STRECK

The Objective Case for Third-Party Quality Controls

A framework for understanding the risks that third-party QC addresses in molecular diagnostic workflows

The case for third-party quality controls

In molecular diagnostics, the integrity of a reported result is influenced by the integrity of every step that produced it. From cell lysis through nucleic acid extraction, amplification, and detection, each stage of the analytical pathway is a potential point of failure — and each failure may carry a direct consequence for the clinician making the treatment decision and the patient receiving it.[1]

Quality control materials exist to help identify those failures before they reach reported results. But not all QC materials are equally capable of doing so. An assay manufacturer's internally developed control — however convenient — shares formulation origins, raw material inputs, and often a production supply chain with the assay it is meant to challenge. The structural risk lies in that shared origin, not in the commercial arrangement under which a control is ultimately distributed. A defect that compromises the assay will frequently go undetected by a co-formulated control in parallel, which may render the QC cycle silent precisely when it should be loudest.[2]

Third-party quality controls help address this concern through their design and manufacturing. Manufactured by a separate entity with a distinct supply chain, formulated without shared inputs from the assay under evaluation, and built with a single commercial purpose — detecting failure — they provide the structural objectivity that manufacturer-supplied controls are limited to depending on their formulation and sourcing.[5]

The case extends beyond structural bias. Third-party controls also solve for the analytical coverage gap left by internal amplification controls, the performance uncertainty introduced at every reagent lot transition and instrument service event, the operator technique variability that instrument diagnostics cannot detect, the supply fragility of patient-based QC programs, and the regulatory exposure created by RUO materials operating inside IVD diagnostic workflows.[3]

When laboratories implement third-party QC programs aligned with current accreditation requirements — ISO 15189:2022, CAP MIC.65200, CLSI EP23 — they are not simply satisfying a compliance checkbox. They are closing the structural gap between a QC program focused on analytical monitoring and one designed to support laboratory quality objectives.[3][4]

The 14 risks cataloged below represent the full spectrum of where quality assurance breaks down when objective, third-party controls are absent — and how each risk is resolved when they are present. Each risk row is annotated with its supporting citation.

Risk	Why it matters	How third-party QC resolves it
STRUCTURAL BIAS IN THE TESTING SYSTEM		
1 **BIAS** **Co-sourced assay and control materials** [2]	When quality control material is formulated using the same raw material inputs, reagent components, or production processes as the assay under evaluation, it cannot function as a true independent challenge. A systematic defect in shared inputs will express identically in both the assay and its control — rendering the QC cycle analytically inert against that class of failure. This risk is specific to controls derived from the assay manufacturer's own production chain; it does not apply to controls manufactured by an independent third party to their own specifications, even when distributed under an OEM label.	A control formulated by an independent manufacturer — using its own raw material supply chain, its own formulation process, and its own quality system — carries no structural relationship to the assay's failure modes, regardless of how it is commercially distributed. The objectivity that matters is formulation independence, not label independence. When the control's inputs, processes, and QA infrastructure are structurally separate from those of the assay, it can detect what a co-formulated control is constitutionally unable to see.
2 **BIAS** **Concomitant degradation of calibrator and control** [2][5]	When calibrators and controls are derived from the same raw material pool, age-related degradation affects both matrices concurrently. The resulting co-drift produces results that appear stable within acceptance criteria while true analytical performance erodes — invisible because the reference and the measured system are moving together.	An independently sourced control maintains a fixed analytical reference point that is decoupled from the assay's production and supply chain events. Calibrator-driven drift registers as a measurable deviation from the control's established baseline — surfacing the shift before it propagates to reported results.
3 **BIAS** **Inherent commercial conflict in manufacturer-supplied QC** [2][3]	Independent and manufacturer-supplied control strategies can offer different approaches to quality monitoring. A structural conflict arises when both system and quality control are produced by the same vendor. A control's primary function — detecting assay failure — is in direct tension with the manufacturer's commercial interest in demonstrating product performance. Objectivity may not be credibly claimed when the evaluator and the evaluated share the same origin.	When the control manufacturer has no economic stake in the assay's pass rate, objectivity is structurally enforced rather than asserted. The control's sole design criterion is sensitivity to failure — unconstrained by any downstream interest in the result it produces.

