Ready to Use Containers for sterile injectables will reduce the Total Cost of Ownership

– A case study –

Abstract

The trend towards personalized medicine presents the pharmaceutical industry with the challenge of having to produce drugs in smaller batch sizes efficiently with frequent changeovers between batches. Pharma companies are therefore looking for a fill & finish / packaging platform that allows glass syringes, vials and cartridges of different sizes and configurations to be filled on a single machine.

This article explains the benefits of flexible filling line technology and ready-to-use (RTU) components and demonstrates how pharma companies can gain flexibility and reduce TCO at the same time using a real-life TCO analysis for RTU containers.

1. Introduction: Industry trends/multiplex filling

The pharmaceutical industry is experiencing sweeping changes with the era of blockbuster drugs ending. The focus is shifting towards small scale personalized medicine based on biotech drugs like monoclonal antibodies (mAb), m-RNA, Antibody-Drug-Conjugates (ADCs), gene or cell therapy. Orphan drugs to treat rare diseases also demand small-scale manufacturing. Currently, more than 3100 injectable drugs are at different stages of development globally. More than 60% of these injectable drugs are biotech-based drugs[1]. Today, the cost of developing a new drug can exceed USD 2.6 billion[2] compared to USD 179 million in 1970s[3]. The pharma industry faces a daunting challenge to bring these products to market faster and at lower costs. With increasing regulatory requirements and emphasis on patient safety, the current drug manufacturing methods are inefficient especially in the field of sterile injectable manufacturing.

In the future, pharma companies have to produce drugs in smaller batch sizes efficiently with frequent changeovers between batches. Just imagine the portfolio pictured in figure 1 was a production schedule for a week:

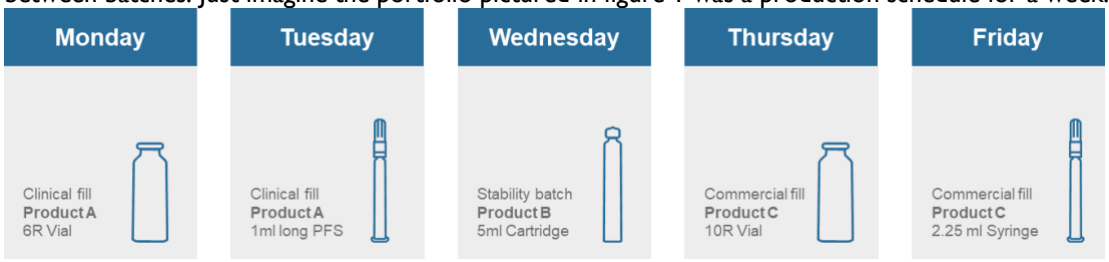

Figure 1: Illustration to show flexibility in sterile injectable manufacturing with flexible filling lines and RTU containers (Source: all figures made by the authors / SCHOTT AG)

As a result, traditional dedicated filling lines are often left idle, as demand changes. This can reduce the overall equipment effectiveness (OEE), which is a product of line availability, performance and uptime down to a mere 20%[3]. Hence, pharma companies are looking for a fill & finish / packaging platform that allows glass syringes, vials and cartridges of different sizes and configurations to be filled on a single machine. For this reason, many companies are turning their eyes towards flexible filling line technology and ready-to-use (RTU) components. These grant pharma manufacturers the desired flexibility, however, are often associated with higher costs. In this paper, we argue that this can be true for individual components but not at Total Cost of Ownership (TCO) level. A real-life example of a TCO analysis for RTU containers will be presented to demonstrate that pharma companies can gain flexibility and reduce TCO at the same time.

2. Benefits from flex filling and RTU containers

Traditional fill and finish operations for sterile injectables use bulk containers and consist of many processing steps for pharma companies (figure 2) with separate filling lines for vials, PFS, and cartridges in separate clean rooms. This translates to higher investments, higher operating costs and lower flexibility. In addition, there is glass-to-glass contact and increased risk of defects, breakage, and particle generation throughout the process.

Figure 2: Process flow for processing and filling injectable drugs in bulk containers (simplified for all containers)

RTU containers and multiplex filling concepts offer a solution. In comparison to bulk solutions, RTU containers come sterilized, washed, depyrogenized etc. and can go straight into filling operation, eliminating many steps at pharma companies (figure 3). The RTU components are delivered in a so-called nest-and-tub configuration, which also prevents glass-to-glass contact and reduces the defects like scratches, breakage, and particles.

Figure 3: Process flow for processing and filling injectable drugs in RTU containers (simplified for all containers)

The nest-and-tub concept was first developed for ready-to-use prefilled syringes and has been the industry standard for roughly 30 years. Today, it is also in place for other packaging categories such as vials and cartridges. Pursuing a single, standard method of filling allows manufacturers to maximize the utilization of each filling line[4]. This leads to more flexibility, which is further enhanced through increasingly flexible machine concepts such as multiplexing.

