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# Maintaining Pharmaceutical Quality When Algorithms and Processes Change Together: A Lifecycle Framework for Artificial Intelligence–Enabled Process Control, Model Updating, and Knowledge Transfer in Pharmaceutical Manufacturing

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**ABSTRACT**

Artificial intelligence is entering pharmaceutical manufacturing through process models, soft sensors, adaptive process analytical technologies, digital twins, and increasingly direct links to advanced process control. These applications create a lifecycle problem that is insufficiently described when manufacturing-process change and algorithmic change are governed as separate maintenance events. A process may move beyond the conditions under which a model was calibrated or validated even when the algorithm itself is unchanged, while a model update may alter state estimation, predicted quality attributes, diversion decisions, or control actions despite unchanged equipment. This article develops a lifecycle account of pharmaceutical quality under such coupled change. It synthesizes evidence from continuous manufacturing, process analytical technology, digital twins, model-predictive control, machine-learning process models, and quality-system digitalization to examine how model applicability, measurement validity, control meaning, validation status, and process knowledge evolve together. The central argument is that the relevant object of lifecycle governance is the joint process–model state: the combination of the physical manufacturing condition, analytical interface, data lineage, model version, applicability domain, control linkage, and evidence supporting quality-relevant decisions. Quality is threatened when one component changes while the others are treated as stationary. The framework therefore treats revalidation and comparability as impact-based questions concerning whether a transition changes a quality-critical inference, action, or evidentiary assumption. This approach also makes knowledge transfer a quality function because process engineers, data scientists, quality units, and regulatory actors must preserve the reasoning that connects process evidence to model behavior and product disposition.

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## Introduction

Artificial intelligence in pharmaceutical manufacturing increasingly sits inside systems that observe, estimate, predict, or influence product and process quality. The resulting governance problem is broader than conventional software maintenance because the relevant models are often connected to physical unit operations, process analytical technology (PAT), soft sensors, digital representations, or control decisions. Risk-based analyses of pharmaceutical process models already emphasize that validation and lifecycle maintenance should be proportional to intended use and the consequences of model failure [1]. At the same time, recent assessments of machine learning in oral solid dosage manufacturing show growing use of data-driven models

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for process understanding and adaptive monitoring while identifying unresolved problems involving extrapolation, uncertainty, interpretability, data sufficiency, and transferability [2]. Together, these literatures suggest that the quality significance of an algorithm cannot be established from algorithmic performance alone. It depends on where the model sits in the manufacturing decision chain and on whether the process conditions that give its outputs meaning remain stable.

The manufacturing environment in which this problem arises is becoming progressively more interconnected. Industry 4.0 perspectives describe pharmaceutical production as moving toward integrated sensing, advanced computing, automation, and digitally coordinated operations; related work on AI–IoT integration and Quality by Digital Design extends that direction toward manufacturing systems in which process knowledge, analytical measurements, models, and control functions are increasingly connected [3-5]. Such integration creates opportunities for more responsive control, but it also strengthens dependency among components that were previously easier to evaluate separately. A change in material behavior can alter the input distribution presented to a model. A change in sensor location can alter the physical state represented by its measurements. A revised model can change the predicted process state that an advanced controller uses. A revised control policy can in turn modify the process trajectory from which subsequent data are generated.

Continuous manufacturing illustrates why these dependencies matter. Its implementation relies on strong process understanding, PAT, advanced control, and sufficiently well-characterized material and process dynamics [6]. Transfer of a marketed product from an established process into continuous direct compression requires preservation of product quality while the manufacturing configuration, flow behavior, and monitoring structure change [7]. Machine-learning models can also be used to predict blending performance and sensitivity to powder and process properties [8], while other learned relationships can translate in-process measurements into estimated tablet quality attributes that may support real-time release testing [9]. In such settings, the physical process and the analytical or computational representation of that process cannot be assumed to evolve independently. The more closely a model is linked to a quality-critical manufacturing decision, the more consequential that assumption becomes.

