

WHITE PAPER

Ensuring Pharmaceutical Quality Through Strategic Raw Materials Testing

INTRODUCTION

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Dr. Jihye Jang-Lee drives Element's pharmaceutical and biologics testing strategy, bringing nearly two decades of expertise in analytical development and regulatory compliance. With her PhD in Biochemistry from Imperial College London, she addresses complex analytical challenges for clients ranging from emerging biotech firms to established pharmaceutical corporations. Her deep command of method development, quality systems, and regulatory requirements, combined with her understanding of both scientific complexities and practical realities, helps companies navigate critical testing decisions throughout the product development lifecycle.

What's the first critical decision point that can make or break pharmaceutical product quality? It happens before manufacturing even begins. Raw materials testing serves as the essential gateway to quality in today's complex global supply chain, yet balancing thorough testing with production timelines creates a persistent challenge across the industry, affecting everyone from QA specialists to production managers.

In today's high-stakes pharmaceutical landscape, a single failure in verifying their identity, purity, or quality can trigger devastating consequences: product recalls, regulatory sanctions, damaged reputations, and most importantly, potential patient harm. While regulatory bodies intensify their scrutiny of pharmaceutical quality systems, manufacturing teams face unrelenting pressure to accelerate production timelines and control costs. This reality creates a challenging balancing act for those who oversee quality: how do you maintain uncompromising quality standards while supporting production efficiency?

The answer lies in developing strategic, risk-based approaches to raw materials qualification that protect patients, prevent costly quality failures, and maintain efficient operations, turning what many view as a necessary burden into a competitive advantage.



CRITICAL DECISIONS AT THE SUPPLY CHAIN GATEWAY

The pharmaceutical supply chain stretches across continents, involving numerous suppliers, manufacturers, and distributors. Without proper verification of incoming materials, manufacturers risk using components that could compromise product quality or patient safety.

Regulatory agencies increasingly scrutinize raw materials testing programs, with expectations extending well beyond acceptance of supplier documentation. The FDA and other regulatory bodies now require comprehensive, risk-based testing programs that demonstrate independent verification of material quality. Recent warning letters highlight heightened regulatory focus on inadequate raw materials testing and over-reliance on supplier Certificates of Analysis (CoA).

Current regulatory expectations include identity testing of every lot, even from qualified suppliers with established track records. For high-risk components such as glycerin and polyethylene glycols (PEGs), verification testing provides essential confirmation beyond supplier documentation. Manufacturers must demonstrate adequate control over elemental impurities, residual solvents, microbial contamination levels, and nitrosamines through appropriate

testing protocols. These requirements reflect regulatory recognition that supplier CoAs, while valuable, cannot substitute for independent verification as part of a robust quality system.

The challenge facing quality professionals becomes clear when considering routine material receipt. A magnesium stearate shipment arrives with supplier documentation showing compliance with all USP specifications. The CoA data appears complete and within range. Quality assurance must design a testing approach that satisfies regulatory requirements, verifies material quality, and supports efficient manufacturing operations, determining which tests provide adequate verification while maintaining appropriate risk-based controls.

The most expensive test is the one you didn't perform, until a quality issue emerges downstream.

Raw materials testing serves as the critical first line of defense against contamination, adulteration, or misrepresentation in the pharmaceutical supply chain. It's the foundation upon which all subsequent quality assurance activities build.



THE THREE FOUNDATIONS OF RAW MATERIALS CONFIDENCE

Pharmaceutical manufacturing stands on three essential pillars that cannot be compromised:

- 1. Identity Verification:** What exactly is this substance?
- 2. Purity Confirmation:** Is the Purity label within the acceptable range for the manufacturing of the final product?
- 3. Quality Assurance:** Is this batch of raw material consistent with historical batches of raw material used in the manufacturing of this product?

These factors must be thoroughly understood regardless of dosage form: tablet, syrup, inhaler, or injectable solution. Raw materials testing represents the first critical control point in the pharmaceutical manufacturing chain. Before production begins, analytical testing must determine whether the quality attributes of incoming materials are suitable for use.

Identity testing isn't optional, even when suppliers are trusted. Materials have been known to travel worldwide under false names, with potentially catastrophic consequences.

