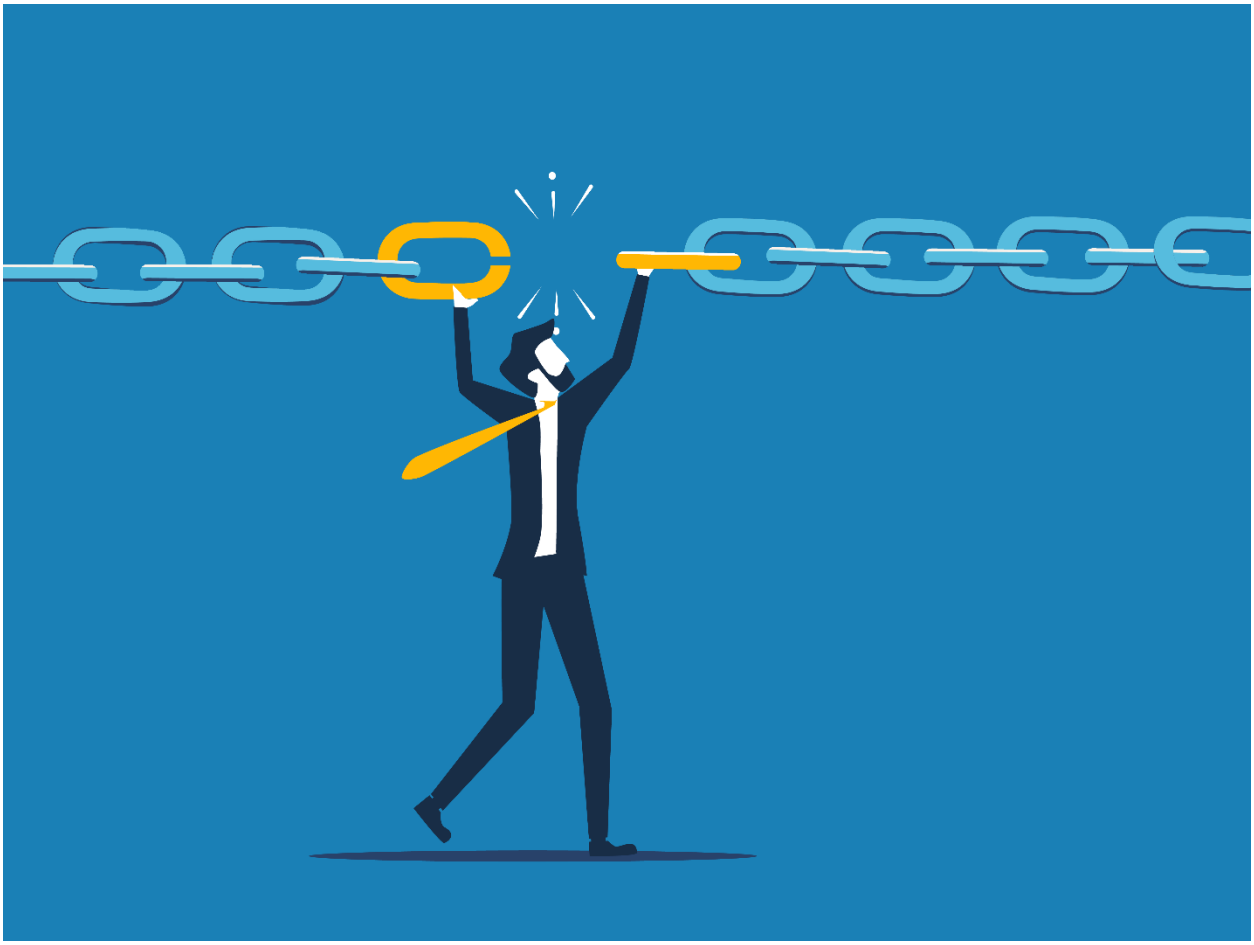
The Clinical-to-Commercial Quality Gap: Closing the Maturity Debt Before Pre-Approval Inspection



A cGMP Consulting White Paper on Phase-Indexed Quality Maturity for Cell and Gene Therapy and Biologics – October 20, 2026

Cell and Gene Therapy | Biologics | Quality Systems | Commercial Readiness

An educational resource for executive and technical leaders in FDA-regulated life sciences.

