SYNTEGON
PROCESSING & PACKAGING

# Liquid pharmaceutical filling.

## How small and micro batches are changing pharmaceutical processes.

The market for ready-to-use containers (RTU) has been growing rapidly for years, especially in small batch production.

**Higher, further, faster – this principle was considered sacrosanct for a long time, especially in the medical field. While the production of drugs in large quantities used to be the benchmark for decades, today individual therapies are playing an increasingly important role in the fight against diseases. These usually very costly drugs require a high level of commitment in research and development – also regarding new machine concepts that can process small and very small batches flexibly while facing changing requirements.**

The pharmaceutical industry has changed dramatically. Just ten years ago, blockbusters and traditional drugs produced in large batches were the focus for many research and manufacturing companies. Today, these medicines continue to make an important contribution to human health. Some of them, such as blood thinners, painkillers, or insulin, have become an indispensable part of the drugstore shelf. They are produced on lines in 24-hour operations, some of them 30 meters long. Thanks to sophisticated process and packaging technologies, this production is assured for the foreseeable future.

## From blockbusters to ATMPs.

Still, increasingly individualized therapeutic approaches to the treatment of diseases require a change of thinking. Special and often personalized medications are now available to cure or at least delay some life-threatening illnesses. Cellular and molecular biotechnology has been accompanied by a revolution in pharmaceutical manufacturing: while high-speed, high-throughput lines used to be in greatest demand, more and more pharmaceutical companies are now investing in the development and commercialization of small-volume medicines, which have very different production and filling requirements. The increasing prevalence of advanced therapy medicinal products (ATMPs), such as cell and gene therapies and bioengineered tissue products, shows that the industry is specializing steadily. These drugs are not manufactured on huge lines. Instead, the focus is on what is commonly known as small batch production.

A precise definition of the term “small batch” is not specified in the ICH guidelines. The US FDA, however, provides an answer for generic parenterals. Following the “Guidance for Industry, ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers”, small batches consist of at least ten percent of the proposed maximum commercial batch size, or less than 15,000 to 60,000 containers based on fill volumes.[1] The batch size shrinks to a few thousand containers for parenterals used in clinical trials. For highly specialized treatments such as autologous cell therapy, batches are even smaller. On average, a patient needs about five to ten containers.

Versynta microBatch. Gloveless isolator, fully automated and compliant with the new Annex 1.

## The highest flexibility at the lowest possible reject rates.

The growing number of cell and gene therapies in the development phase underlines the importance of ATMPs. Conventional high-speed machines can no longer meet the requirements of these new products. But how to produce these small or even very small batches economically? What must a line do to satisfy both pharmaceutical companies and patients? Flexibility is at the top of the list of requirements.

A wide variety of products must be filled into different container sizes and types such as vials, syringes, or cartridges. Single-use technologies are particularly popular for handling and processing these biotech drugs in a flexible manner since they eliminate the effort and costs involved in cleaning validation. Another criterion for flexibility is the reduced number of format parts, which obviates the need for lengthy format changes. In addition, these very small quantities require maximum product yield or low rejects. In a nutshell, any product loss must be avoided.

1 FDA: Guidance for Industry. ANDAs: Stability Testing of Drug Substances and Products – Questions and Answers, May 2014.

## Automation for even higher safety.

Human intervention is still the main reason for contaminated pharmaceuticals. Automation is essential to reduce or eliminate these interventions. For example, as far back as 2004, the FDA required that "the design of equipment used in aseptic processing should limit the number and complexity of aseptic interventions by personnel." In addition, the FDA states that "automation of other process steps, including the use of technologies such as robotics, can further reduce risk to the product."[2] In the long run, aseptic filling will evolve from human-centered to fully automated production with the use of appropriate technologies.

This change is already in full swing. For example, if containers within the isolator are conveyed to the filling station and on to the crimping station by a robotic arm, the risk of contamination is reduced manifold. Robots can also decrease the number of format parts and eliminate any glass-to-glass contact. Newly developed systems, such as Syntegon's **Versynta FFP** (Flexible Filling Platform), also feature a laminar flow-optimized design to make sure that the air flow can reach the containers and flow around them without obstruction. One hundred percent in-process control (IPC) during the filling process reduces product loss to a minimum and ensures that almost every milliliter of the high-quality product is filled.