NAVIGATING THE QUALITY-SPEED-COST TRIANGLE

The fundamental tension between quality assurance and operational efficiency creates significant challenges for pharmaceutical manufacturers. Even as quality remains non-negotiable, the pressures of production schedules and cost control cannot be ignored.

Pharmaceutical companies face a fundamental challenge: maintaining impeccable quality standards while meeting production deadlines and controlling costs. This tension creates a cascade of interrelated problems throughout the manufacturing process.

Production bottlenecks develop when testing results aren't available in time to support manufacturing schedules, creating costly delays and potential supply disruptions. Quality blind spots emerge when testing isn't comprehensive enough to catch problematic materials, introducing risks that may only surface during manufacturing or after product release.

Regulatory obstacles arise when testing methods don't align with constantly evolving requirements, potentially leading to compliance issues during inspections. Market access delays occur when documentation doesn't satisfy increasingly demanding regulatory reviewers, postponing revenue generation while competitors advance.

Compounding these challenges, many facilities lack the specialized equipment and expertise needed for advanced testing methods like USP <232>/<233> trace metal analysis or unknown impurity identification using mass spectrometry. Even well-equipped laboratories struggle to keep pace with evolving regulatory expectations in areas like packaging leachables and data integrity.

When faced with the triangle of quality, speed, and cost, most companies choose two. The best find ways to optimize all three through strategic testing approaches.

FROM COMPLIANCE CHECKBOXES TO STRATEGIC MATERIAL INTELLIGENCE

Effective raw materials testing isn't about running a standard battery of tests on every incoming material. Instead, it requires a thoughtful, risk-based, systematic approach that addresses the specific risks and requirements of each material based on material criticality, supplier history and its intended use.

The testing process moves through progressive stages, each building on the previous to create a complete quality picture:

First comes verifying the identity, which ensures the material is exactly what it claims to be. Established analytical techniques like infrared spectroscopy (IR), UV analysis, and specific optical rotation tests help confirm the nature of the material.

Once identity is confirmed, potency and purity analysis determine the material's strength and quantify any

impurities present. These assessments typically involve chromatographic techniques, with HPLC widely used for non-volatile compounds and gas chromatography (GC) for volatile and semi-volatile substances.

Next, understanding physical properties: appearance, pH, volatility, melting point, and optical characteristics provide initial insights into material consistency and quality indicators.

Finally, comprehensive contaminant analysis evaluates known and unknown impurities, particulates, residual solvents, and trace metals, representing perhaps the most technically challenging aspect of raw materials testing.

A strategic approach asks not just "What tests are required?" but "What information do we need to protect our patients and our products?"



ADVANCED ANALYTICAL STRATEGIES FOR COMPLEX ANALYTICAL CHALLENGES

While fundamental testing approaches establish a baseline for material quality, today's complex supply chains and sophisticated formulations demand more advanced analytical capabilities. Pharmaceutical manufacturers face increasingly nuanced analytical challenges that require specialized techniques and expertise to resolve.

The globalization of pharmaceutical supply chains has introduced new vulnerabilities, with materials sometimes passing through multiple distributors across different regulatory jurisdictions. Meanwhile, formulations continue to grow more complex, with lower impurity thresholds and increasingly potent active ingredients. These factors combine to create analytical challenges that cannot be addressed through basic analytical techniques. Modern day labs employ a whole arsenal of sophisticated techniques such as HPLC, GC, LC-MS, GC-MS, NMR, ICP-MS, and ICP-OES. . These methods not only meet compendial requirements but also provide early warning for quality risks in increasingly globalized supply chains.

Leading laboratories are deploying increasingly powerful analytical techniques to identify, characterize, and mitigate these emerging risks. From trace contaminant identification to comprehensive material characterization, these advanced methods provide critical insights that protect both manufacturing processes and patient safety.

Cracking the Contamination Code: Identifying Unknowns

When manufacturing processes change or unexpected peaks appear in chromatographic analyses, identifying unknown compounds becomes essential. Advanced laboratories employ sophisticated techniques including but not limited to LC-MS, GC-MS and NMR to solve these analytical puzzles.

For example, in a widely reported case, contaminated heparin was traced back to an unverified raw material source, leading to adverse patient reactions and product recalls. Timely detection through advanced chromatographic analysis could have prevented this crisis.

An unexplained peak on a chromatogram is like a smoke alarm going off; ignoring it could mean missing a critical warning sign.

