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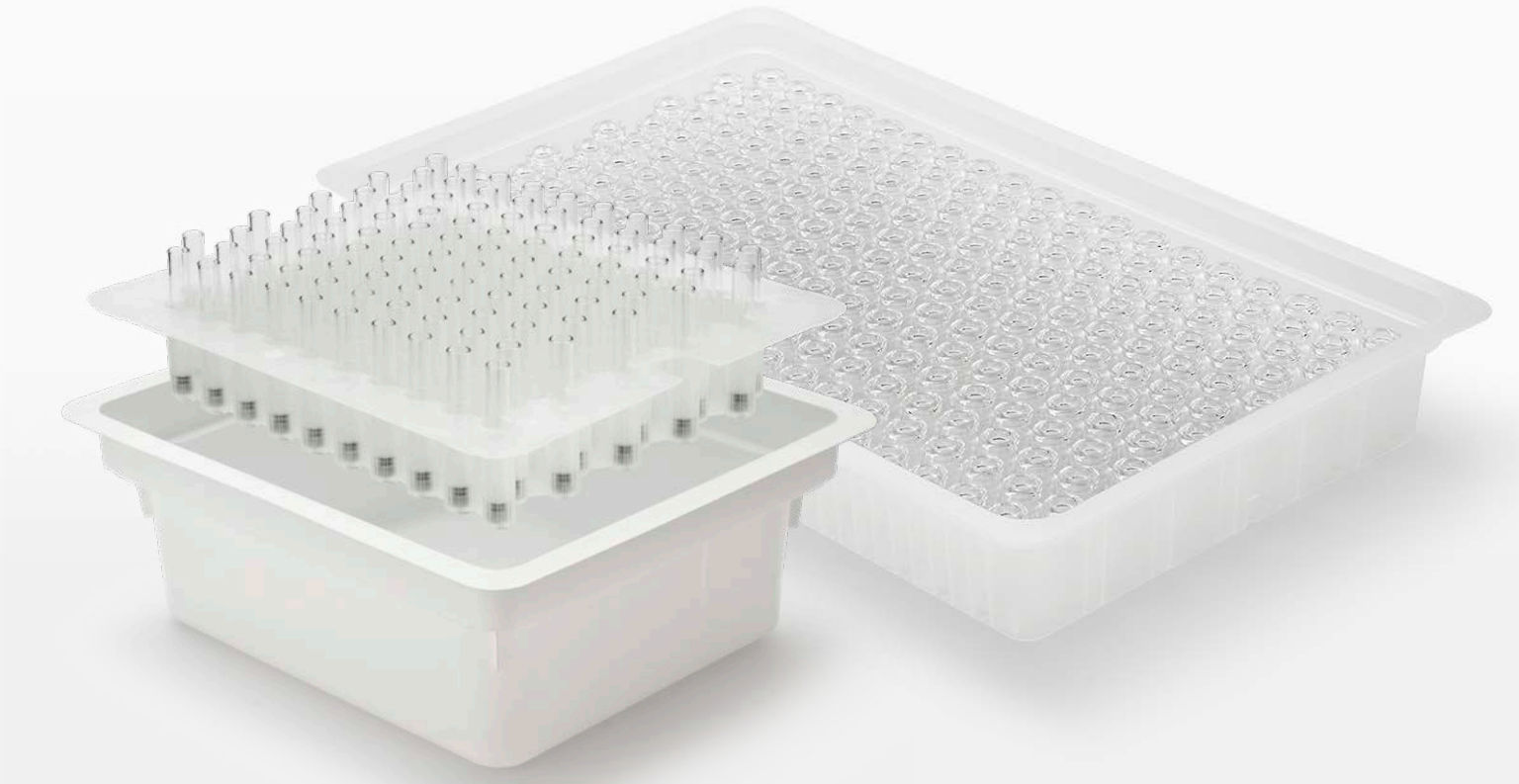


Stevanato Group EZ-fill cartridges (left) and vials (right).

Fill-Finish Contract Manufacturing: Enhancing Compliance and Flexibility with RTU Solutions

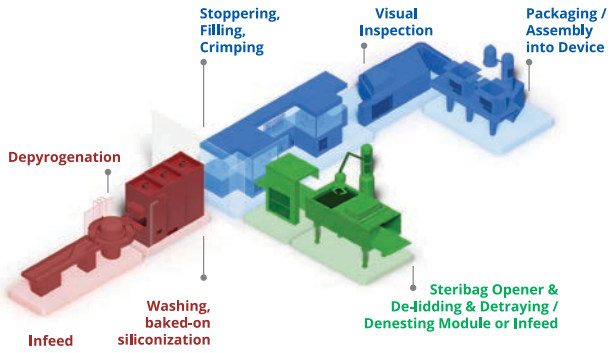
Leveraging ready-to-use technology to streamline fill-finish manufacturing, enhance compliance, and minimize contamination risks.