## Gloveless production of micro batches.

Following the small batch principle described above, the process goes even further – in a numerically downward way. While a modular small batch system such as the Versynta FFP still handles up to 3,600 vials, syringes, or cartridges per hour, its little sister processes a mere 120 to 500 containers per hour. The highly flexible, fully automated **Versynta microBatch** production cell fills and seals the smallest batches in different containers. Batch changes are possible in only two hours. Syringes, cartridges, and vials made of glass or plastic can be filled with virtually no product loss.

The dimensions of the machine are just as small as its output. With a length of barely 3.5 meters, a width of around two meters, and a height of three meters, the machine can easily be integrated into existing production environments. The isolator cell itself measures just 1.6 x 1.5 meters. It houses tub opening, the filling station including one hundred percent in-process control, and the combined stoppering and crimping station. Thanks to the integrated air treatment system, hardly any interfaces to the building or technical ceiling installations are required. The new development sets new standards, particularly in terms of automation. The gloveless isolator with integrated air treatment significantly reduces the risk of contamination by eliminating manual intervention on the part of the operating personnel. The microBatch set-up meets the highest sterility requirements as specified by Annex 1. Steam-sterilized parts are fed via port systems and installed by the robot.

With Versynta FFP, Syntegon offers pharmaceutical manufacturers, development labs, and biotech startups a combination of standardization, high modularity, and short delivery times.

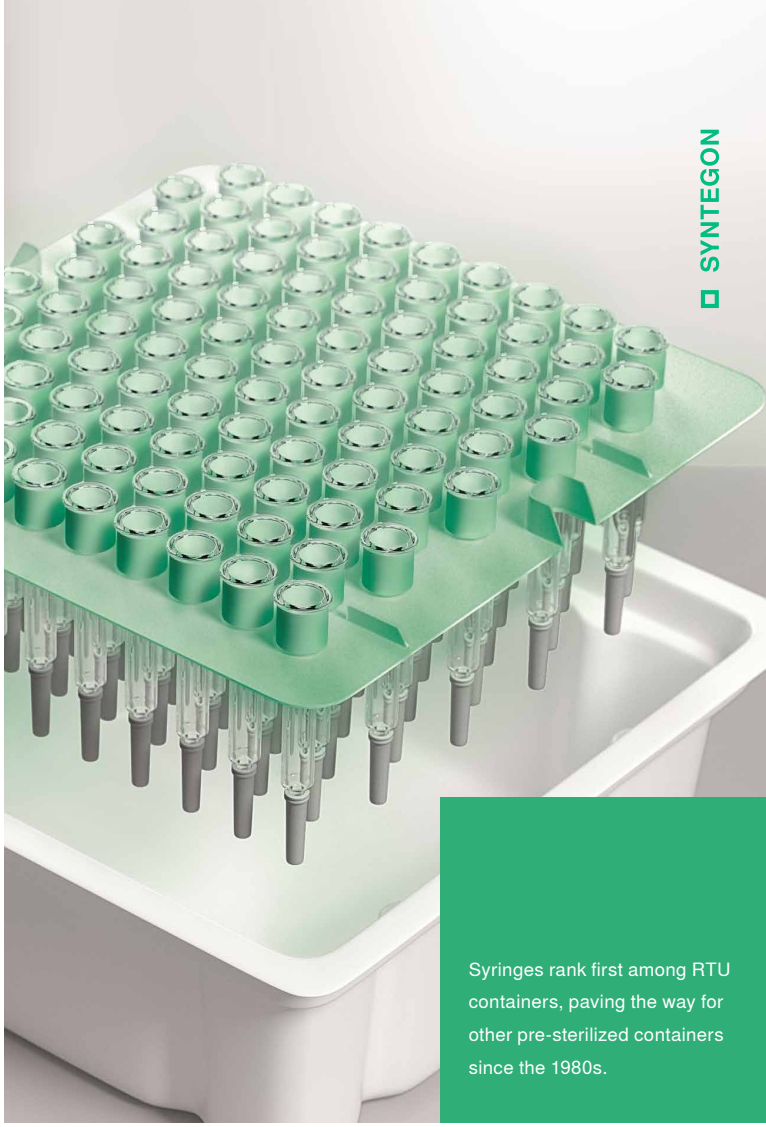
Versynta microBatch is a highly flexible and fully automated gloveless production cell for filling and closing liquid (bio)pharmaceuticals.