Beyond the Heavy Metals Test: Analytical Complexity and Evolving Expectations

The pharmaceutical industry has undergone a revolutionary shift in how it approaches metal contamination. In 2018, the century-old "heavy metals test" was officially replaced by significantly more specific and sensitive methods outlined in USP <232> and <233>.

Today's compliant approach employs inductively coupled plasma (ICP) technology through two complementary methods:

- **ICP-OES (Optical Emission Spectroscopy):** Provides rapid screening with excellent throughput
- **ICP-MS (Mass Spectrometry):** Delivers precise quantitative analysis, distinguishing between specific metal contaminants with extreme sensitivity

For specific metals or specialized applications, atomic absorption spectroscopy offers targeted analysis with varying sensitivity levels.

These sophisticated analytical capabilities enable manufacturers to detect and resolve quality issues earlier in the process, preventing costly delays and potential patient safety concerns.

The shift from the century-old heavy metals test to - updated methodologies isn't just a technical upgrade; it represents a fundamental change in how we think about controlling metal contamination in pharmaceuticals.

Packaging Material Testing: A Critical Component

Container closure systems represent an important component of raw materials testing that can significantly impact product quality. Both glass and plastic packaging components require specific testing approaches:

- **Glass Containers:** Various compositions (borosilicate, soda-lime) and classifications (types 1-3) with different chemical resistance properties. USP <660> testing evaluates hydrolytic resistance and surface characteristics.
- **Plastic Components:** Testing under USP <661.1> and USP <661.2> focuses on evaluating the suitability of the plastic materials of construction, as well as the entire packaging system, including components like containers, closures, and seals. Each polymer type introduces different compatibility considerations.

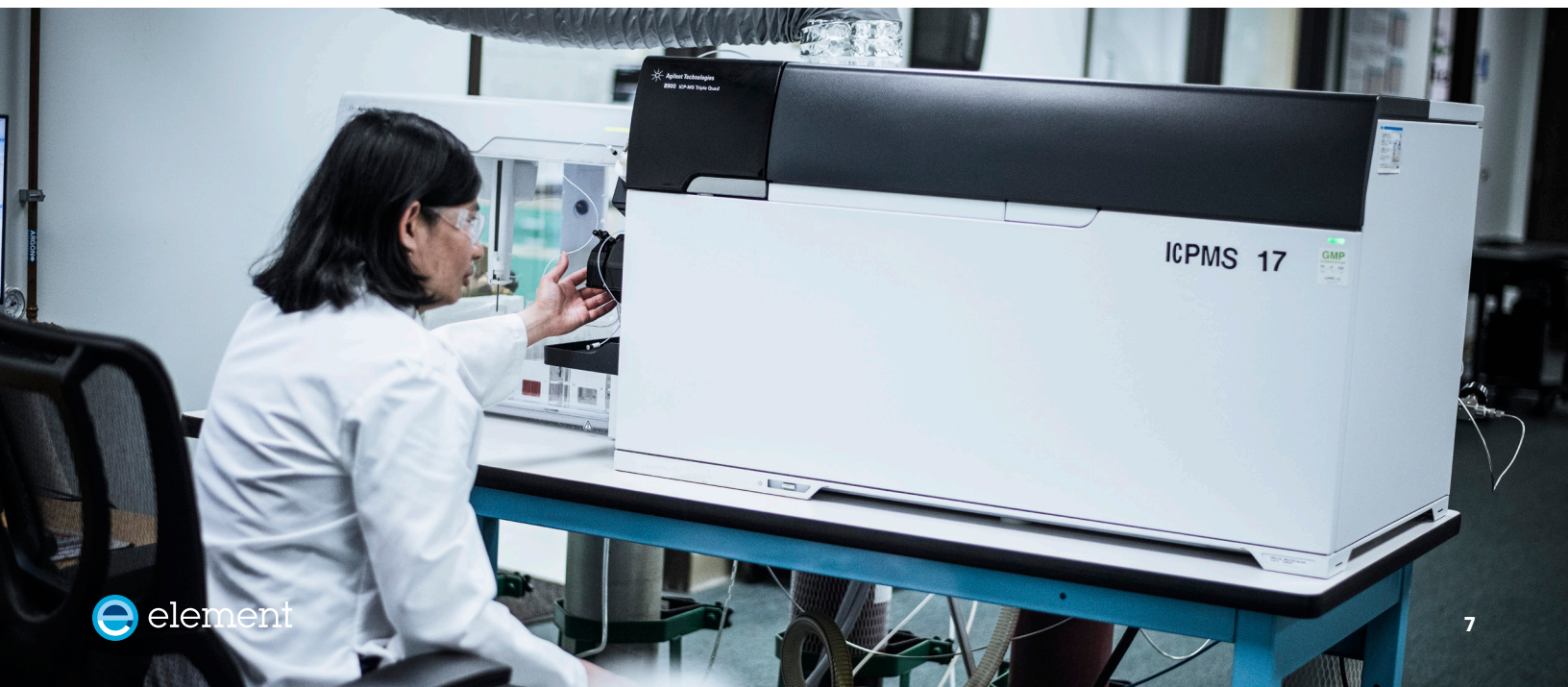
Regulatory agencies have significantly increased their scrutiny of extractables and leachables in raw packaging materials. The infamous case of musty-smelling tablets, which resulted from a fumigating agent migrating from wooden pallets through packaging into the product, highlighted the importance of comprehensive testing for packaging components.