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DIRECT IMPACT ON PATIENT RESULTS		
4 **PATIENT SAFETY** Clinically significant assay drift propagating to reported results [1][2]	Laboratory results inform approximately 70% of clinical decisions. A systematic performance shift — even one operating within a narrow magnitude — can propagate across thousands of reported results before an external proficiency testing cycle provides an opportunity for detection. The interval between drift onset and external discovery may increase the likelihood that affected results detrimentally impact clinical decisions.	A third-party control with a defined, lot-specific expected range provides a run-level sentinel against systematic drift. Each passing control result constitutes documented evidence of analytical integrity at that point in time. Each failure prompts laboratories to investigate assay performance before releasing patient results — compressing the interval between drift onset and corrective intervention to a single analytical run.
5 **PATIENT SAFETY** Routine QC as a leading indicator of proficiency testing risk [1][4]	Proficiency testing evaluates laboratory performance at discrete, low-frequency intervals — typically weeks to months after an analytical problem first manifests. The external sample arrives after the damage is done. Laboratories that rely on proficiency testing as their primary performance signal are operating with a structural lag between failure onset and detection.	A continuous third-party QC program generates a high-frequency internal performance signal that precedes any external audit finding. Analytical issues identified and resolved through routine QC do not persist in the proficiency testing cycle — the laboratory arrives at external evaluation having already corrected what would otherwise become a finding.
ANALYTICAL PROCESS COVERAGE		
6 **PROCESS INTEGRITY** Internal amplification controls leaving pre-amplification steps unmonitored [3][5]	Internal amplification controls (IAC) confirm that the amplification reaction occurred — but their ability to monitor the full analytical pathway depends entirely on their design. Off-panel IACs, which use a sequence or organism unrelated to the diagnostic target, confirm only that amplification was possible; they cannot validate whether the target organism would have been detected had it been present. Even on-panel IACs, which use the target organism and do exercise the lysis and extraction steps, monitor only a single concentration point and provide no information about assay performance at clinically relevant low-positive thresholds. A false-negative originating from partial inhibition, suboptimal extraction efficiency, or near-cutoff target concentrations can pass through either IAC design without generating a detectable signal.	A third-party control formulated with intact, inactivated organisms at defined, clinically relevant concentrations — including near-cutoff low-positive levels — must traverse the complete analytical pathway from lysis through detection before a result is generated. It monitors the full workflow at the concentration range where clinical decisions are most consequential, additional monitoring of workflow steps that may not be fully assessed by internal controls, ultimately closing likely coverage gaps.
7 **PROCESS INTEGRITY** Unverified performance equivalence across reagent lot transitions [3]	Each reagent lot change constitutes an uncontrolled performance variable unless bracketed by a documented equivalence assessment. Lot-to-lot differences — including variability within identical extraction chemistry or enzyme preparations — may introduce a clinically meaningful shift in sensitivity or specificity that falls within acceptable ranges but represents genuine performance change.	Bridging runs with a third-party control at every lot transition generates a prospective, documented performance record with a defined expected range. Third-party controls may provide an additional source of information when evaluating lot-to-lot consistency. Any performance divergence is identified at the point of introduction, before patient specimens are processed under the new lot conditions.
8 **PROCESS INTEGRITY** Absence of a verified performance baseline following instrument service events [3]	Following a service event, software update, component replacement, or instrument relocation, there is no validated method for confirming restored analytical performance without an external reference standard. Rerunning assay-supplied materials confirms only that the instrument is capable of producing a result — not that the result is accurate relative to the pre-event performance state.	A third-party control with defined lot-specific expected performance provides the fixed external standard against which post-service requalification is objectively assessed. It answers the question OEM-supplied materials structurally cannot: has the instrument returned to a verified analytical baseline, or has it returned to producing results?

Risk	Why it matters	How third-party QC resolves it
PERSONNEL AND COMPETENCY DOCUMENTATION		
9 OPERATIONS Pre-analytical operator errors below the detection threshold of instrument-based controls [1][3]	Pipetting imprecision, incorrect sample introduction technique, and pre-analytical handling deviations occur upstream of any step an internal control can observe. A control that bypasses manual sample handling — by design — is constitutively blind to the failure modes most frequently associated with operator-introduced error.	A control processed identically to a clinical specimen — from initial handling through introduction to the analytical system — exercises the human element of the workflow alongside the instrumental one. Technique-dependent failures produce a control result that deviates from expectation, creating a mechanism for identifying operator-specific performance issues that instrument diagnostics alone cannot surface.
10 OPERATIONS Competency documentation lacking audit-defensible traceability [3]	Accreditation frameworks require documented, individualized competency assessments tied to specific assays and time periods. Residual patient specimens and internally developed materials lack the lot consistency, defined expected performance ranges, and chain-of-custody documentation required to help support the efforts associated with quality programs like CAP, CLIA, or ISO 15189 compliance.	A commercially manufactured third-party control with lot-specific certificates of analysis, documented stability data, and defined expected ranges provides the consistent, traceable reference required to support and produce audit-ready competency records. Each operator's performance is evaluated against the same fixed analytical standard — not a variable reference that changes with every use.
SUPPLY CONTINUITY AND MATERIAL INTEGRITY		
11 OPERATIONS Patient-derived QC materials subject to prevalence-dependent supply failure [5]	Laboratories using remnant patient specimens as external controls are operationally dependent on a supply variable they do not control. Positivity rates fluctuate with season, endemic prevalence, referral patterns, and clinical demand. Low-volume and low-prevalence assays are disproportionately exposed: the specimens needed for QC are precisely the ones least likely to be available when needed most.	A commercially manufactured third-party control at defined, clinically relevant analyte concentrations is available independent of patient volume, disease season, or testing site geography. Laboratories running low-frequency or low-prevalence assays maintain the same QC coverage as high-volume workflows — without adjusting their quality program to accommodate specimen availability.
12 OPERATIONS In-house reference materials with unverified analytical traceability [3][5]	Laboratories that develop QC materials internally assume responsibility for characterization, performance validation, stability assessment, and ongoing documentation. The resulting records are produced under the same quality system being evaluated, creating a circularity that accreditation inspectors are trained to identify and question.	A third-party control carries its own quality infrastructure — lot-specific performance data, stability documentation, and certificate of analysis produced under a separate, audited quality system. The laboratory inherits a complete traceability record rather than generating one internally, removing both the resource burden and the circular documentation risk.
REGULATORY AND ACCREDITATION COMPLIANCE		
13 REGULATORY QC program design misaligned with current accreditation guidance [3][4]	CAP Checklist MIC.65200, CLSI EP23, ISO 15189:2022, CMS/CLIA regulations, and their international counterparts increasingly specify that QC materials should be independent of the assay manufacturer. Programs built on OEM-supplied or internally developed materials may satisfy earlier interpretations of these standards while falling short of current expectations — a gap that frequently surfaces only during inspection cycles.	A third-party control used in accordance with current accreditation guidance — and meeting the composition standards those frameworks specify — helps support alignment of each major framework without requiring interpretive argument. Compliance is demonstrated by doing precisely what the standards recommend.
14 REGULATORY RUO-labeled materials deployed within IVD diagnostic workflows [3]	FDA regulatory guidance explicitly defines Research Use Only (RUO) materials as products in the laboratory phase of development, not cleared for use in clinical diagnostic procedures. FDA regulates products labeled RUO and IVD differently; laboratories should evaluate products according to their intended use and applicable requirements.	An IVD-labeled third-party control has undergone the design validation, performance characterization, and regulatory registration required for deployment in clinical diagnostic settings. The IVD designation is documented evidence, reviewed by a regulatory authority, that the control was developed for the environment and workflow in which it is being used — with intended use specific to the instrument and test system.