PAT provides much of the evidence infrastructure for these systems. Practical implementation frameworks for advanced process control emphasize that an analytical technology must be connected to a defined monitoring purpose, appropriate process integration, data interpretation, and ultimately the control task it is expected to support [10]. Broader reviews of PAT across pharmaceutical processing similarly show that real-time analytical information can contribute to monitoring and control across multiple unit operations [11]. However, a well-integrated measurement system does not guarantee that the associated model remains valid after process change. The model may have been trained or calibrated on a narrower operating range, a different material state, a different probe interface, or a different dynamic relationship among critical variables.

Digital-twin research makes the distinction between model construction and model validity particularly visible. In continuous direct compression, development of a high-fidelity digital twin has required explicit characterization of material behavior, selection of modeling assumptions, and calibration against process response [12]. Subsequent work on the same platform treated validation as a separate activity in which the calibrated representation was tested against relevant process behavior and disturbances [13]. This distinction is important for AI-enabled process control because lifecycle governance must ask more than whether a model was once calibrated successfully. It must determine whether the model remains an adequate representation of the process state that now exists and whether the decisions based on that representation remain justified.

The central question of this article is therefore how pharmaceutical quality should be maintained when algorithmic and manufacturing changes occur together or alter one another's meaning. The analysis focuses on models that participate in quality-relevant inference or control rather than on low-impact analytical tools whose outputs remain purely exploratory. The distinctive problem is the joint process–model state: the combination of physical process conditions, measurement interfaces, data transformations, model version and applicability domain, control relationships, validation evidence, and knowledge required to interpret a quality decision. The following sections first examine the reciprocal pathways by which physical and algorithmic changes interact, then define the evidence that must remain coherent across the AI lifecycle before an integrated process–model lifecycle account can be formulated.

*Coupled Algorithmic and Manufacturing Change*

The first form of coupling arises when a physical change modifies the conditions under which an algorithm operates. In continuous granulation, closed-loop Quality by Control approaches can compensate for disturbances by adjusting operating conditions in response to process behavior [14]. Yet the ability of a controller to remain effective depends on the range and structure of variability it encounters. In-silico assessment of model-predictive control in continuous direct compression has shown that robustness must be examined under stochastic process variability rather than inferred from satisfactory behavior under nominal conditions [15]. A manufacturing-process change can therefore become a model-validity problem even when no software has changed. New raw-material properties, different disturbance patterns, modified residence-time behavior, changed throughput, altered equipment configuration, or a wider operating region may create process states that were poorly represented during model development.

The reciprocal pathway is equally important. An algorithmic update can change the effective manufacturing-control strategy even when the equipment and nominal operating instructions remain unchanged. Data-driven modeling using dynamic mode decomposition with control has been embedded within model-predictive control for pharmaceutical granulation, demonstrating that a learned representation can directly determine how the controller interprets system dynamics and calculates subsequent action [16]. End-to-end digital-control concepts similarly depend on timely estimation of material state across connected

operations so that corrective action can be coordinated along the manufacturing line [17]. Machine-learning approaches are also being applied directly to real-time control of continuous granulation processes characterized by interdependent critical material attributes and process parameters [18]. When such a model is updated, the change is not confined to prediction accuracy. It may alter state estimation, disturbance interpretation, optimization behavior, set-point selection, or the timing and magnitude of corrective action. The quality significance of the update therefore depends on what changes in manufacturing behavior downstream of the model.

A third coupling pathway runs through the measurement layer. Machine-learning analysis of roller compaction demonstrates that nonlinear relationships among formulation properties, process parameters, and ribbon quality can be learned and interpreted to support fault prediction [19]. End-to-end monitoring studies in oral solid dosage development have likewise used in-line near-infrared spectroscopy at multiple interfaces to follow quality-relevant information through successive manufacturing stages [20]. In semi-continuous blending, NIR spectroscopy has been used to characterize blend uniformity under changing process conditions [21]. These approaches generate increasingly dense process information, but their value still depends on what physical state the analytical interface actually observes. Model-based integration of Raman spectroscopy into continuous liquid and semisolid manufacturing has shown that immersion conditions, flow characteristics, and material properties can affect the representativeness of the analytical measurement [22]. At the decision end of the chain, feed-frame NIR measurements have been linked to tablet-diversion strategies [23]. Thus, a change in probe geometry, measurement location, sampling dynamics, preprocessing, or analytical model can propagate into a different product-disposition decision without any mechanical change to the tablet press itself.