A risk-based approach to leachables assessment based on USP <1664> categorizes products according to both the administration route and potential packaging interaction:

Risk Level	Route of Administration	Common Examples
Highest Risk	Inhalation, Injection	MDIs, Intravenous solutions, Prefilled syringes
High Risk	Ophthalmic, Transdermal	Eye drops, Patches, Nasal sprays
Lower Risk	Oral, Topical	Tablets, Capsules, Creams

This framework helps manufacturers determine the appropriate level of analytical scrutiny required for their specific products.

What contains your product may ultimately affect what your product contains; packaging components cannot be an afterthought in a comprehensive testing strategy.



BUILDING QUALITY SYSTEMS THAT DELIVER RELIABLE RESULTS

Generating high-quality analytical data is only the beginning of an effective raw materials program. Transforming that data into reliable decisions requires robust quality systems that ensure accuracy, maintain data integrity, and satisfy increasingly stringent regulatory expectations.

Modern pharmaceutical quality systems must address every aspect of the testing lifecycle, from sample receipt and storage through testing, data analysis, and final reporting. Each step presents unique challenges and opportunities for process optimization. Without careful attention to these systems, even the most sophisticated analytical methods may fail to deliver reliable, defensible results.

The consequences of inadequate quality systems extend far beyond regulatory concerns. Testing data drives critical business decisions about supplier qualification, material acceptance, and production scheduling. Organizations that establish comprehensive, well-designed quality systems create a foundation for both compliance confidence and operational excellence.

Raw Materials Stability Testing: Predicting Long-term Performance

Beyond initial characterization, understanding how raw materials perform over time is essential for ensuring consistent product quality. Material stability represents a critical consideration that directly impacts both manufacturing and finished product performance.

Stability testing under ICH-compliant conditions provides critical insights into how raw materials and finished products behave over time:

- **25°C/60% RH:** Long-term storage
- **30°C/65% RH:** Intermediate conditions
- **40°C/75% RH:** Accelerated testing
- **5°C:** Refrigerated storage

This data helps manufacturers establish appropriate storage conditions and retest periods for products to ensure they maintain critical quality attributes throughout their use cycle.

Stability testing doesn't just tell you how long your product will last; it reveals how your product will behave throughout its entire lifecycle.

The ALCOA+ Principle and Quality Process: Building Regulatory Trust

Data integrity has become a particular focus of regulatory inspections, with increased emphasis on electronic data (metadata) rather than paper records alone. Regulatory agencies emphasize data integrity as much as testing accuracy. The ALCOA principles ensure all data is:

- **Attributable** (linked to a specific person/event)
- **Legible** (clear and readable)
- **Contemporaneous** (recorded in real time)
- **Original** (not transcribed or rewritten)
- **Accurate** (free from errors and falsification)
- **Complete** (all data is recorded)
- **Consistent** (recorded in a chronological and orderly manner)
- **Enduring** (records maintained for the required duration)
- **Available** (data is available when needed)

These principles are embedded within an effective three-stage quality process that transforms test data into trusted results. After testing is performed, results should undergo a two-tiered review: first verifying data for technical accuracy, then checking for adherence to GMP requirements. Only after both reviews are completed is a certificate of analysis released.

