Challenging the Tiered Paradigm for Raw Materials Testing

How Unified Lifecycle Characterization Could Reduce Risk, Lower Cost, and Accelerate Commercialization

Executive Summary

For decades, biopharmaceutical manufacturers have employed a tiered approach to raw materials testing. During early research and process development, organizations typically rely on supplier Certificates of Analysis (CoA), limited incoming verification, and fit-for-purpose analytical methods. As products progress toward clinical development and commercialization, analytical characterization expands, eventually culminating in extensive qualification, release, and lifecycle management programs.

This approach evolved for practical reasons. Comprehensive characterization of complex biological materials has historically been expensive, slow, technically demanding, and difficult to standardize across organizations. Consequently, manufacturers have generally reserved the most sophisticated analytical testing for later stages of development, when regulatory expectations increase and the economic consequences of failure become more severe.

Today, however, the industry faces a fundamentally different reality. Cell therapies, regenerative medicine products, gene therapies, and other advanced biologics increasingly depend on complex biological raw materials whose composition and variability can directly influence process performance, product quality, and manufacturing success. At the same time, advances in multiplex analytical technologies have dramatically reduced the cost and complexity of generating actionable characterization data.

These developments raise an important strategic question:

What if identity, quantity, and integrity testing of critical biological raw materials were performed from the earliest stages of process development and maintained throughout the product lifecycle using a single analytical platform?

Rather than viewing raw material characterization as a progressively expanding activity, could manufacturers benefit from a unified lifecycle testing strategy that begins during process development and continues through commercial manufacturing? More importantly, how might such an approach affect development risk, overall cost, and time to market?

The Origins of the Tiered Testing Paradigm

The concept of tiered analytical characterization is deeply embedded within modern biopharmaceutical development. Industry guidance and common practice generally advocate increasing levels of analytical rigor as products mature and development risks become better understood.

For example, BioPhorum's framework for media fingerprinting exemplifies this philosophy, proposing a structured three-tier approach that escalates from relatively simple characterization methods toward increasingly sophisticated analytical techniques as development advances and risk increases.[1] FDA guidance documents for gene therapy and cellular therapy products similarly emphasize progressively increasing process understanding, control strategy development, potency assurance, and raw material qualification throughout development and commercialization.[2–4]

The logic behind this model is straightforward: early-stage programs face substantial uncertainty and limited resources, and investing heavily in analytical characterization before a manufacturing process has matured may appear inefficient, particularly when many development candidates ultimately fail to reach commercialization.

Historically, the economics supported this strategy. Methods such as Western blotting, ELISA, HPLC, LC-MS, and other orthogonal analytical approaches required significant investments in instrumentation, specialized personnel, method development, and laboratory time. Organizations therefore focused analytical resources where they appeared most necessary and delayed more comprehensive characterization until later development stages.

In an era of expensive and fragmented testing technologies, the tiered paradigm represented a rational compromise between information generation and resource allocation.A linear plot of VaxArray results versus ELISA results in a slope of 1.2, with a Pearson's correlation coefficient (R) of 0.94. In this case, the slope implies that the VaxArray Influenza Assay typically yields a ~20% higher value for HA content.

Raw Materials Have Become Strategic Process Variables

While the analytical landscape has evolved, the biological complexity of modern manufacturing processes has increased even more rapidly.

Many advanced therapeutics depend on raw materials that are themselves complex biological products. Serum-derived supplements, extracellular matrix components, recombinant growth factors, cytokine mixtures, and specialized media additives can all exert profound effects on cellular behavior and process outcomes. Unlike relatively simple chemically defined media, advanced cell culture media often contain numerous interacting biological components whose collective effects may not be fully understood.

Rathore and colleagues highlighted the growing importance of raw material risk management in biopharmaceutical manufacturing, arguing that variability in raw materials can substantially influence process performance and product quality.[5] As manufacturing processes become increasingly dependent on living cells and complex biological systems, the significance of these inputs continues to grow.