Executive Summary

Organizations moving from investigational to commercial manufacturing often discover, at pre-approval inspection, that their quality system matured more slowly than their product. The procedures that worked fine for early phase material, when batch volumes were small and the quality unit knew every operator by name, do not satisfy commercial phase expectations. The gap is rarely a failure of intent. It is the predictable result of a development timeline that rewards speed to clinic while the quality system quietly accrues debt because everyone's attention is somewhere else.

The exposure is sharpest in cell and gene therapy, where accelerated pathways can compress the interval from investigational new drug application to biologics license application dramatically, manufacturing complexity is high, batch sizes are small, and the process may still be evolving as the product approaches licensure. Reach a licensure decision on a compressed timeline and you may have built a commercial-scale ambition on a clinical-scale quality system.

The regulatory framework anticipates this progression. Current good manufacturing practice requirements apply to investigational drugs, with the FDA's phase 1 guidance recognizing that the approach appropriate for early phase material differs from what commercial scale requires, and ICH Q10 explicitly addressing the pharmaceutical quality system across the full lifecycle from development through discontinuation. Nobody expects a phase 1 system to meet commercial standards. The expectation is that the system matures as the product does, so that by the time a licensure application is filed, the quality system supporting it is a commercial one.

This paper examines the regulatory expectations across the lifecycle, the specific quality dimensions that most commonly lag, why pre-approval inspection is where the debt comes due, and the business cost of finding the gap late. It provides a phase-indexed maturity model, an implementation roadmap that ties quality investment to clinical milestones, and guidance on the governance that keeps commercial ambition from outrunning quality capacity. Plan maturity deliberately and you arrive at licensure with a quality system that supports the approval rather than threatening it.

Introduction

A quality system is built for the product it currently makes. Early in development, when a handful of batches support a small trial, procedures are lean, the organization is small, and informal communication does the work of formal process. That is appropriate, and mostly expected. Building a commercial quality system around a phase 1 product would burn resources the program cannot spare on something that will probably fail.

The trouble is that the product advances and the quality system does not automatically advance with it. Batch volumes rise, sites multiply, staff turn over, processes change, and the informal mechanisms that worked at small scale stop working. Meanwhile the organization's attention is on the clinical data, the financing, and the regulatory strategy. Quality system maturation is nobody's milestone, so it happens late, incompletely, or under the pressure of a looming inspection.

Regulators run into the result all the time. A facility that has manufactured clinical material successfully for years may operate a quality system whose investigation practices, change control, data governance, and process validation program would not survive commercial scrutiny. The organization has not done anything wrong in any specific instance. It has simply carried forward a system designed for a different stage. When the pre-approval inspection arrives, that mismatch becomes visible all at once.

This paper is for the quality, manufacturing, and executive leaders of organizations advancing toward commercialization, particularly in cell and gene therapy and biologics, where the timelines are most

compressed and the manufacturing complexity is highest. It focuses on how to index quality maturity to clinical phase so the debt is paid deliberately rather than discovered.

Industry Background

The regulatory framework has long recognized that quality expectations scale with product stage. Current good manufacturing practice requirements apply to investigational products, and the statutory obligation that drugs be manufactured in conformance with current good manufacturing practice does not exempt clinical material. At the same time, the FDA has acknowledged that the approach appropriate for phase 1 material differs from what later phases and commercial production require, and its guidance on current good manufacturing practice for phase 1 investigational drugs describes an approach suited to that stage.

ICH Q10 is explicit about the lifecycle. It describes the pharmaceutical quality system across pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation, identifying how the system's elements apply differently at each stage while staying a coherent whole. Its four elements, process performance and product quality monitoring, the corrective action and preventive action system, the change management system, and management review, are the dimensions along which maturity has to be measured. ICH Q8, Q9, and Q11 provide complementary frameworks for pharmaceutical development, quality risk management, and drug substance development.

Process validation follows the same lifecycle logic. The FDA's process validation guidance describes three stages: process design, process qualification, and continued process verification. That third stage, ongoing verification that the process stays in a state of control during commercial manufacture, is by definition a commercial activity, and an organization arriving at licensure without having designed it is arriving without a required element. For cell and gene therapy products, where process understanding may be less mature and batch data are limited, stage 3 design is both harder and more important.

Cell and gene therapy brings its own complications. Manufacturing may be patient-specific or use small batches, which limits the data available for statistical approaches. Processes may change during development as understanding improves, requiring comparability assessment. Accelerated regulatory pathways may compress the time available for quality system maturation. The FDA has issued guidance addressing chemistry, manufacturing, and control information for human gene therapy investigational new drug applications and potency assurance for cellular and gene therapy products, which reflects the specific challenges these products present.