Regulatory agencies have issued warning letters and import bans due to data falsification, as seen in high-profile cases where manufacturers failed to maintain proper electronic records and audit trails.

In the eyes of regulators, excellent test results with poor data integrity are worse than no testing at all, because they create a false sense of security.

THE MAKE-OR-PARTNER DECISION: MAXIMIZING TESTING VALUE

Once a comprehensive testing strategy is defined, pharmaceutical manufacturers face a fundamental decision: develop in-house capabilities or partner with specialized laboratories? While building internal capacity provides direct control, the complexity and breadth of modern testing requirements make external partnerships increasingly attractive for many organizations.

Pharmaceutical companies must decide whether to invest in in-house testing capabilities or partner with specialized laboratories. While in-house testing provides direct control, external partners offer distinct advantages:

- **Expertise Without the Learning Curve:** External laboratories focus on analytical testing, developing deep expertise in specific methodologies and regulatory requirements.
- **Advanced Technology Without Capital Investment:** Specialized testing equipment represents a significant investment that may be difficult to justify for individual manufacturers.
- **Capacity That Flexes with Your Needs:** External partners can accommodate fluctuating testing volumes without staffing challenges.
- **Regulatory Confidence Built on Experience:** Working with laboratories that undergo regular regulatory inspections provides additional assurance that testing methods and documentation will satisfy agency requirements.

The true cost of in-house testing isn't just equipment and staff; it's the ongoing investment in keeping methods, training, and systems current with evolving regulations, increased scrutiny on data integrity, and new expectations.



TURNING THEORY INTO PRACTICE: IMPLEMENTATION ROADMAP

Moving from concept to execution requires careful planning and pragmatic decision-making. A well-designed raw materials testing program must balance theoretical best practices with operational realities.

When establishing or enhancing a raw materials testing program, several practical factors deserve careful consideration:

Aligning testing timelines with production realities is essential. Consider how testing turnaround times will impact manufacturing plans and whether expedited testing options are needed for time-sensitive materials.

Implementing robust method transfer protocols becomes critical when transitioning methods between laboratories or from suppliers to in-house testing. Comprehensive transfer protocols ensure comparable results across different testing environments.

Identifying specialty testing requirements early in the planning process prevents delays. Certain materials may require specialized techniques beyond standard

pharmacopeia methods that demand additional expertise or instrumentation.

Developing trending and data management systems enables proactive quality management. Track testing results over time to identify shifts in material quality or supplier performance before they become critical issues.

Creating comprehensive regulatory documentation supports smoother filings and inspections. Ensure testing generates the necessary documentation, particularly for materials used in validation batches.

Risk-based testing, tailored to material criticality, supplier history, and dosage form, is increasingly the expectation, allowing resources to be focused where they are most impactful.

By addressing these considerations proactively, pharmaceutical manufacturers can develop testing programs that effectively balance quality, compliance, and operational requirements.



THE FUTURE OF RAW MATERIALS TESTING: EMERGING TRENDS

The raw materials testing landscape continues to evolve, shaped by technological innovation, changing regulatory expectations, and industry transformation. Looking ahead, several interrelated developments will likely redefine how organizations approach materials qualification.