Importantly, raw material variability is not confined to commercial manufacturing. It exists throughout development. Studies examining cell culture media have demonstrated that manufacturing conditions, storage duration, handling procedures, and preparation methods can all alter material composition and performance. Krattenmacher and colleagues showed measurable changes in chemically defined media associated with manufacturing temperature and storage duration.[6] Brunner and co-workers demonstrated that media preparation itself can influence process robustness and culture performance.[7] Sun and colleagues further illustrated the analytical complexity required to comprehensively characterize media composition through high-throughput LC-MS methodologies.[8]

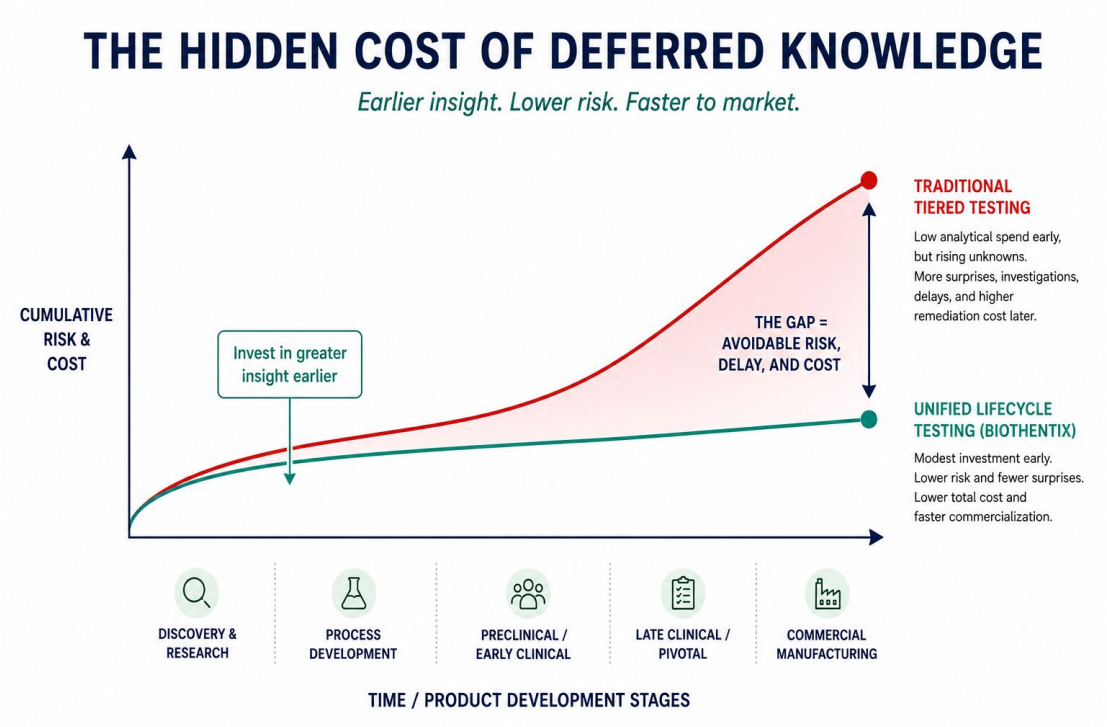
Collectively, these findings support a simple conclusion: critical raw material attributes are present, changing, and potentially influential long before commercial manufacturing begins.

The question is not whether variability exists. The question is when manufacturers choose to characterize it.

The Cost of Delayed Characterization

The tiered testing paradigm implicitly assumes that delaying comprehensive characterization carries little consequence during early development. Yet every experiment, process optimization study, scale-up activity, and comparability assessment is performed using raw materials whose characteristics may only be partially understood.

When variability remains unmeasured, its effects do not disappear. Instead, they become embedded within process data, development decisions, and manufacturing assumptions.