This measurement-to-action pathway is becoming more consequential as PAT moves from descriptive monitoring toward real-time quality control [24]. A control system that depends on estimated process state must account for the uncertainty and limitations of the underlying measurements. Data-reconciliation work in continuous tablet manufacturing has demonstrated how measurement uncertainty and process or material variability can influence the information available for active quality control [25]. Multivariate spectroscopic systems can simultaneously quantify several drug components during continuous processing [26], increasing the amount of quality information available in real time but also making the integrity of calibration, preprocessing, and signal interpretation central to the control strategy. A highly instrumented process is therefore not necessarily a more stable process–model system. It is a system in which the consequences of analytical-model drift may be transmitted more rapidly into quality decisions.

Transfer and previously uncaptured variability make this problem especially visible. A NIR-based potency-deviation method developed at laboratory scale has been applied at manufacturing scale while being challenged by raw-material, instrument, and process sources of variation [27]. Hybrid NIR and soft-sensor work in continuous direct compression has shown that variability not represented in the original calibration environment can produce prediction deviations and increase model-maintenance requirements [28]. Hybrid potency soft sensors can also produce real-time estimates that feed tablet-diversion or advanced-process-control functions [29]. The combined implication is that process transfer, site transfer, raw-material change, or operating-range expansion cannot be treated only as physical manufacturing events when model-generated estimates are part of control. They may alter the validity of the digital representation through which the changed process is being interpreted.

This reciprocal relationship defines the core lifecycle hazard. A process can change while its associated model remains technically unchanged, creating an apparently stable algorithm whose applicability has deteriorated. A model can change while the process hardware remains technically unchanged, producing different manufacturing decisions from the same nominal equipment configuration. A measurement interface can change while both the process equipment and model code appear unchanged, altering the data-generating mechanism that connects the two. Hidden quality drift becomes plausible whenever one component of this chain moves to a new state while the validation assumptions attached to adjacent components are carried forward without sufficient examination.

The practical distinction is summarized in **Table 1.** Its purpose is to separate superficially similar change events according to what actually changes in the process–model system and what that change can alter in the interpretation of pharmaceutical quality.

**Table 1.** Coupled change configurations that can alter the meaning of pharmaceutical process-control evidence.

| Coupled change configuration | Physical manufacturing state | Algorithmic or analytical state | What can change in the quality-control meaning | Principal hidden-risk condition | Evidence needed before continuity can be assumed |
|---|---|---|---|---|---|
| **Process change with model held constant** | Material attributes, scale, throughput, equipment dynamics, operating region, residence behavior, or disturbance profile changes | Existing model version and control logic retained | Inputs may no longer represent the population or dynamics for which the model was calibrated or validated | Model appears stable because software is unchanged while applicability has shifted | Evidence that the changed process remains inside supported model and measurement domains |

| | | | | | |
|---|---|---|---|---|---|
| **Model update with process equipment held constant** | Nominal equipment and process configuration unchanged | Retrained, recalibrated, replaced, or reparameterized model | State estimates, predicted quality attributes, optimizer behavior, diversion logic, or control actions may change | Software update is treated as analytical maintenance although manufacturing behavior changes downstream | Comparison of old and new decision behavior under quality-relevant operating conditions |
| **Measurement-interface change** | Core process may remain unchanged | Probe position, optical geometry, analytical method, preprocessing, calibration, or sampling logic changes | The observed process state or interpretation of the signal can change | New measurement is assumed equivalent because it targets the same nominal attribute | Demonstrated comparability of measurement meaning, representativeness, and downstream model performance |
| **Material or site transfer** | Formulation inputs, supplier attributes, local equipment behavior, environment, or site practice changes | Existing model, calibration, or soft sensor transferred | Input distributions and latent relationships may shift | Model portability is inferred from acceptable prior-site performance | Transfer evidence addressing new variability and the model's supported operating domain |
| **Control-model change** | Process remains within similar mechanical configuration | Predictive or state-estimation model used by APC/MPC changes | Corrective-action timing, magnitude, direction, or set-point trajectory may change | Validation focuses on prediction statistics while control consequences are not compared | Closed-loop or decision-relevant testing of the revised model within the intended control architecture |
| **Data-processing change** | Physical process unchanged | Filtering, normalization, reconciliation, feature extraction, or data-selection logic changes | The numerical state delivered to a quality model can change | Data pipeline is treated as background infrastructure rather than part of model behavior | Traceable comparison of transformed inputs, uncertainty propagation, and downstream decisions |
| **Simultaneous process and model change** | Physical and digital states change together | New process conditions accompanied by revised model or controller | Effects may interact and cannot reliably be attributed to either component in isolation | Separate qualification activities obscure an interaction effect | Joint assessment preserving process, analytical, model, control, and quality-decision traceability |

