

Mastering sterile fill–finish in the age of advanced therapies

Tommy Schornak, Senior Vice President of Injectables at Kindeva, outlines the main challenges impacting the sterile fill–finish sector and how manufacturers can leverage advancements like automation to future-proof their operations.

The sterile fill–finish market is currently experiencing a period of unprecedented growth. Valued at approximately $15.4 billion in 2023, projections indicate a robust growth trajectory, expecting to reach $33.5 billion by 2032 – a compound annual growth rate of 9.1 percent.[1] This surge is primarily the result of the increasing global prevalence of chronic diseases, which necessitates a continuous pipeline of advanced therapeutic solutions. Additionally, the pharmaceutical R&D landscape is increasingly embracing injectable drug delivery, with two-thirds of the current pipeline requiring this route of administration. This shift is notable, as it includes innovative treatments such as GLP-1 receptor agonist therapies, which have recently seen a dramatic rise in demand.

However, this rapid expansion is not without its complexities. Beyond the fundamental need for increased capacity, the industry faces complex technical and operational challenges that require sophisticated solutions. Ensuring absolute sterility consistency across diverse production batches remains the primary concern, particularly as manufacturing processes become more intricate. Also, the integration of advanced automation, while offering transformative benefits, introduces its own set of implementation and validation challenges. Finally, the evolving nature of therapeutic modalities, particularly the growing dominance of complex biologics, presents unique demands on fill–finish processes, requiring specialised handling and precise environmental controls.



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At this critical juncture for the pharmaceutical industry, proactive adaptation and robust quality assurance systems are essential. They ensure the safe, efficient and compliant delivery of life-saving therapies, safeguarding patient wellbeing and maintaining the integrity of the global pharmaceutical supply chain. This article examines these critical challenges and explores the strategies for successfully navigating the future of sterile fill–finish manufacturing.

The challenge of sterility assurance and batch variability

The assurance of sterility is paramount in injectable pharmaceutical manufacturing, as any compromise poses significant risks to patient safety and regulatory compliance. While aseptic processing principles are well-established, maintaining consistent sterility across diverse production batches, especially with increasing process and product complexity, remains a formidable challenge for the fill–finish sector.

Batch-to-batch variability in sterility often arises from subtle factors. Environmental control, despite stringent cleanroom classifications, can be impacted by nuanced challenges like variations in air circulation or transient non-viable particulates. Historically, human intervention has been a primary contamination risk, underscoring the limitations of relying solely on procedural controls. Additionally, minute fluctuations in process parameters, such as sterilisation cycle times or filling-pump speeds, can influence drug product quality and stability. »



In the past few years, the regulatory landscape has significantly evolved, notably with the 2022 revision of EU GMP Annex 1. This updated guideline emphasises advanced technology and engineering solutions over procedural controls for minimising risks to sterility assurance. This shift requires substantial capital investment in facility upgrades or new Annex 1-compliant greenfield capacity, as retrofitting existing facilities is often impractical due to the high costs and disruptions associated with it.

To strategically mitigate these challenges, the industry is increasingly adopting advanced solutions. Restricted access barrier systems (RABS) provide physical separation, but the trend is decisively moving towards isolator technology, which offers a fully contained, automated environment, virtually eliminating direct human intervention.

Isolators are becoming the preferred standard for future-proofing manufacturing. Complementing these are robust environmental monitoring systems, transitioning to real-time, continuous monitoring. Finally, the integration of process analytical technology (PAT) for real-time process understanding and comprehensive data integrity and traceability systems is indispensable for accountability, audits and continuous improvement, enhancing overall sterility assurance.

The shift to highly automated facilities also requires a workforce evolution, creating a demand for skilled personnel to operate and maintain complex machinery

The practicalities of automation

Automation has become an indispensable force in modern sterile fill–finish manufacturing, extending beyond mere efficiency to mitigate contamination risks, enhance product quality and ensure regulatory compliance. Its core benefits directly address aseptic processing challenges.