Regulatory Landscape

The expectations governing the transition from clinical to commercial manufacturing come from good manufacturing practice regulation, lifecycle guidance, and the inspection practices that apply at licensure.

Current Good Manufacturing Practice Across Phases

The current good manufacturing practice requirements in 21 CFR Parts 210 and 211 apply to drug products including investigational products, and biologics are additionally subject to the requirements in 21 CFR

Parts 600 through 680. The FDA's guidance on current good manufacturing practice for phase 1 investigational drugs describes an approach appropriate to that stage, recognizing that manufacturing controls suited to early development differ from those required later. The important point is that this is a graduated expectation, not an exemption followed by a sudden obligation. As a product advances through phases, the expectation rises continuously, and the organization is responsible for meeting the expectation appropriate to its current stage.

The Pharmaceutical Quality System Lifecycle

ICH Q10 is the framework most directly applicable to the maturity question. It describes the pharmaceutical quality system across the product lifecycle and identifies how its elements apply at each stage, and its four elements furnish a natural maturity assessment structure. Process performance and product quality monitoring gets more demanding as commercial production begins. The corrective action and preventive action system has to handle a volume and complexity that early phase operations never generated. Change management has to govern changes to a licensed process rather than an evolving development process. And management review has to function as genuine governance rather than an informal conversation among people who see each other every day.

Process Validation and Continued Process Verification

The FDA's process validation guidance establishes the three-stage lifecycle, and its third stage, continued process verification, is a commercial obligation that has to be designed before commercial manufacturing begins. Organizations frequently complete stages 1 and 2 in preparation for licensure and treat stage 3 as a later concern, only to find that the program, the statistical approach, and the data infrastructure it requires were never built. For products with small batch numbers, designing a stage 3 program that can actually detect drift takes deliberate statistical thinking that cannot be improvised.

Pre-Approval Inspection

The pre-approval inspection is where the accumulated quality maturity debt becomes visible. Investigators assess whether the facility can manufacture the product reliably at commercial scale under a quality system that meets commercial expectations, and they examine the data supporting the application. The inspection tests readiness for commercial manufacture, not the history of clinical manufacture, which means a track record of successful clinical production does not by itself establish readiness. Findings at this stage can delay approval directly, which is why the timing of the debt's discovery matters as much as its size.

Cell and Gene Therapy Specific Considerations

The FDA has issued guidance addressing chemistry, manufacturing, and control information for human gene therapy investigational new drug applications, potency assurance for cellular and gene therapy products, and related topics. These documents reflect the distinctive characteristics of these products, including limited batch data, patient-specific manufacturing, evolving processes, and the analytical challenges of characterizing complex biological products. Organizations in this space have to reconcile accelerated development timelines with quality system expectations that do not accelerate to match.

> *The regulatory expectation is a quality system that matures alongside the product, not one that is adequate at phase 1 and transformed at licensure. Because pre-approval inspection assesses commercial readiness rather than clinical history, a strong record of clinical manufacturing does not offset a quality system that never scaled.*

Current Industry Challenges

The dimensions along which quality maturity most commonly lags are consistent across organizations, which makes them predictable and therefore manageable.

Investigation Practice at Scale

Early phase investigation can lean on institutional memory. The people who ran the batch are down the hall, the process is familiar, and root cause is often obvious. At commercial scale, with higher volumes, more staff, and turnover, investigation has to function as a system rather than a conversation. Organizations that never built rigorous investigation practice watch their deviation volume rise faster than their investigative capacity, and the quality of investigations fall precisely when regulatory scrutiny is highest.

Change Control for a Licensed Process

During development, change is constant and largely unconstrained, which is appropriate. After licensure, change is governed, requiring assessment against the filed process, comparability considerations, and potentially regulatory notification or approval. Teams accustomed to development-style change routinely underestimate this shift. The transition is cultural as much as procedural: people who have improved the process continuously have to adapt to a regime where improvement requires justification and, sometimes, permission.

Data Governance and Integrity at Volume

Data integrity expectations do not vary by phase, but the difficulty of meeting them rises with scale. Audit trail review before batch release, controlled system access with individual attribution, and retention of original records are demanding in a commercial environment generating far more data than a clinical one. Organizations that managed data adequately through diligence at small scale often lack the systems and processes required at commercial volume, and data integrity findings at pre-approval inspection are especially damaging because they call the application data itself into question.