*Maintaining Pharmaceutical Quality across the AI Lifecycle*

Recognizing coupled change shifts lifecycle governance away from the question "Has the model changed?" toward the question "Has the validated relationship among process state, measurement, model, and quality decision changed?" Digital-twin work in continuous direct compression illustrates why that distinction matters. Hybrid flowsheet models can represent the behavior of a continuous manufacturing line and support process and product design before physical implementation [30]. Such a representation can preserve useful process knowledge, but its lifecycle value depends on synchronization between the assumptions embedded in the model and the physical manufacturing state to which it is applied. A model version cannot function as a reliable lifecycle reference merely because it is digitally persistent.

Measurement configuration forms part of the same state. Characterization of different NIR interfaces in continuous granulation has demonstrated that measurements taken at different locations can represent different stages and conditions of the process [31]. Work on blend-uniformity assessment in continuous tablet manufacturing has similarly linked measurements from flowing blends and downstream product states to final dosage-unit information [32]. These examples show why process evidence must retain its location and context. "NIR measurement," "blend potency," or "predicted CQA" are not self-contained lifecycle objects. Their meaning depends on where the measurement was taken, what material state existed there, how the signal was transformed, and which downstream inference or decision used it.

A lifecycle approach should therefore define revalidation or comparability triggers according to the potential effect of a transition on quality-critical inference and action. Risk-based model-validation principles already support proportionality to intended use and product impact [1]. Robustness analyses show that controller performance can depend on process-variability assumptions [15], while data-driven control architectures demonstrate that changes in model behavior can alter closed-loop decisions [16]. A PAT output used for diversion has a different quality consequence from the same output used only for exploratory process understanding [23]. Hybrid-model maintenance work further demonstrates that previously unrepresented sources of variability can alter predictive performance [28]. The resulting decision rule is impact based: reassessment becomes necessary when a transition may move the process outside the model's supported domain, change the meaning of a quality-

critical measurement, modify a quality-relevant model output, alter control behavior, or break traceability to the evidence supporting the prior state.

This logic avoids the opposite error of treating every software or process modification as requiring the same lifecycle response. A process adjustment demonstrably contained within an established robustness space need not be governed like a transition into a new material or dynamic regime. Likewise, a model update used only in a nonbinding analytical context does not have the same quality significance as one that changes a release-related prediction or controller response. The relevant question is whether the transition changes the evidentiary basis on which a product-quality decision depends.

High-density PAT can strengthen that evidentiary basis, but it cannot substitute for representativeness and transferability. End-to-end monitoring can expose variability across successive interfaces [20], semi-continuous blend monitoring can reveal process-condition effects [21], and systematic sensor-integration analysis can identify interface conditions that affect analytical validity [22]. These complementary observations support a distinction between evidence density and evidence validity. A manufacturing line may generate large quantities of real-time data while still relying on an obsolete calibration, a shifted measurement interface, an extrapolative model, or an outdated relationship between estimated state and control action.

Lifecycle evidence should consequently preserve four connected meanings. First, the measurement meaning identifies what physical state an analytical signal represents and under which interface conditions. Second, the model meaning identifies the version, calibration or training context, intended use, supported operating domain, and relevant uncertainty. Third, the control meaning identifies how the model output influences an operator, controller, diversion mechanism, or product-disposition decision. Fourth, the validation meaning identifies which evidence justifies continuing to rely on that measurement–model–action relationship after change.

These meanings are easily fragmented when manufacturing responsibilities are distributed across analytical development, data science, process engineering, automation, validation, quality assurance, and regulatory functions. PAT guidance emphasizes the need to connect monitoring purpose with implementation and control use [10], while broader PAT literature shows how analytical technologies are increasingly embedded across processing stages [11, 24]. Data-reconciliation work adds a further requirement: uncertainty and disagreement among process measurements must remain visible rather than being silently converted into apparently precise states [25]. A lifecycle record that captures only the model version or software release therefore provides insufficient information for a quality-critical system.