In the evolving landscape of pharmaceutical production, fill-finish contract manufacturing has become a crucial area of focus, particularly as new regulatory standards and market demands shape industry practices. Key regulatory updates include the revised GMP Annex 1, which has a direct impact on sterile manufacturing processes. These changes underscore the importance of maintaining high standards of sterility, quality and safety in pharmaceutical manufacturing. In this context, Ready-to-Use (RTU) containers, including syringes, vials and cartridges, can offer pharmaceutical manufacturers several operational advantages to ensure a comprehensive contamination control strategy (CCS) as a basis for a compliant production condition for their sterile product.

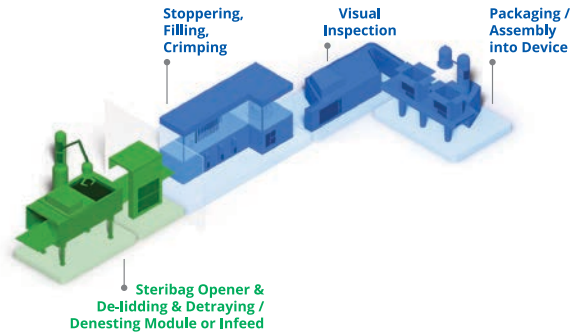
FILL-FINISH CONTRACT MANUFACTURING

The growing complexity in the pharmaceutical industry creates an even bigger challenge for fill-finish contract manufacturers having to cope with the various solutions required by their customers.

Traditional pharmaceutical processes using bulk containers place a comparatively high burden on the production chain for both manual and semi-automated applications. They are subject to quality control (QC) testing and documentation review prior to their release for filling. Bulk packaged containers are exposed to glass-to-glass contact throughout the washing and depyrogenation. This can increase the risk of visual defects, sub-critical defects not instantly leading to breakage but accu-



Option 1: Bypass Washer and Depyrogenation tunnel



Option 2: Substitute the Washer and Depyrogenation tunnel

mulate over time, glass particles or contamination by particles that are not inherent to the product.

Depyrogenation to remove endotoxins poses further risks as it involves high temperatures. Glass-to-metal contact inevitable in such equipment can lead to damage, particularly due to the lower glass resistance at high temperatures. In addition, a documented correlation has been found between the failure of fogging of freeze-dried vials, the quality of the inner surface of the vials and the temperature exposure during depyrogenation.

Reducing complexity and de-risking production processes demand innovations that streamline the manufacturing process, improve efficiency, and ensure compliance.

Innovative RTU concepts are a key solution enabling fill-finish contract manufactures to overcome these challenges as part of their GMP Annex 1 implementation.

RTU SOLUTIONS IN CONNECTION WITH FILL-FINISH

RTU systems such as pre-sterilized vials, syringes and cartridges, simplify the fill-finish process. Time-consuming and labor-intensive steps such as washing, depyrogenation and sterilization are eliminated in the fill-finish process. This results in less complex production equipment that requires less maintenance, a reduction in validation and re-validation activities and a lower inventory of spare parts.

Overall production time is significantly reduced as production line set-up is simplified and the risk of line stoppages due to washing and depyrogenation issues is mitigated. In addition, the more compact filling line requires fewer environmental and process controls. Altogether, this leads to an overall reduction in the risk of product defects and most importantly cost.

Flexibility and scalability are key to fill-finish contract manufacturers. RTU systems enable the production of small batches without compromising quality and allow for scalability that does not require a change to the chosen primary packaging solution. This is a major advantage in fill-finish contract manufacturing, where adaptability to fluctuating production volumes is crucial.

COMPLIANCE AND EFFICIENCY BENEFITS OF RTU SOLUTIONS

Compliance with GMP regulations—the updated EU GMP Annex 1, which regulates the manufacture of sterile medicinal products, came into force on August 25, 2023. In addition to the regulatory authorities of the EMA, the Pharmaceutical Inspection Cooperation Scheme (PIC/S) and the World Health Organization (WHO) were also involved in the revision. While the provisions of Annex 1 do not apply directly to products sold outside the EU and participating countries, members of the FDA were also represented on the PIC/S Committee to ensure consistency between the two agencies.

One of the big changes in GMP is the application of quality risk management (QRM), which is based on ICH Q9 and Q10 from 2009. The new QRM updates require manufacturers to identify measures to mitigate potential risks associated with their processes. This requires a holistic assessment of the infrastructure as well as the production process, including plant design and product components such as primary packaging materials.

In addition, manufacturers of sterile products must establish a comprehensive contamination control strategy (CCS) that relates to its manufacturing processes to ensure that the sterile product is manufactured under compliant conditions and is therefore safe for patients.