Continued Process Verification

Stage 3 process verification is a commercial obligation frequently deferred until commercial manufacturing is imminent, at which point the program, the statistical approach, and the data infrastructure all have to be built under time pressure. For cell and gene therapy products with small batch numbers, designing a program that can detect drift with limited data requires statistical thinking that takes time to develop and validate. Treat stage 3 as a post-approval concern and you arrive at inspection without a required element.

The Compressed Timeline Problem

Accelerated pathways compress the interval available for quality system maturation without compressing the maturation required. An organization on a standard timeline has years to build commercial quality capability; one on an accelerated pathway may have a fraction of that, while facing higher manufacturing complexity. The result is a structural squeeze in which the fastest programs face the largest maturity gaps, and the acceleration that benefits patients creates the exposure that could delay their access.

Organizational Attention and Ownership

Quality system maturation is rarely anyone's milestone. Clinical milestones, financing milestones, and regulatory submission milestones have owners, deadlines, and visibility. Quality maturity has none of these, so it gets deferred by default rather than by decision. Organizations that do not make maturation an explicit, owned, milestone-linked program will find it deferred until the pre-approval inspection makes it urgent, which is the most expensive possible moment to address it.

Risks of Poor Implementation

The consequences of arriving at licensure with a clinical-phase quality system land at exactly the moment the organization can least absorb them.

Risk Category	Potential Consequence
Approval delay	Pre-approval inspection findings that delay licensure, postponing revenue and patient access while the organization remediates under time pressure.
Application integrity questions	Data integrity findings that call into question the manufacturing data supporting the application itself, extending well beyond a procedural observation.
Commercial launch failure	Inability to manufacture reliably at commercial scale after approval, producing supply interruptions at the moment of launch.
Emergency remediation cost	Quality system remediation compressed into the interval before or after inspection, at multiples of the cost of deliberate, phased investment.
Investor and partner confidence	Delays attributable to quality readiness rather than clinical or regulatory substance, which are particularly damaging to confidence because they were avoidable.
Patient access delay	For products addressing serious conditions on accelerated pathways, a quality-driven approval delay directly postpones patient access to therapy.

The timing of the exposure is what makes it distinctive. Quality maturity debt accumulates invisibly and comes due at a single, scheduled, high-stakes event. An organization can carry the debt for years with no apparent consequence, which reinforces the impression that the debt does not exist, and then meets its full weight at the inspection that decides whether the product reaches patients on schedule.

For cell and gene therapy organizations, the risk is compounded by the accelerated pathways that make these products commercially viable in the first place. A program that reaches licensure quickly on strong clinical data, only to be delayed by a quality system that never scaled, has converted its greatest advantage

into its critical vulnerability. The clinical acceleration regulators granted to speed patient access gets squandered by a quality gap the organization could have closed deliberately.

Best Practices

The organizing principle is to index quality maturity to clinical phase, making maturation an explicit, owned program tied to development milestones rather than a task deferred until inspection.

Build a Phase-Indexed Maturity Model

Define what quality maturity is required at each development phase, using the ICH Q10 elements as the structure: process performance and product quality monitoring, corrective action and preventive action, change management, and management review. The model should specify what each element looks like at phase 1, phase 2, phase 3, and commercial stage, so the organization can see where it stands and what remains. That converts an abstract worry into a measurable position and a defined gap.

Tie Quality Investment to Clinical Milestones

Because quality maturation lacks natural milestones, attach it to the ones that exist. Entry into pivotal trials, initiation of process qualification, and submission planning are all points at which specific quality capabilities should be in place. Linking maturation to these milestones gives it visibility, ownership, and a deadline, and it ensures the investment gets made when it is affordable rather than when it is urgent.

Design Continued Process Verification Early

Design stage 3 process verification during process qualification planning, not after approval. For products with small batch numbers, the statistical approach requires deliberate development, and the data infrastructure to support ongoing monitoring has to be built before commercial manufacturing begins. Designing stage 3 early also improves stage 2, because the questions ongoing verification has to answer inform what qualification should establish.

Mature Investigation Practice Ahead of Volume

Build investigation capability before the deviation volume that will test it arrives. That means establishing evidentiary standards for root cause, effectiveness verification that tests the failure mode, and the investigative capacity to handle commercial volume, while the organization still has time to develop the capability deliberately. Wait until deviation volume rises and you are building capability under the very pressure the capability was meant to relieve.