**Table 2** organizes the lifecycle evidence problem around the states that must remain traceable and the kinds of transitions that should reopen comparability or revalidation questions. These triggers are qualitative and impact based; they are not universal numerical thresholds.

**Table 2.** Lifecycle evidence states and impact-based revalidation triggers for AI-enabled pharmaceutical process control

| Lifecycle evidence state | What must remain traceable | Transition that can invalidate continuity | Quality question to reopen | Proportionate reassessment focus |
|---|---|---|---|---|
| **Physical process state** | Equipment configuration, operating range, material attributes, scale, throughput, disturbance profile, relevant environmental conditions | New operating regime, equipment modification, scale/site transfer, material shift, new disturbance pattern | Does the model still represent the process that now exists? | Applicability-domain and process-behavior comparison |
| **Measurement state** | Sensor identity, location, interface geometry, calibration, acquisition conditions, sampling dynamics, preprocessing | Probe relocation, sensor replacement, analytical-method revision, changed acquisition or preprocessing | Does the measurement still represent the same process state with equivalent uncertainty? | Analytical comparability and representativeness |
| **Data state** | Source lineage, transformations, reconciliation rules, feature construction, missing-data handling, versioned datasets | New preprocessing, data-integration rule, source substitution, changed reconciliation logic | Has the numerical input meaning changed even if the physical process has not? | Input comparability and uncertainty propagation |
| **Model state** | Version, architecture, parameterization, calibration/training context, supported range, intended use, uncertainty characterization | Retraining, recalibration, model replacement, new features, changed hyperparameters or mechanistic assumptions | Does the revised model make materially different quality-relevant inferences? | Old–new model comparison in intended domain |
| **Control-link state** | How model outputs affect set-points, control moves, alarms, diversion, release support, or operator intervention | Revised controller tuning, new optimizer, changed model-to-action interface, altered decision rule | Has the effective manufacturing strategy changed? | Closed-loop or decision-level testing |
| **Validation state** | Evidence supporting calibration, verification, robustness, transfer, comparability, and limitations | Process/model/interface transition beyond prior evidence | Which prior conclusions remain valid and which must be regenerated? | Risk-proportionate partial or broader revalidation |

| | | | | |
|---|---|---|---|---|
| **Knowledge state** | Assumptions, rationale, deviations, model limitations, process history, decision ownership, prior change evidence | Team/site handoff, vendor change, system migration, personnel turnover, fragmented documentation | Can later users reconstruct why the current process–model state is considered acceptable? | Provenance and knowledge-transfer completeness |
| **Joint process–model state** | Linkage among physical process, measurement, data, model, control behavior, validation evidence, and quality disposition | Two or more interacting changes, or any change that breaks one of those linkages | Does the previous validated state still describe the actual system used to make quality decisions? | Integrated comparability assessment across affected components |

This state-based view identifies several forms of hidden drift. The first occurs when the physical process changes but an unchanged model is assumed to retain its previous applicability. The second occurs when a model is updated but the altered decision behavior is evaluated only as a software-performance issue. The third occurs when a sensor, analytical interface, or preprocessing step changes while the downstream model is treated as though its inputs retain the same meaning. The fourth occurs during transfer, when apparently familiar variables are reproduced at a new site or scale but their distributions and interactions differ sufficiently to alter the behavior of a soft sensor or controller. In each case, the visible component may appear stable while the relationship among components has changed.

The lifecycle problem is therefore one of continuity of justified meaning. Pharmaceutical quality does not require a manufacturing system to remain static. Processes, analytical technologies, and models will change. What must remain controlled is the evidentiary chain explaining why the current process state, current measurement system, current model, and current control behavior still support the intended quality decision. When that chain changes materially, the previous validated state cannot simply be carried forward by naming continuity at the component level. The next section develops this observation into a joint process–model lifecycle framework in which transitions are evaluated by their effect on process knowledge, model applicability, validation state, control meaning, and the transfer of decision-relevant knowledge.