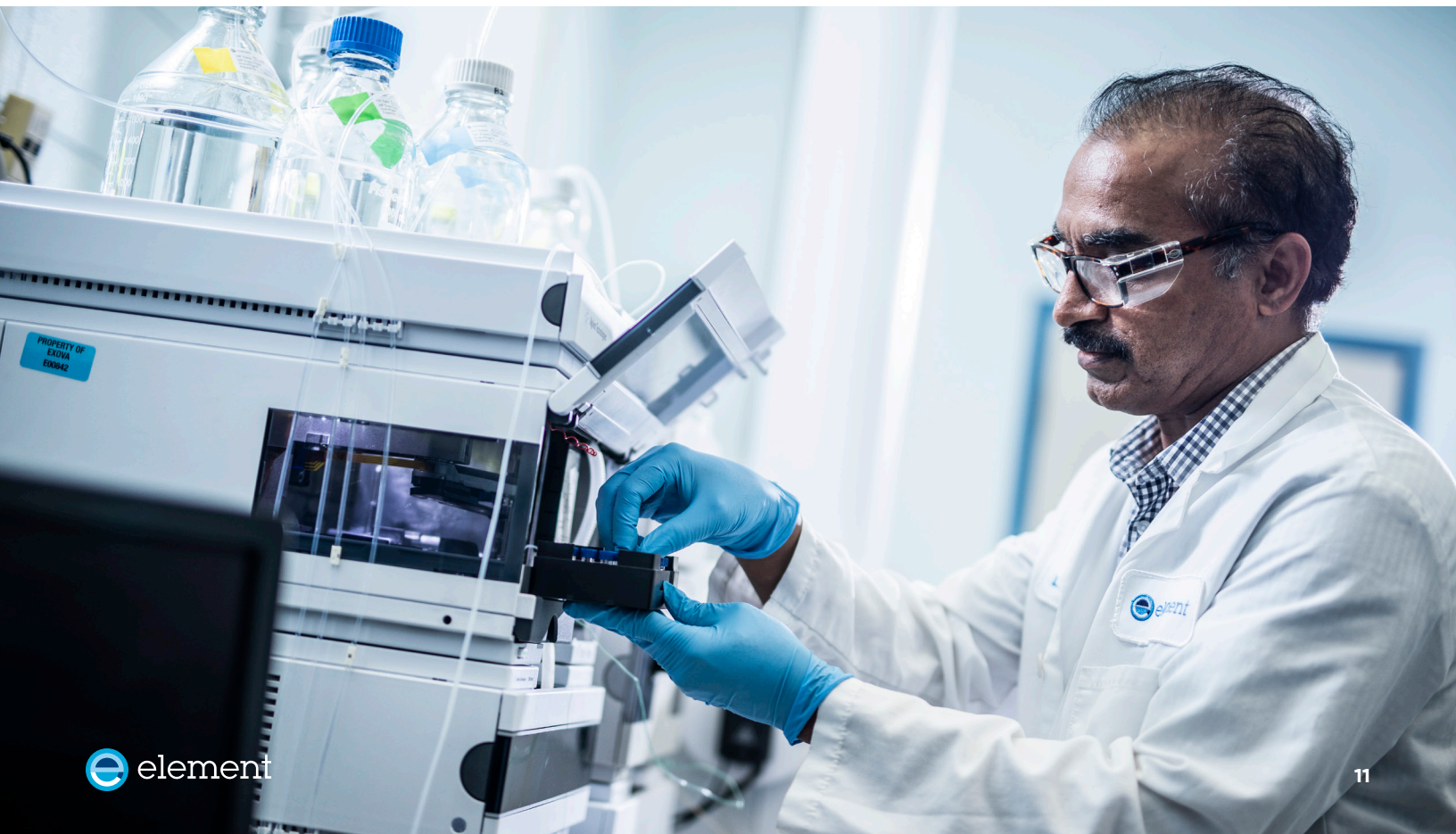
The integration of artificial intelligence into quality systems represents perhaps the most significant opportunity on the horizon. Beyond simple automation, advanced analytics platforms can now process vast datasets from multiple testing sources, identifying subtle patterns and correlations that might escape even experienced analysts. These capabilities enable more sophisticated supplier quality trending and may eventually support predictive quality models that anticipate issues before they affect production.

This evolution coincides with the industry's gradual shift toward continuous manufacturing. As batch processing gives way to continuous operations for suitable products, the traditional "test and release" paradigm for raw materials becomes inadequate. Forward-thinking organizations are already developing real-time monitoring strategies that combine rapid analytical methods with process analytical technology (PAT) to ensure materials maintain critical quality attributes throughout production.

The increasing focus on supply chain security is driving another transformation in raw materials management. Blockchain and other distributed ledger technologies are beginning to supplement traditional documentation, creating tamper-evident records of material origin, handling, and testing results. These systems promise to enhance raw materials traceability while potentially streamlining testing requirements for materials with comprehensive, verified provenance information.

Meanwhile, global regulatory harmonization continues to progress, albeit unevenly. The gradual alignment of pharmacopeial standards and expectations around data integrity, elemental impurities, and nitrosamine control creates opportunities for more standardized testing approaches across markets. Organizations that actively engage with these harmonization efforts gain early insight into emerging requirements while potentially influencing their development.