Manufacturing injectables in multiplex is suggested as one of the solutions to address the challenges of sterile injectable manufacturing[5]. Multiplexing is built upon the selection of standard technologies and equipment that can flexibly produce smaller batches. The term is borrowed from large movie theaters, where you can decide which movies to show in each of the theaters depending on customer demand. This is also the case for truly modular pharmaceutical manufacturing. Where traditionally a filling line is custom designed around a specific drug to be filled many years prior to launching the product, multiplexing or modular manufacturing turns this paradigm on its head. When each filling module is equipped to fill a number of different RTU containers, a pharma manufacturer can install filling capacity first, then decide on what to fill and shift capacity and even the filling location as needed. Such flexible filling lines can process different RTU containers (PFS, vials, and cartridges) and closures on the same line allowing variable batch sizes to meet the changing market demand or manage a multi-product portfolio. Novel,

flexible filling lines can operate at much higher OEE rates due to the lack of lengthy interruptions and downtime, which translates to time and money saved.

The true key to leverage the advantages of RTU containers and multiplexing, however, is standardization. It enables implementation, validation, and ramp-up of new filling lines in a shorter time and preserves the quality of containers. This applies especially as automation of the filling steps increases to ensure sound aseptic concepts with barrier technologies and avoid contamination as well as glass breakage and particles. For example, if nested ready-to-use (RTU) syringes, vials and cartridges are provided in a single industry standard tub (i.e. a 3-inch tub as per ISO 11040-7), they can be processed seamlessly on a single machine. Subsequently, manufacturers can reduce the number of filling lines needed to produce various drugs, cutting the total cost of machinery and energy. Additionally, using the same tub means fewer format parts to swap during changeovers. This significantly reduces the complexity in sterile injectable manufacturing, enhances the quality of containers and more importantly, can reduce the TCO for the customers. Respective concepts have recently been introduced to the market[6].

3. Case study – TCO calculation for RTU vials

Often people look at only the container and in our opinion to understand the true value of RTU it is important to evaluate the Total Cost of Ownership (TCO).

This graph is based on a customer case study to evaluate the TCO for bulk vs. RTU vial components. The grey bars represent the "reference cost" for bulk components and the blue bars represent the RTU vial components. RTU components are more expensive than the bulk containers by almost 2.4 times, as suppliers have an increased effort to prepare, sterilize and certify the containers. However, considering only the components cost, as often done, would be misleading. As we move along the process steps, the bulk containers need to be washed and sterilized by pharma and biotech companies, which impacts the investment and operating costs for utilities like WFI and energy. Whereas the RTU containers are pre-washed and sterilized by suppliers so, there is less upfront investment and running costs for pharma and biotech companies. The savings for RTU components are illustrated in the graph for cleanroom space, capital expenditure (CapEx) and operational expenditure (OpEx).

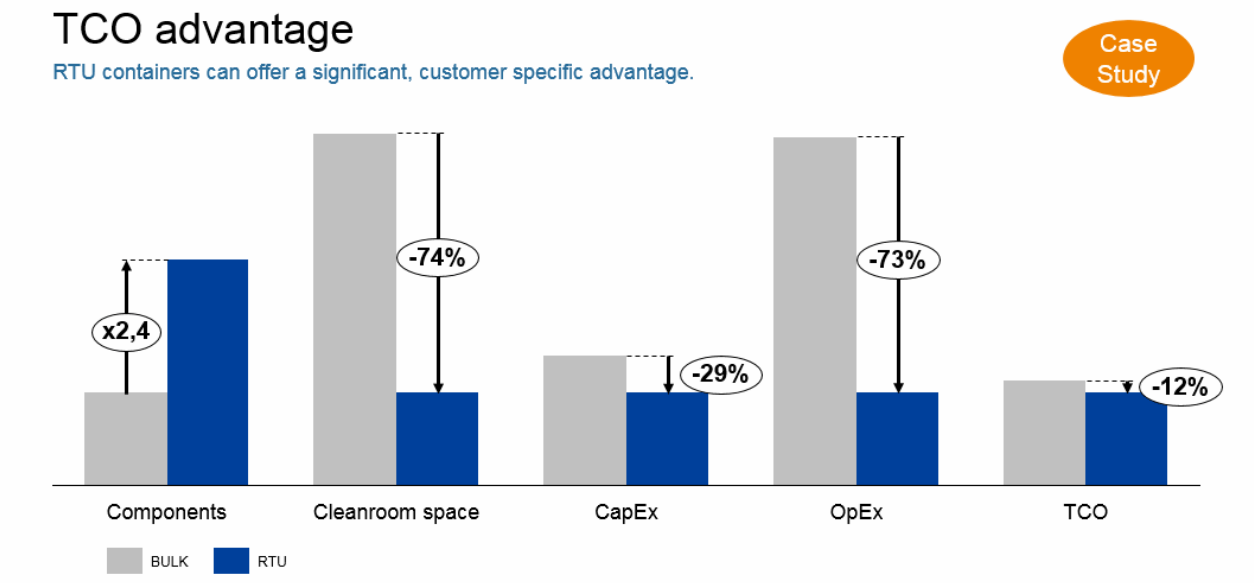

Figure 4: Cost savings in processing RTU containers versus bulk containers

By using the RTU containers, the footprint of the filling line is significantly reduced and thus the clean room space required for installing the machines. In this particular case study the clean room space is reduced by 74% which translates into savings of 735,000 EUR (based on table 1 – cost per m^2). The capital expenditure for installing a new filling line is reduced by 29%. In addition, for bulk containers more change parts are needed on filling line whereas for RTU the number of change parts can be reduced. Significant savings can be realized also on the operating costs