*Proposed Process–Model Lifecycle Framework*

The evidence developed above supports a lifecycle framework in which the governed object is the joint process–model state. Maintaining this state requires continuity among physical manufacturing conditions, analytical measurements, data transformations, model behavior, control actions, and the evidence supporting product-quality decisions. Digital continuity research in pharmaceutical maintenance illustrates the importance of preserving relationships among operational information and technical resources [33]. Historical manufacturing deviations can also provide knowledge for subsequent investigations, although proposed language-model applications do not establish autonomous decision-making authority or validated investigation performance [34]. The development of end-to-end digital twins for continuous mRNA manufacturing further demonstrates that digital integration extends beyond oral solid dosage production, while remaining dependent on platform-specific process assumptions [35].

The proposed framework defines a joint validated state as a documented combination of process conditions, measurement configuration, model version, applicability domain, control relationship, and supporting validation evidence. Its central analytical operation is to examine whether a transition preserves the meaning of that combination. A physical change may move observations beyond the domain of a previously acceptable model. An algorithmic update may change quality-critical predictions or manufacturing actions. A measurement change may alter the information delivered to the algorithm. These possibilities must be considered together because their interaction can generate consequences that separate process and software assessments overlook.

Four response conditions follow from this reasoning. Continued operation is supported when the changed configuration remains within the demonstrated applicability of the existing evidence. Targeted reassessment is appropriate when a transition affects a defined component but continuity can be established through proportionate comparability or validation evidence. Broader revalidation becomes relevant when the interaction among components alters the basis for quality-critical inference or control. Where the available evidence cannot support a quality-critical decision, the affected activity requires appropriate restriction, intervention, or escalation through the pharmaceutical quality system.

These conditions are proposed decision principles, not numerical thresholds or claims of regulatory approval. Their purpose is to preserve the distinction between an unchanged component and an unchanged manufacturing-control relationship. **Figure 1** represents this distinction through reciprocal process–model transitions and their effects on validation and quality-control boundaries.

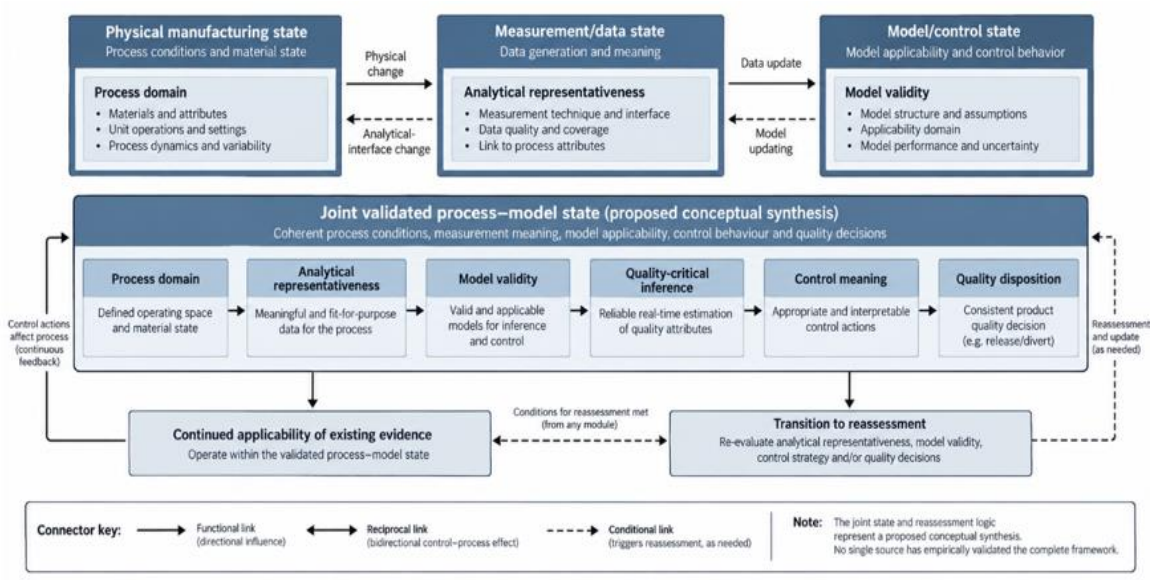



**Figure 1.** Reciprocal transitions in the validated process–model state.

Knowledge transfer is the mechanism through which the framework retains continuity across organizational and technical transitions. Process engineers must communicate the manufacturing conditions and assumptions represented by the model. Data scientists must preserve training and calibration context, data transformations, uncertainty, and model-version history. Automation and operational personnel must understand how revised predictions affect control actions. Quality functions require evidence connecting those changes to product impact, deviations, validation status, and disposition decisions. Regulatory functions require the corresponding change rationale and documentation relevant to applicable commitments. These responsibilities are interdependent because information lost at one handoff can weaken the validity of decisions made elsewhere.

