

WHITE PAPER

# Breaking Through the Testing Bottleneck

How Rapid Detection Methods  
Are Modernizing Quality Control  
in Biologics Manufacturing

# THE TESTING TIME CHALLENGE

**Traditional microbial testing methods, while reliable, pose significant challenges in biologics manufacturing. Release testing protocols (including Sterility and Mycoplasma Testing) require 14-28 days – a timeframe that frequently leads to manufacturing bottlenecks and delayed product release. These extended testing periods are especially problematic for therapeutics with short shelf lives. The consequences of these extended test periods include disrupted production workflows, increased inventory hold times, potential product stability concerns, and – most critically – delayed delivery of life-saving treatments to patients. In an environment where speed to market, productivity, and safety underpin organizational health, drug developers must adopt faster, more efficient testing strategies to meet both modern production demands and compliance requirements.**

## AUTHOR

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Melisa Byrd specializes in environmental monitoring and quality assurance within the microbiology field. With progressive experience across laboratory roles, she applies expertise in Corrective and Preventive Action (CAPA) methodologies to ensure regulatory compliance and product safety. Her Cell/Cellular and Molecular Biology background from San Francisco State University underpins her technical approach to solving critical contamination challenges.

The biologics industry is increasingly turning to alternative approaches that increase testing sensitivity while reducing time-to-result. Rapid detection technologies provide a transformative solution, cutting sterility testing to roughly seven days and mycoplasma testing to just one to three days. However, implementing these methods requires careful consideration of technical, regulatory, and operational factors.

“There are several reasons why rapid sterility may not be suitable for organizations to implement in-house, including the need to meet specific validation criteria, lengthy method validation process, complex therapy workflows, and cost and resources associated with new equipment, training, and validation efforts.” Says Jihye Jang-Lee, Director of Technical Services at Element Materials Technology. Jang-Lee further explains that in her experience, “Most of the drug developers we engage are looking to gain efficiencies in expediting product route to market while keeping key resources focused on growing their pipeline and maintaining a favorable cost profile. And that’s exactly where we can help.”

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Director of Technical Services at Element Materials Technology

# WHY FASTER TESTING MATTERS IN BIOLOGICS MANUFACTURING

The implications of traditional testing timelines extend throughout the manufacturing process, disrupting production schedules and complicating inventory management. Standard sterility testing, per USP <71>, requires a minimum 14-day incubation period, with a potential extension to 18 days when subculturing is necessary. In the case of products with high cell counts or inherent turbidity, the additional subculture step adds days to an already lengthy testing timeline. This requirement applies to substances, preparations, and articles which, according to the

pharmacopeia, must be sterile – encompassing everything from parenteral preparations to ophthalmic products.

For mycoplasma testing, traditional culture methods demand a minimum of 28 days testing length for definitive results, involving both agar and broth culture methods with multiple intermediate checks. These extended testing periods significantly impact inventory management, manufacturing scheduling, and facility utilization efficiency.

## Figure 1: Advancements in technology offer efficiency and increase productivity

Testing for mycoplasma should occur at multiple points including when the cells are first obtained, cultured, passaged, transfected and just prior to re-introduction to the patient. Leveraging rapid mycoplasma testing techniques provide drug developers with efficiencies across the manufacturing workflow.



Beyond timeline considerations, traditional methods present additional technical constraints. These methods often demand large sample volumes - problematic for high-value biologics, where every milliliter represents significant value. Limited opportunity for in-process testing reduces the ability to detect contamination events early in the manufacturing process. Product matrix effects may necessitate additional

subculture steps, creating further delays in the availability of results.

Where appropriate, the use of rapid microbial detection methods help mitigate these risks by enabling real-time decision-making and improving process efficiency.



# TRANSFORMATIVE APPROACHES TO MYCOPLASMA TESTING

The biologics industry faces unique mycoplasma detection challenges that conventional pharmaceuticals don't encounter. In protein-based therapeutics, mycoplasma contamination can trigger post-translational modifications, alter glycosylation patterns, and introduce host cell protein impurities—issues that may evade detection in standard potency assays yet significantly impact clinical efficacy and immunogenicity profiles. Regulatory authorities, including the FDA and EMA, have recognized the limitations of traditional mycoplasma testing for advanced therapies. Their guidance documents acknowledge that conventional 28-day culture methods may be impractical for cell and gene therapy products with inherently short shelf-lives, creating a pathway for alternative method adoption when properly validated.