Transition Change Control Deliberately

Plan and communicate the shift from development-style change to governed change rather than letting it be discovered. Teams should understand when the transition happens, what it requires, and why, and the change control system should be capable of the comparability assessment and regulatory impact analysis a licensed process demands. Making the transition explicit reduces the cultural friction that otherwise produces either uncontrolled change or paralysis.

Close the Data Governance Gap Before It Scales

Because data integrity expectations do not vary by phase but the difficulty of meeting them rises with volume, establish the systems and processes for audit trail review, access control, and record retention before commercial volume arrives. Organizations that manage data through individual diligence at clinical scale should recognize that this approach does not survive contact with commercial volume, and should invest in systems that make integrity structural rather than dependent on attention.

Assign Ownership and Report Maturity

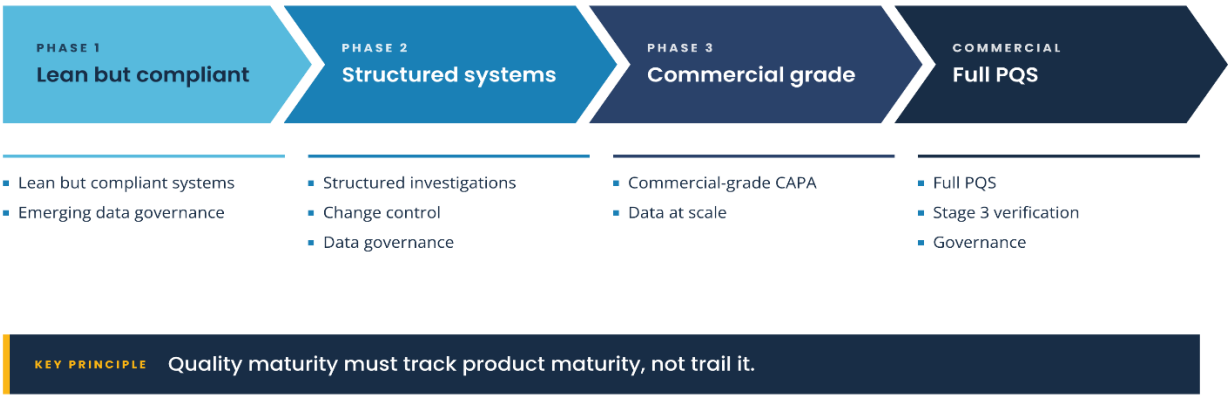
Quality maturity should have a named owner and should be reported to leadership alongside clinical and regulatory progress. When the executive team reviews program status, quality readiness should sit next to enrollment and submission timelines, so a maturity gap shows up as a program risk rather than a quality department concern. Governance that makes maturity visible is what keeps commercial ambition from outrunning quality capacity.

Implementation Roadmap

The roadmap below builds quality maturity in step with product advancement rather than in response to inspection.

FIGURE 1

Phase-Indexed Quality Maturity Progression



Step 1: Assess Current Maturity

Assess the quality system against the maturity appropriate to the product's current phase and against commercial expectations, using the ICH Q10 elements as the structure. Be honest about the gap, since the value of the exercise depends entirely on its candor.

Step 2: Define the Phase-Indexed Target

Define what each quality element must look like at each remaining phase and at commercial stage. This target state establishes what has to be built and when, converting a vague sense that the system needs work into a specific program.

Step 3: Map Gaps to Clinical Milestones

Attach each required capability to the clinical or regulatory milestone by which it must exist, giving maturation the deadlines and visibility it otherwise lacks. Prioritize capabilities with long build times, particularly data systems and process verification infrastructure.

Step 4: Build Investigation and Change Control Capability

Develop investigation rigor and governed change control ahead of the volume and constraint that will test them. Both are capabilities rather than documents, and both take time to develop through practice.

Step 5: Establish Data Governance at Scale

Implement the systems and processes that make data integrity structural rather than diligence-dependent, including audit trail review before release, individual attribution, and record retention adequate to commercial volume.

Step 6: Design and Implement Stage 3 Verification

Design continued process verification during qualification planning, including the statistical approach appropriate to the product's batch characteristics and the data infrastructure required to support it. Implement before commercial manufacturing begins.

Step 7: Prepare for Pre-Approval Inspection

Assess readiness against commercial expectations rather than clinical history, using mock inspection to test whether the system operates as claimed. Address findings before the inspection rather than explaining them during it.

Step 8: Govern and Sustain

Report quality maturity to leadership alongside clinical and regulatory progress, and sustain the system through commercial operations with management review that functions as genuine governance. Maturity is maintained, not achieved once.