Companies that recognize these converging trends and adapt their testing strategies accordingly will not merely maintain compliance; they'll transform their raw materials quality operations into a competitive advantage, supporting faster development, more reliable manufacturing, and better patient outcomes.



TRANSFORMING COMPLIANCE INTO COMPETITIVE ADVANTAGE

Raw materials testing is not just a regulatory requirement; it's a strategic investment in product quality, manufacturing efficiency, and ultimately patient safety. A risk-based approach ensures resources are allocated effectively, balancing compliance with operational efficiency.

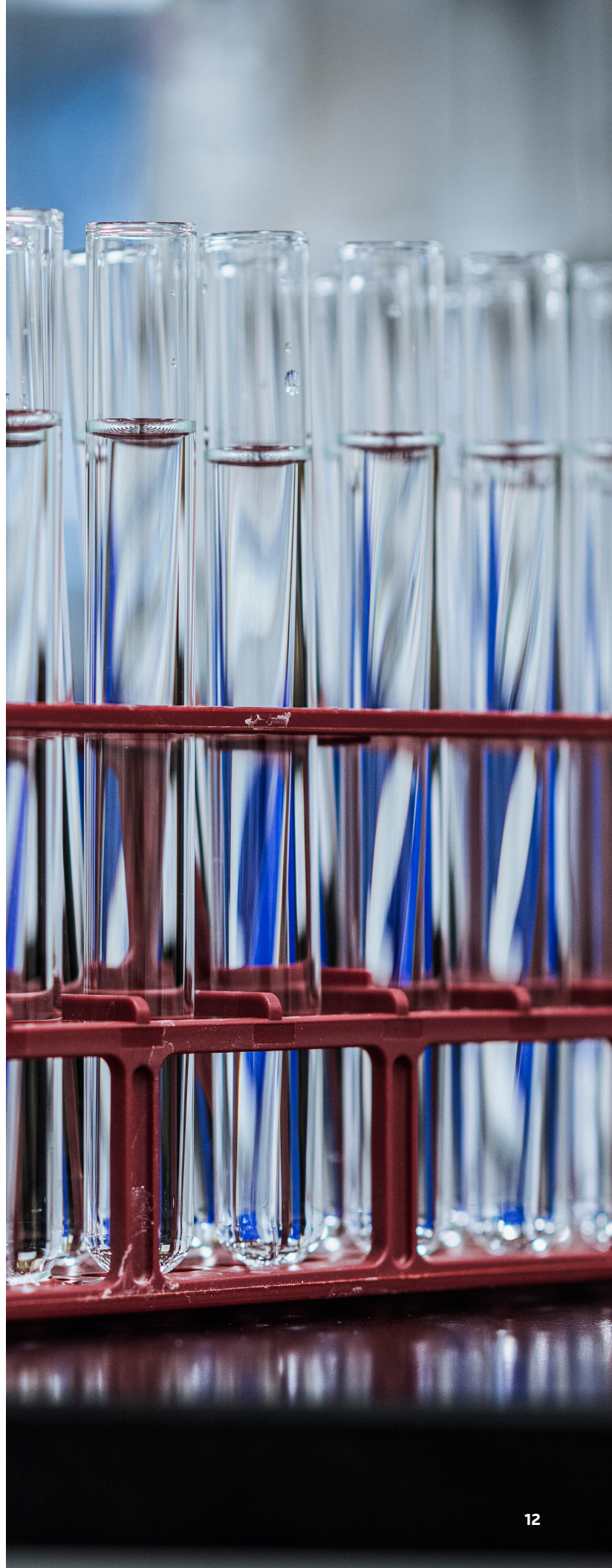
As regulatory expectations evolve, pharmaceutical manufacturers who stay ahead of these developments gain significant advantages in compliance, time-to-market, and quality assurance.

The pharmaceutical companies that lead their markets aren't those that test more; they're the ones that test smarter, using data to drive both quality and efficiency.

READY TO STRENGTHEN YOUR RAW MATERIALS TESTING PROGRAM?

Element offers comprehensive raw materials testing services designed to help manufacturers ensure quality, maintain compliance, and optimize production efficiency. Our network of laboratories provides access to advanced instrumentation, specialized expertise, and flexible capacity to support your specific testing needs.

To explore a partnership with Element, scan or click the QR code to get in touch with an expert.





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