Nucleic acid-based mycoplasma detection techniques have gained acceptance through validation approaches that demonstrate comparable or superior detection capabilities relative to traditional methods. These molecular methods typically target the highly conserved 16S rRNA gene region found across mycoplasma species known to contaminate

biologics manufacturing processes. Implementing rapid methods in biologics manufacturing presents unique challenges. Products with inherent fluorescence, high cell density, or complex formulations often require customized sample preparation protocols to prevent test interference. Method validation must demonstrate effective control of inhibitors through internal amplification controls that verify each individual test's performance.

The economic benefits of rapid mycoplasma detection are particularly relevant in biologics facilities where manufacturing capacity is limited and valuable. Traditional testing methods that require holding product or production suites for extended periods represent significant opportunity costs and can impact manufacturing schedules across multiple products. Contract development and manufacturing organizations supporting biologics production increasingly offer rapid mycoplasma testing approaches that have been validated across common expression systems and manufacturing processes. This availability helps biopharmaceutical companies implement advanced methods while managing regulatory considerations effectively.



# NEXT-GENERATION DETECTION TECHNOLOGIES

Modern rapid detection methods improve speed and reliability, employing various analytical principles to achieve faster, more reliable contamination detection. Each technology offers distinct advantages for specific applications, requiring careful evaluation for specific product types and manufacturing processes.

## STERILITY VIA RESPIRATION DETECTION

Respiration detection technology enables continuous monitoring of microbial metabolism through the measurement of CO<sub>2</sub> production. Advanced automated systems maintain precise environmental conditions in separate chambers for aerobic and anaerobic organisms. The technology utilizes sophisticated monitoring capabilities with automated data management, ensuring complete traceability from sample preparation through final reporting.

The automated nature of detection significantly reduces time-to-result compared to traditional methods. While conventional testing requires 14-18 days, respiration detection has the ability to deliver results in less than 7 days. This improvement stems from continuous monitoring capabilities combined with the elimination of subjective visual inspection steps. An integrated barcode tracking system provides complete traceability from sample preparation to final reporting, ensuring data integrity.

Figure 2: Rapid sterility by respiration detection process

Each bottle has a unique barcode, which is scanned in by the analyst. The system records product and client information, which is correlated in the analyzer. To the naked eye, there is a visual color change; to the monitoring system, respiration in the test sample is measured.



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# THE REGULATORY RESPONSE AND INDUSTRY-WIDE ADOPTION CHALLENGES

As the industry moves toward adopting rapid methods, regulatory authorities are developing new guidance while maintaining rigorous standards for microbial detection. While USP <71> remains the cornerstone for sterility testing, the concurrent release of USP chapters <72> and <1071> lays out the framework for performing rapid sterility via respiration detection for short shelf-life sterile products. This chapter introduces a risk-based approach for method selection and validation, reflecting growing regulatory acceptance and the importance of rapid methods in modern biologics manufacturing. In addition to these chapters, the USP has also released chapter <73>, which focuses on ATP bioluminescence-based microbiological methods. Altogether, the development of these chapters is evidence of the demand and use of these evolving testing methods on an industry-wide scale.

Regulators in different regions are progressing at varying rates, with the US Food & Drug Administration (FDA) and European Medicines Agency (EMA) showing increasing acceptance of rapid methods, provided they demonstrate equivalency to traditional approaches. Industry groups such as the Parenteral Drug Association (PDA) and the International Society for Pharmaceutical Engineering (ISPE) are advocating for clearer pathways to regulatory approval, but harmonization across global agencies remains a challenge.

One of the most significant hurdles in the industry-wide adoption of rapid detection approaches is the need to validate rapid detection methods against traditional culture-based techniques. Regulators require extensive comparability studies to ensure that alternative methods can reliably detect contamination across a range of biologic products. Method validation must demonstrate not only technical performance but also appropriate

integration with existing quality systems. Key validation considerations include:

- Sensitivity and specificity evaluation across different product types and contamination scenarios
- Assessment of matrix effects and potential interference
- Establishment of appropriate system suitability parameters
- Development of robust statistical methods for data analysis
- Documentation of equivalency to traditional methods

The validation approach must consider both technical performance and practical implementation factors. Early regulatory engagement often proves valuable in establishing appropriate validation strategies. Method validation protocols should demonstrate a thorough understanding of potential failure modes and their impact on product quality and patient safety.

Another key regulatory consideration is data integrity. Because rapid methods generate significantly larger and more complex datasets than traditional testing, regulators expect robust audit trail management and compliance with ALCOA+ principles (A: Attributable, L: Legible, C: Contemporaneous, O: Original, +: Complete, Consistent, Enduring, and Available). Automated systems must be validated to ensure electronic records are secure, accurate, and resistant to unauthorized modifications. Inspector familiarity with rapid methods also varies, leading to heightened scrutiny during regulatory inspections. Companies implementing rapid testing must be prepared to provide comprehensive documentation supporting method validation and system suitability.