As programs advance, previously unrecognized raw material variability may emerge as unexplained process drift, inconsistent cellular performance, unexpected comparability outcomes, supplier-related deviations, or manufacturing investigations. By that point, organizations have often invested years of development effort and generated substantial data sets using incompletely characterized inputs.

The resulting costs are rarely limited to analytical testing. They frequently include repeated studies, extended investigations, delayed milestones, additional process development work, supplier qualification activities, and, in some cases, manufacturing failures.

At a strategic level, these downstream consequences can be viewed as the hidden cost of deferred knowledge.

A Thought Experiment: What If Testing Began Earlier?

Consider an alternative model:

Rather than increasing analytical characterization only as products progress toward commercialization, imagine that identity, quantity, and integrity testing of critical raw materials begins during the earliest stages of process development and continues throughout the entire product lifecycle using the same analytical, multiplex platform.

Under this model, each incoming lot of critical material contributes to a continuously expanding knowledge base. Relationships between material attributes and process outcomes become visible earlier. Supplier-to-supplier and lot-to-lot variability can be tracked over time. Stability trends emerge naturally. Historical baselines are established before investigations become necessary.

Most importantly, process understanding accumulates continuously rather than episodically.

When later-stage development activities occur - including comparability studies, supplier qualification efforts, process validation exercises, and commercial readiness programs - organizations are no longer attempting to reconstruct historical knowledge. Instead, they are building upon information that already exists.

This distinction may appear subtle, but its implications are significant. In the traditional model, characterization frequently follows questions. In a unified lifecycle model, characterization often precedes them.

Reframing the Economics of Testing

One reason the tiered paradigm persists is the assumption that more testing inevitably means higher costs. Historically, that assumption was largely correct.

Today, however, the economics deserve reconsideration. The true cost of raw material characterization should not be measured solely by the price of an analytical assay. It should also account for the costs associated with uncertainty.

Every development delay, root cause investigation, failed experiment, comparability challenge, supplier qualification issue, and manufacturing deviation represents an economic consequence of incomplete information. While not all such events originate from raw material variability, many are influenced by it.

As multiplex analytical platforms reduce the cost of generating information, the balance begins to shift. Instead of asking whether organizations can justify additional testing, a more relevant question emerges: can organizations afford the cost of not knowing?

Viewed through this lens, earlier characterization may represent an investment in risk reduction rather than an increase in analytical expense.

Enabling a Unified Lifecycle Testing Strategy

The feasibility of continuous lifecycle characterization depends on the availability of analytical technologies capable of supporting both development and quality control applications.

Traditionally, organizations relied on collections of specialized methods, each optimized for a specific question. The resulting workflows were fragmented, labor-intensive, and difficult to harmonize across suppliers, manufacturers, CDMOs, and testing laboratories.

Multiplex analytical platforms offer a fundamentally different approach. By enabling simultaneous measurement of multiple analytes on a standardized platform, they create the possibility of maintaining analytical continuity throughout development and commercialization.

For example, InDevR's Biothentix™ platform was developed around this concept. Rather than serving as a single-purpose analytical assay, the platform is designed to support identity, quantity, and integrity testing of complex biological raw materials using standardized, customer-defined reagent kits, digital workflows, and rapid turnaround times. The same platform can support process development, supplier qualification, incoming quality control, investigations, and lifecycle management activities.

The significance of this approach is not merely analytical efficiency. It is the possibility of replacing fragmented, stage-specific testing strategies with a continuous framework for generating and leveraging process knowledge.

Conclusion

The tiered approach to raw materials testing emerged for valid historical reasons. Analytical characterization was expensive, fragmented, and difficult to deploy broadly, making it sensible to concentrate testing efforts later in development when risks and regulatory expectations increased.

However, both the products being developed and the analytical technologies available to support them have changed substantially.

Modern biotherapeutics increasingly depend on complex biological raw materials whose variability can directly influence process performance and product quality. Simultaneously, multiplex analytical technologies have reduced the cost and complexity of generating actionable characterization data.