Streck MDx-Chex® molecular quality controls are third-party manufactured and designed to address each of the risks identified above across the full sample-to-result workflow.

Supporting literature

[1]	**van Moll C, Egberts T, Wagner C, Zwaan L, ten Berg M.** *The Nature, Causes, and Clinical Impact of Errors in the Clinical Laboratory Testing Process Leading to Diagnostic Error: A Voluntary Incident Report Analysis.* Journal of Patient Safety. 2023;19(8):573–579. doi: 10.1097/PTS.0000000000001166 Use in this document: Documents that analytical phase errors in clinical laboratory testing produce severe clinical impact and lead to diagnostic errors — including delayed or wrong diagnoses — in 60% of affected cases. Establishes the direct patient harm pathway that external QC is designed to interrupt.
[2]	**Lima-Oliveira G, Lippi G, Salvagno GL, Brocco G, Guidi GC.** *In vitro diagnostic company recalls and medical laboratory practices: an Italian case.* Biochemia Medica (Zagreb). 2015;25(2):273–278. doi: 10.11613/BM.2015.028 Use in this document: Documents a real IVD recall in which assay manufacturer-supplied controls failed to detect a 13–45% performance shift in a parathyroid hormone assay, potentially affecting 40,000 patient results across 19 laboratories. Authors explicitly conclude that independent third-party controls would have detected the shift. The foundational case study establishing structural failure of co-formulated controls derived from the assay manufacturer's own production chain.
[3]	**Carey RB, Bhattacharyya S, Kehl SC, Matukas LM, Pentella MA, Salfinger M, Schuetz AN.** *Practical Guidance for Clinical Microbiology Laboratories: Implementing a Quality Management System in the Medical Microbiology Laboratory.* Clinical Microbiology Reviews. 2018;31(3):e00062-17. doi: 10.1128/CMR.00062-17 Use in this document: Authoritative peer-reviewed guidance from the American Society for Microbiology outlining the quality management system framework for clinical microbiology laboratories. Operationalizes ISO 15189 and CLSI standards — including external quality control requirements — as direct patient safety mechanisms.
[4]	**Laudus N, Nijs L, Nauwelaers I, Dequeker EMC.** *The Significance of External Quality Assessment Schemes for Molecular Testing in Clinical Laboratories.* Cancers. 2022;14(15):3686. doi: 10.3390/cancers14153686 Use in this document: Peer-reviewed review establishing that external quality assessment by an independent party is what allows laboratories to guarantee reliable test results to patients and clinicians. Directly links independent external QC to minimizing false positives and false negatives in molecular diagnostic testing.
[5]	**Plebani M.** *Internal quality control and external quality assurance: a great past opens the way to a bright future.* Advances in Laboratory Medicine. 2022;3(3):215–217. doi: 10.1515/almed-2022-0075 Use in this document: Written by the most-cited author in laboratory medicine quality, this article specifically identifies third-party source and commutability to patient sera as the key advancements in internal quality control — enabling result comparability across time, methods, and test versions.


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