# IMPACT ON BATCH RELEASE TIMELINES AND MANUFACTURING EFFICIENCY

Reducing microbial testing timelines has a direct impact on batch release strategies, particularly for time-sensitive biologics. Traditional sterility testing can hold batches for two to four weeks before final release, significantly affecting production cycles, inventory costs, and ultimately revenues. Rapid sterility testing reduces these delays by providing the needed results approximately seven days faster, allowing manufacturers to move products through quality control processes more efficiently. Mycoplasma detection timelines are reduced even more dramatically, from 28 days to as little as one to three days, enabling faster decision-making and reducing the risk of production bottlenecks.

The ability to accelerate batch release is particularly critical for advanced cell and gene therapies where each dose is specifically manufactured to an individual patient's unique needs. Rapid microbial detection supports real-time release testing, minimizing the time between production and administration. While regulatory agencies still require robust validation before approving real-time release strategies, the shift toward faster detection aligns with broader industry trends in continuous manufacturing and process analytical technology (PAT).

# TRANSFORMING DATA MANAGEMENT FOR NEXT-GENERATION TESTING

Modern rapid detection systems generate complex datasets requiring sophisticated approaches to data acquisition, storage, and analysis. Electronic records must satisfy ALCOA+ principles while accommodating real-time monitoring and automated analysis. Unlike traditional methods where primary data consists primarily of growth/no-growth observations, rapid methods generate rich datasets including multiple parameters measured over time.

Raw data management requires particular attention in rapid detection systems. Clear definitions of raw data become crucial, as does determining appropriate retention strategies for large datasets. System architecture must support

complete data retention while maintaining accessibility for routine review and investigation. Data analysis algorithms require thorough validation, with appropriate controls to prevent unauthorized modifications.

Audit trail requirements demand particular attention given the volume of data generated by automated systems. Risk-based approaches to audit trail review must be carefully documented and validated to ensure regulatory compliance while remaining practically manageable. Version control becomes critical for both software and analysis parameters, requiring robust change control processes that maintain system effectiveness.



# SELECTING THE RIGHT PARTNER FOR RAPID MICROBIOLOGICAL TESTING METHODS

The implementation of rapid detection methods requires careful selection of testing partners with appropriate technical expertise and infrastructure. Strong testing laboratories should demonstrate mastery of both traditional and rapid methods, as this dual capability proves essential during method validation and routine testing. Understanding traditional culture-based approaches alongside modern molecular techniques enables proper comparability studies and method optimization.

“There is no shortage of testing partners in the marketplace...”, adds Jang-Lee. “Part of what makes a service provider an ideal partner, aside from the technical capabilities both traditional and rapid methods, includes flexibility, responsiveness, and a partnership-driven approach in order to work through nuances quickly and effectively.”

In addition, data management capabilities warrant particular attention when evaluating potential partners. Testing laboratories must maintain robust systems for data integrity, sample tracking, and result reporting. Experience with automated systems and complex data analysis helps ensure the reliable implementation of rapid methods.

Validation expertise represents another critical consideration. Testing partners should demonstrate a thorough understanding of current regulatory requirements and experience navigating method validation across different product types. This expertise proves particularly valuable when adapting rapid methods for challenging products or unique manufacturing processes.

Rapid detection methods continue to advance through developments in both technology and regulatory science. Next-generation sequencing technologies show increasing potential for manufacturing applications, offering enhanced characterization of microbial populations. Improvements in sample preparation automation promise greater standardization and reduced operator intervention.

Integration with process analytical technology creates opportunities for more responsive manufacturing control. However, careful validation strategies remain essential as systems become more sophisticated. The convergence of rapid testing methods with advanced data analytics suggests future possibilities for real-time release testing, though regulatory frameworks continue to evolve.



# THE PATH FORWARD

## SMARTER, FASTER, MORE RELIABLE QUALITY CONTROL IN BIOLOGICS MANUFACTURING

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The implementation of rapid detection methods represents a significant advancement in biologics quality control, offering substantial benefits in time-to-result while maintaining or exceeding traditional method sensitivity. Success requires careful attention to method selection, validation strategy, and quality system integration. While implementation demands significant technical investment, the operational benefits through reduced hold times and improved process control often justify the commitment.

As these technologies continue to evolve, manufacturers must balance the desire for increased testing speed against requirements for reliable, compliant systems. Organizations that successfully navigate this transition position themselves to improve manufacturing efficiency while maintaining the highest standards of quality control.





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