2 FDA: Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, September 2004.

## RTU containers on the rise.

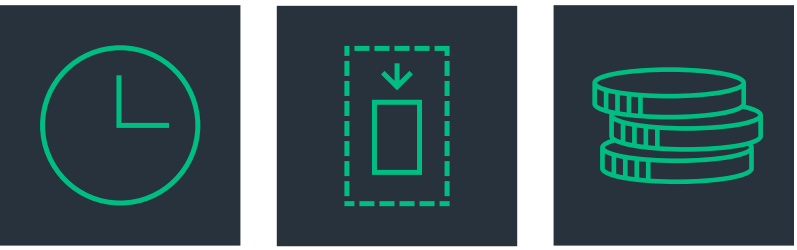
The latest developments in the field of small and micro batches pay tribute to another trend. The market for ready-to-use (RTU) containers has been growing rapidly for years. This is not surprising, as pharmaceutical manufacturing companies benefit from simpler processing procedures, reduced total cost of ownership, and greater flexibility. RTU containers are the preferred choice for small batch production, and their number is growing steadily. According to a recent report[3], the market for RTU vials alone is expected to generate global sales of around 1.18 billion US dollars over the next ten years, with an estimated growth rate of 14.5 percent.

However, in addition to vials, pre-sterilized cartridges are also becoming increasingly popular. First and foremost, however, RTU syringes paved the way for other pre-sterilized containers as early as the 1980s. In fact, the advantages of smaller batches of RTU containers are enormous. Bulk syringes, for example, are supplied non-sterile. Since they are not stable-standing, they require complex handling in the machine and filling process. Syringes also require siliconization, which involves a special, format-dependent process. The latter depends on the way the syringes are filled. Biotechnologically produced drugs, for example, require a particularly low level of siliconization.




Syringes rank first among RTU containers, paving the way for other pre-sterilized containers since the 1980s.

## Savings in time, space, and costs.



The advantages of RTU containers become particularly clear in the process steps described above. Although they are currently still quite cost-intensive, they save pharmaceutical manufacturers a great deal of time, space, and money. Numerous steps, such as cleaning, siliconization, and sterilization of components, are outsourced to the packaging suppliers of RTU containers. They have the expertise and make sure that all processes are qualified and validated according to current global requirements and that containers are delivered with a certified endotoxin, germ, and particle concentration. In the case of pre-sterilized syringe systems, this also includes the required siliconization process.

The demand for high-priced ATMPs and the variety of RTU packaging materials are rising steadily – as are the requirements for new equipment for small and very small batch sizes. The latter should not only be flexible in the processing of the packaging materials; appropriate machines must also meet the trends in terms of automation and the least possible human intervention. In the best-case scenario, primary packaging material and machine manufacturers work closely together to develop new solutions. Systems that ensure flawless processing for pharmaceutical manufacturers and the highest level of product safety for patients can only be developed if both partners not only react to trends, but proactively shape them together from the outset.

3 https://www.psmarketresearch.com/market-analysis/rtf-rtu-vials-market-trends

# Questions? Contact us.

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## About Syntegon.

Processing and packaging for a better life – this is what 5,800 Syntegon employees work for every day. Be it with individual machines, systems, or services, Syntegon helps its customers in the global pharmaceutical and food industries to improve people's lives. The company, which is headquartered in Waiblingen, Germany, looks back on more than 160 years of experience and achieved annual sales of 1.4 billion EUR in 2021. In the pharma sector, the company's intelligent solutions enable the safe and high-quality production, processing, filling, inspection, and packaging of liquid and solid pharmaceuticals. In the food industry, Syntegon's flexible and reliable technologies produce and pack confectionery, dry food, frozen food, and dairy products. With 1,100 service experts and a comprehensive service portfolio throughout the entire machine lifecycle from spare parts management to digital line optimization, Syntegon lays the foundation for smooth production processes for all customers. More than 30 sites in almost 20 countries keep a firm eye on Syntegon's impact on the environment and society. Syntegon is a leader in the development of sustainable packaging solutions, reduces the energy consumption of its machines and pursues ambitious goals to lower its emissions.

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