as there is no need for Water for injection loops, high-energy costs for the heat tunnels and less rejections or breakage in the filling lines due to no glass-to-glass contact.

Table I shows the comparison for CapEx and OpEx for bulk and RTU containers based on a customer case study. It lists various components which have to be considered for the TCO calculation.

Table 1: Cost components for processing Bulk Vs. RTU containers		
	Bulk	**RTU**
Invest (CapEx)	**7,560,000**	**5,360,000**
D/C class clean room (Avg. cost per 5.250 EUR/m²)	190m²	50m²
Washing line, depyrogenation tunnel	2,450,000€	0€
Filling station	5,110,000€	5,360,000€ (incl. debag, delid)
Operating costs (OpEx)	**940,000**	**250,000**
Washing area, cleaning utilities, clean room - WFI production (Avg. cost per ~1 EUR/l) - Heating tunnel energy usage (e.g. 12.000pcs/h (10R) require approx. 80kW/h electricity and 35 kW cooling water)	590,000€	50,000€
Staffing	7 (350,000€)	4 (200,000€)
Cost of quality		
Qualification and validation	For each line and container	Reduced efforts with one flex filling line
Glass-to glass contact	Yes	-
Particles	high	low
Breakage	high	low

The efforts to qualify and validate different bulk containers on the filling line would take significant resources and time. For RTU containers the total number of process steps is reduced and focus can be put on qualification of the aseptic filling and closure steps. However, if the different containers are provided in bespoke packaging, the qualification steps are multiplied again and required per each specific packaging.
A standardized platform for all containers results in lower costs and efforts for line qualification and validation, as the transfer steps to get the containers into the aseptic core (debagging, decontamination, delidding) are unified and need to be qualified only once. This can ultimately speed up installation projects of new filling lines and reduce valuable time to market (figure 5). In this case study, the customer realized an overall savings of 12% on TCO using RTU vials. This does not consider the synergies and cost savings associated with filling PFS and cartridges on the same line.

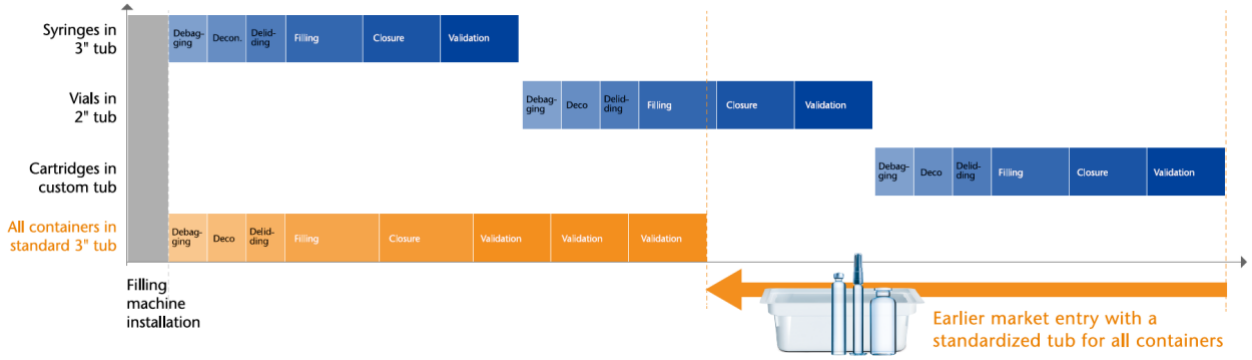

Figure 5: Standardization accelerates drug development and market launch

Limitations

The savings could vary depending on the customer situation. However, tools are available to do similar calculations for specific cases and help make an informed decision.

Summary & Outlook

Automation and standardization will shape the future of sterile injectable manufacturing. Standardization enables flexibility while simplifying and speeding up processes, and thus most importantly saving costs. It is important to consider the TCO approach rather than looking at individual components price. RTU containers, which are processed on flexible filling lines, offer an opportunity for significant cost savings and enhance the quality of the containers with a direct impact on patient safety and regulatory compliance. Suppliers are working together to offer pre-validated systems further reducing the time and efforts the pharma companies have to invest in testing the different combinations of packaging. There is a growing need in the pharma industry to increase efficiency and flexibility. In the future, pharma companies can focus more on their core activity to develop best in class drugs and help people live healthier and longer lives and worry less about packaging components.

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