These include:

- **Minimised human error and contamination** by replacing manual interventions with precisely controlled robotic systems. This shift to engineering controls aligns with the regulatory expectations outlined in GMP Annex 1.
- **Increased throughput and efficiency**, enabling higher production volumes and predictable schedules.
- **Generation of comprehensive and reliable data**, which is vital for real-time monitoring, quality control and streamlined audits, providing an indisputable record of manufacturing conditions.
- **Consistent dosing accuracy and reduced product loss** thanks to the precision and reproducibility of robotic handling and automated filling.

Key automated technologies now standard in fill–finish include automated filling and stoppering lines, robotic handling for sterile transfers, advanced automated visual inspection systems and automated container closure integrity testing (CCIT).

Despite these advantages, adopting automation presents practical challenges. Significant capital investment is required, necessitating clear ROI strategies. Integrating disparate automated systems into a cohesive workflow can be complex and requires specialised expertise.

The shift to highly automated facilities also requires a workforce evolution, creating a demand for skilled personnel to operate and maintain complex machinery, thus requiring investment in training. Finally, rigorous validation and qualification of automated systems are paramount to ensure consistent and reliable performance. Effectively navigating these practicalities is crucial to realise the full transformative potential of automation in sterile fill–finish.

This fundamental shift in product landscape presents a distinct set of challenges for sterile fill–finish operations, moving beyond the traditional demands of small-molecule manufacturing

The intricacies of advanced therapies

The pharmaceutical pipeline is increasingly dominated by complex therapeutic modalities, including monoclonal antibodies (mAbs), cell and gene therapies (CGT) and mRNA vaccines. This fundamental shift in product landscape presents a distinct set of challenges for sterile fill–finish operations, moving beyond the traditional demands of small-molecule manufacturing.

The unique properties of biologics require specialised handling and processing. A primary concern is the high cost of their drug substances, which makes minimising line losses and preventing batch failures vital. Even minor deviations can have significant financial implications. Also, the inherent temperature sensitivity of many biologics demands rigorous cold chain management throughout the



entire manufacturing and distribution process, from formulation to final delivery. This requires sophisticated infrastructure and meticulous control to maintain product integrity.

The trend towards highly targeted therapies also translates into smaller batch sizes and increased manufacturing complexity, challenging existing commercial capacities typically designed for larger, recurring volumes. Additionally, many biologics exhibit high viscosity or shear sensitivity, requiring specialised filling equipment and gentle handling to prevent aggregation or degradation. The potent nature of some advanced therapeutic ingredients also necessitates robust containment solutions to ensure operator safety and to avoid cross-contamination.

Answering these complex needs requires specialised facilities and formulation suites tailored for these advanced therapies. Also, adoption of single-use technologies offers benefits such as reduced risk of cross-contamination, enhanced facility flexibility and minimised downtime between runs. Crucially, robust cold chain infrastructure and expertise are needed to support the unique temperature requirements of next-generation therapies. Additionally, the need for flexibility to accommodate diverse product pipelines must be balanced with the scalability required for potential market surges, signifying an evolving partnership dynamic with innovators.

Future-proofing fill–finish operations

As the sterile fill–finish field continues to evolve rapidly, the industry must adopt forward-thinking strategies to ensure long-term resilience, quality and efficiency. A key imperative lies in embracing integrated data and innovative manufacturing approaches. Future integration of artificial intelligence (AI) also holds promise, with potential opportunities for process optimisation, predictive maintenance and real-time quality control.

By leveraging these advanced analytical capabilities, manufacturers can gain deeper insights into process performance, enhance operator aseptic training and enable more agile, data-driven decision-making. The comprehensive analysis of integrated system data will serve as the foundation for continuous improvement and proactive problem-solving.

Specialist CDMOs' capabilities in managing complex biologics, actively adopting best automation practices and commitment to exceeding regulatory compliance are shaping a more resilient supply chain, meeting the demand for GLP-1 products. Ultimately, the collaborative efforts between innovators and CDMOs, coupled with continuous investment and organisational agility, will play a big part in defining the industry's success in delivering safe, effective and accessible therapies to patients globally.

Reference

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At Kindeva, he is focused on advancing injectable capabilities that aid customers' commercial success and public health impact, supporting capacity expansion through to continuous improvement.