Technology Considerations

Technology is central to closing the maturity gap, because several dimensions of commercial quality are infeasible at scale without it.

Electronic quality management systems structure investigation, change control, and management review at commercial volume, and they enforce discipline informal processes cannot sustain as an organization grows. Organizations that manage quality through documents and spreadsheets during clinical development frequently find that approach untenable at commercial scale, and the transition to a structured system takes longer than expected because it involves process design, not just software deployment.

Data infrastructure supports both integrity and process verification. Systems that capture manufacturing and laboratory data with appropriate controls, audit trails, and attribution make data integrity structural,

while the same infrastructure supplies the data continued process verification requires. For cell and gene therapy products with limited batch data, the analytical capability applied to that data matters more than its volume, and the infrastructure should support the statistical approaches the product's characteristics demand.

Manufacturing execution systems and electronic batch records cut the transcription errors and documentation gaps manual records produce, and they get more valuable as batch volume rises. For patient-specific therapies, systems that maintain chain of identity and chain of custody are essential rather than optional. Any computerized system supporting the quality system falls within the risk-based assurance expectations that apply to such software, and organizations should plan assurance alongside implementation rather than after it.

Future Outlook

The pressures that create the clinical-to-commercial gap are intensifying, not easing. Accelerated pathways keep compressing development timelines, and the cell and gene therapy pipeline keeps expanding, which means more organizations will face this transition on shorter timelines with more complex products. The structural squeeze between accelerated approval and unaccelerated quality maturation will hit more programs, not fewer.

Regulatory attention to this transition is likely to sharpen as the pipeline matures and more products reach licensure. As agencies accumulate experience with organizations arriving at pre-approval inspection carrying clinical-phase systems, their inspection focus will reflect that pattern. Expect the maturity question to be examined directly rather than encountered incidentally.

The organizations that navigate this well will treat quality maturity as a program with milestones, owners, and executive visibility rather than a task that happens when time permits. The maturity debt is entirely predictable, which makes it entirely manageable, and the difference between organizations that plan for it and those that discover it shows up where it matters most: in whether the product reaches patients on the schedule the clinical data earned.

How cGMP Consulting Can Help

Closing the clinical-to-commercial quality gap takes knowing what commercial expectations actually are, assessing honestly where an organization stands, and building capability on a timeline that fits the development program. cGMP Consulting works with cell and gene therapy, biologics, and pharmaceutical organizations advancing toward commercialization.

Our consultants assess quality system maturity against the expectations appropriate to a product's phase and against commercial requirements, using a structure grounded in ICH Q10 and the process validation lifecycle. We help organizations build phase-indexed maturity roadmaps that tie quality investment to clinical milestones, develop investigation and change control capability ahead of the volume that will test it, establish data governance that scales, and design continued process verification appropriate to the product's batch characteristics. We support pre-approval inspection readiness, testing whether the

system operates as claimed and addressing findings before an investigator does. For organizations on accelerated pathways, we help compress the maturation program without compromising the maturity.

Our approach is consultative and grounded in how pre-approval inspections actually proceed and what investigators examine. We aim to leave organizations with a quality system that supports their approval and their commercial operations, built deliberately rather than assembled under inspection pressure.

Conclusion

Quality maturity debt accumulates quietly and comes due at a scheduled, high-stakes moment. Organizations advancing from clinical to commercial manufacturing frequently carry a quality system built for a product they no longer make, and pre-approval inspection is where that mismatch becomes visible, at the point when remediation is most expensive and most consequential.

The dimensions that lag are predictable: investigation practice that relied on institutional memory, change control designed for a development process rather than a licensed one, data governance that depended on diligence rather than systems, and continued process verification treated as a post-approval concern. Because they are predictable, they are addressable, and the phase-indexed maturity model gives you the structure for addressing them deliberately.

The work is to make maturation an explicit program: define what maturity is required at each phase, tie the required capabilities to clinical milestones that already have owners and deadlines, build the capabilities that take longest first, and report maturity to leadership alongside clinical and regulatory progress. Organizations that do this arrive at licensure with a quality system that supports the approval. Those that do not arrive with a clinical-phase system, a commercial ambition, and an inspection that will find the difference.

> *If your organization is advancing toward commercial manufacturing and evaluating whether its quality system will meet commercial expectations, the experienced consultants at cGMP Consulting can help assess your current state, identify the maturity gaps, and develop a practical roadmap tailored to your development timeline. To start a confidential conversation, complete the Contact Us form at* cgmpconsulting.com/contact-us*.*

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