**Table 3** assigns the relevant knowledge-transfer obligations according to the information that must remain usable after each handoff.

**Table 3.** Knowledge-transfer obligations that preserve process–model validity across manufacturing lifecycle transitions

| Knowledge-transfer interface | Information transferred | Assumption that must remain explicit | Quality-relevant consequence of information loss | Proposed continuity requirement |
|---|---|---|---|---|
| **Process engineering → data science** | Material attributes, operating range, disturbance history, process configuration | Training conditions represent the intended physical process | Undetected loss of model applicability | Version-linked process-domain record |
| **Analytical development → data science** | Sensor configuration, calibration, sampling, preprocessing | Model inputs retain their analytical meaning | Biased or nonrepresentative quality estimates | Traceable measurement and data lineage |
| **Data science → automation and operations** | Model version, intended use, supported domain, uncertainty | Revised predictions remain appropriate for control | Unintended changes in set-points, alarms, or diversion | Documented old–new decision comparison |
| **Operations → quality unit** | Process history, interventions, deviations, product impact | Operational evidence supports the current control state | Unsupported continuation or disposition | Reconstructible quality-impact assessment |
| **Quality unit ↔ regulatory function** | Validation state, change rationale, comparability evidence | Existing commitments remain applicable or are appropriately addressed | Incomplete change classification or supporting documentation | Traceable assessment of applicable requirements |
| **Site, vendor, or personnel transition** | Model limitations, process knowledge, unresolved deviations, prior decisions | Receiving personnel understand the basis of validated use | Loss of institutional knowledge and hidden quality drift | Controlled handoff with retained provenance |

The framework is most vulnerable when apparently routine maintenance conceals a substantive change in the meaning of the controlled system. A model may remain statistically satisfactory on familiar data while the process has shifted into a different operating regime. A revised soft sensor may preserve aggregate predictive performance while changing decisions near a quality-relevant boundary. A transferred process may reproduce nominal settings without reproducing material dynamics or analytical representativeness. Such configurations challenge governance based exclusively on component versioning.

The framework's value consequently depends on demonstrating that joint assessment detects interaction effects that would otherwise remain unresolved. It does not assume that every model update requires complete revalidation or that conventional pharmaceutical change control is inadequate. An existing quality system that already captures these interactions may perform the same function. The proposed contribution is the explicit treatment of process state, model state, measurement meaning, and quality decision as one interdependent object of lifecycle assessment.

*Quality, Regulatory and Knowledge-Transfer Implications*

For pharmaceutical quality management, the primary implication is that change classification should consider the consequences of altered relationships among manufacturing components. A model update that changes a quality-critical control action has a different significance from an update affecting only an exploratory analytical report. Similarly, a process adjustment within a demonstrated robustness range differs from a change that invalidates the assumptions underlying an established predictive model. Risk-based model governance provides the foundation for proportionate treatment of such differences [1].

Validation documentation should preserve the reasoning connecting process conditions, measurement validity, model applicability, and control behavior. Digital manufacturing and PAT can strengthen this connection by generating more frequent process evidence, but additional data cannot automatically establish that a model remains valid under changed conditions [5]. Where quality decisions depend on end-to-end digital control, the relevant evidence should extend beyond individual model statistics to the behavior of the connected manufacturing system [17].

Regulatory implications should be interpreted through applicable product, process, and jurisdictional requirements rather than through an assumed universal approval pathway. Process transfer, analytical modification, model replacement, or revised control behavior may require different levels of supporting evidence according to their quality impact and the established control strategy [7]. The framework provides a way to organize that assessment. It does not replace pharmaceutical quality-system responsibilities, establish a new regulatory category, or imply that a successful technical comparison constitutes regulatory acceptance.