The pharmaceutical quality system (PQS) includes general controls, change controls, non-conformance management and supplier control, focusing on management's role in providing the necessary resources.

RTU solutions are inherently aligned with these new requirements as they minimize manual intervention, eliminate rough handling such as depyrogenation tunnels, reduce glass-to-glass and glass-to-metal contact and potential contamination risks. Compared to the challenges faced by pharmaceutical companies working with bulk processes, RTU solutions offer a real alternative ensuring compliance with the revised GMP require-

ments from a supplier that is entirely focusing on this process.

Focus on operational efficiency—compared to a bulk line, the benefits of an RTU filling line are:

- Reduction in extraordinary and preventive maintenance
- Reduction in calibration effort (extraordinary and preventive/ routine)
- Reduction in requalification effort
- Reduction in environmental and process controls specifically related to the washing and depyrogenation steps
- Reduction in downtime related to washing and depyrogenation (elimination of breakages, dropped or stuck products, etc.)
- No defects resulting from the washing and tunneling steps like subvisible cracks or subvisible breaks
- No defects due to sub-cracks or sub-breaks in the washing and tunneling equipment leading to real cracks in the container and discarded during filling or visual inspection
- Fewer staff, only half the required full-time equivalents (FTE) needed
- Flexibility in using combi-lines able to process RTU syringes, cartridges and vials on a single platform

All these attributes contribute to smoother, more cost-effective fill-finish process. In addition, CAPEX of an RTU filing line is much lower and, over time even more important, the space populated is considerably less leading to lower cost and a higher added value per square meter.

Compatibility with existing set-up—adapting the infrastructure is not an impossible hurdle to overcome. For CMOs operating bulk lines, there are two options to implement RTU besides the purchase of a new line. One option is to bypass the washer and depyrogenation tunnel of the current fill-finish equipment in adding de-lidding and de-traying/de-nesting equipment for the automatic infeed and extraction of RTU containers. Or as second option, to substitute the washer and depyrogenation tunnel with de-lidding and de-traying / de-nesting equipment. These options are available for pre-capped or uncapped RTU cartridges or uncapped RTU vials (see Figure 1)

FLEXIBILITY AND RISK MITIGATION

Flexibility in fill-finish processes—RTU containers offer greater flexibility, a critical factor for contract manufacturers who often need to meet varied client demands with different production volumes. The ability to quickly switch between small and large batch production without extensive reconfiguration or to run different container types on a combi-line helps contract manufacturers stay agile.

Risk mitigation—RTU systems contribute to reducing contamination risk due to fewer manual handling steps and virtually no glass-to-glass contact ensuring that only high-quality products reach the market, reducing the risk of costly recalls or compliance failures.

Downstream advantages for visual inspection—The higher quality level of RTU solutions also leads to less scrap and waste during the fill-finish process, generating a lower risk of glass container failure in downstream processes and a lower reject rate during visual inspection.

Stevanato Group RTU Solutions

Stevanato's EZ-fill RTU solutions create a streamlined, agile and cost-effective fill-finish contract manufacturing process that meets both, industry needs and regulatory requirements. The EZ-fill platform has become the market reference offering a fully integrated pre-sterilized containment solution which includes vials, cartridges and syringes that are pre-washed, pre-siliconized (where applicable), pre-sterilized and ready to fill. EZ-fill solutions include:

- EZ-fill Vials and Cartridges are available in both nest and tray configurations with single and double steribags in compliance with ISO 21882 and ISO 21881.
- EZ-fill Cartridges can be supplied as pre-capped or uncapped and they come in a wide range of formats, from small volume (1.5ml, 2ml, 3ml) to large volume (5ml, 10ml, 20ml).
- EZ-fill Vials are available in various formats (2R,4R,6R,8 R,10R,15R,20R,25R,30R,50R) and they can be provided in either standard or upside-down configurations.

The Nest-and-Tub configuration is compatible with multi-purpose fill-finish lines, while tray is compatible with a wide range of fill-finish processes, from manual to automatic, including high-speed lines. For more information visit: Stevanatogroup.com/en/offering/drug-containment-solutions/ez-fill-platform.

CONCLUSION: THE FUTURE OF FILL-FINISH MANUFACTURING

The implementation of RTU primary packaging offers clear added value in form of a significant increase in quality, de-risking pharmaceutical company operations throughout the process, minimizing recalls and ensuring the best results. RTU solutions meet the requirements for improved compliance, flexibility and operational efficiency.

Under the updated Annex 1 regulations, a contamination control strategy (CCS) will be the primary document used to demonstrate to an inspector that all potential risks have been identified, and a mitigation strategy is implemented to control and minimize the impact on patient safety. Among these measures, the use of RTU primary packaging material is a prime choice to meet these requirements by providing the relevant documentation. **CP**