Organizationally, the central requirement is preservation of decision-relevant knowledge across technical and institutional boundaries. Digital continuity can connect maintenance information with operational resources [33], while historical deviation records can support the retrieval of prior manufacturing experience [34]. Their usefulness nevertheless depends on whether the information retains context, assumptions, limitations, and accountable decision ownership. An accessible repository is insufficient when users cannot reconstruct which process conditions supported a model, why its outputs were accepted, or how a subsequent change altered the basis for that judgment.

**Figure 2** represents this continuity through the transfer of evidence from physical and analytical systems into model, operational, quality, and regulatory decisions.

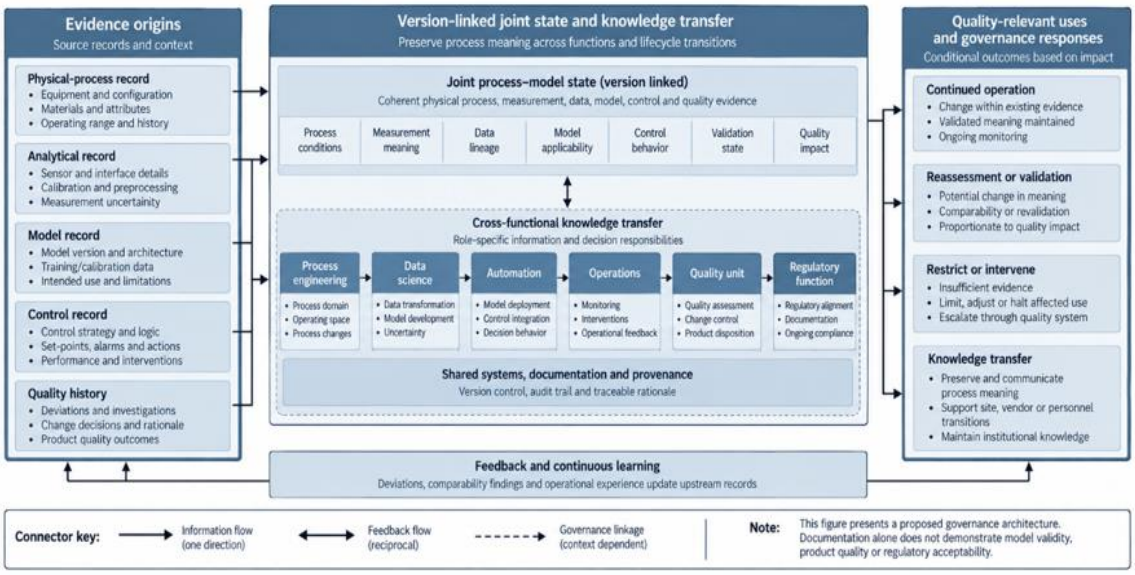



**Figure 2.** Custody of process meaning across lifecycle handoffs.

The framework also creates a discriminating research agenda. Comparative studies could examine whether integrated process–model change assessment identifies loss of applicability, altered control behavior, or incomplete knowledge transfer that separate component-level assessments miss. Robustness testing under process variability [15], evaluation of data-driven control behavior [16], and assessment of model performance across manufacturing conditions [18] provide methodological starting points.

The strongest counterfactual is an integrated conventional quality system that already preserves the same relationships. If such a system detects and resolves coupled-change risks equally well, the incremental benefit of a separately articulated joint-state framework would be limited. Conversely, evidence that component-wise qualification misses consequential interactions would support the framework's distinctive analytical claim. Its practical relevance is therefore conditional on the complexity of the manufacturing-control relationship and on the adequacy of existing governance.

**Conclusion**

Maintaining pharmaceutical quality when algorithms and manufacturing processes change together requires continuity of the evidence connecting physical process conditions, analytical measurements, model behavior, control actions, and product-quality decisions. Neither an unchanged algorithm nor unchanged equipment establishes continuity of the validated manufacturing state.

The proposed lifecycle framework identifies coupled process–model change as a distinct object of quality assessment. Its central principle is that revalidation, comparability, and knowledge-transfer obligations should follow the consequences of a transition for quality-critical inference and action. The framework is most relevant where model outputs influence manufacturing control and where physical or analytical changes can alter the model's supported domain. Its added value remains conditional on whether joint assessment reveals interaction effects that existing integrated quality systems would otherwise miss.

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