

# FROM PREFILLED SYRINGES TO COMBI-FILLING

Here, Klaus Ullherr, Senior Product Manager, Bosch Packaging Technology, summarises the state of modern packaging technology in the pharmaceutical industry in the light of the biotech boom, ready-to-fill and pre-sterilised containers and the trend towards individualised healthcare.

Prefilled syringes have become a preferred format for delivering parenterals, as they make it easier to handle drugs and increase dosing accuracy. In addition, the ongoing boom in biopharmaceuticals has also promoted the growth of the prefilled syringe market. At the same time, other pre-sterilised packaging types are also on the rise, posing new challenges for pharmaceutical companies. Accordingly, machine manufacturers are working at a fever pitch to offer new, more flexible solutions – and are presenting pioneering results.

In comparison to conventional packaging, prefilled syringes not only offer greater ease of use and more precise dosing, modern prefilled syringes are also characterised by reduced product loss, which is a major advantage when it comes to expensive biopharmaceuticals. These highly individualised products, used to treat autoimmune disorders for instance, can best be administered in liquid form using syringes.

## PROCESSING: A HIGH DEGREE OF AUTOMATION

As manufacturing becomes ever more automated, manual handling on the part of human operators, and subsequently the chief cause of particulate and bacterial contamination, can be reduced to a minimum (Figure 1). For some time now, the fully automated opening of sterile syringe packages has been a standard requirement for new filling lines. Moreover, isolators

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In-process controls (IPCs) are also an important factor in further improving the quality of the filling process. Currently, the focus is on determining the fill weight and on monitoring the presence of the stopper. In the future, there is likely to be more emphasis on additionally checking the quality of the packaging directly before filling. Is the silicone seal intact? Is the safety cap present and still in the correct position? If the answer is no, faulty syringes can be sorted out before the filling process, thus reducing product loss.

Highly automated filling machines with flexible handling units allow syringes to be precisely removed from the nest. As a result, individual syringes can be fed into an integrated inspection station. Furthermore, methods are now available for checking the thickness and distribution of the silicone layer within the syringe, thus ensuring that the stopper can glide smoothly, a particularly important factor for syringes used in autoinjectors.



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Figure 1: Filling of nested vials. (© Bosch)

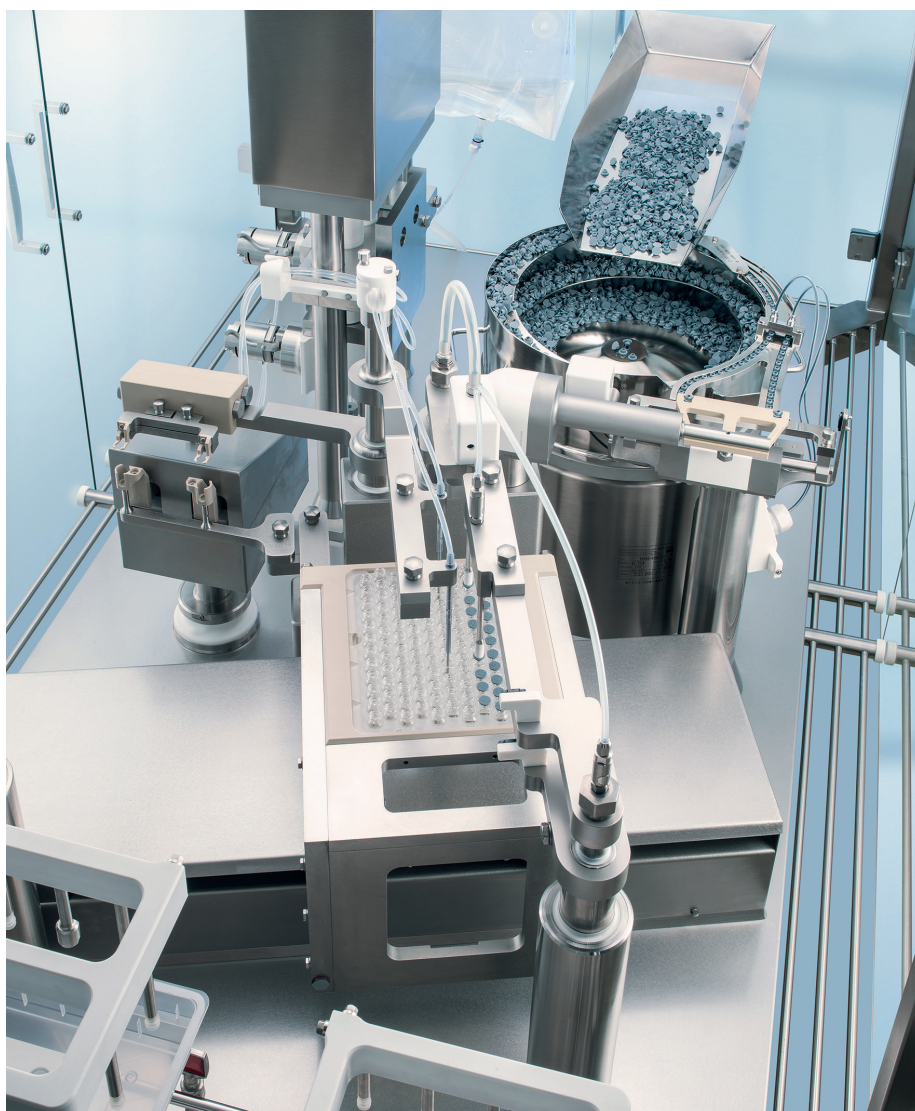


Figure 2: Complete combination filling line for nested containers. (© Bosch)

In this context, it is worth mentioning that an ever increasing number of silicone-free systems are becoming available for plastic syringes. There have also been reports of silicone-free stoppers for glass syringes, which could potentially open the door for silicone-free glass systems.

#### FILLING AND CLOSING: VARIOUS METHODS

In connection with prefilled syringes, single-use filling systems are increasingly being discussed in the pharmaceutical industry. This approach does away with the need to clean and validate the components that come into contact with the product, which is especially cost intensive for biotech products. In this regard, peristaltic pumps are enjoying renewed popularity, since they never touch the material to be filled. This also considerably improves machine availability, as there is no need for time-intensive cleaning in place or sterilising in place processes (CIP/SIP).

Once the filling process has been completed, a vent tube is used to close the syringe with a stopper. Due to the biotech boom, coated stoppers are becoming increasingly common, yet their coating makes them less suited for this method. Vacuum stopper insertion offers an alternative: a vacuum is created inside the syringe, sucking the stopper into place. Though this more complex approach compresses the stopper to a minor extent, it does not allow the stopper to be placed as precisely as with the vent tube insertion method. Depending on the requirements for precise stoppering and the desired residual air bubble size, the output can also be affected.

#### NEW PACKAGING TYPES ON THE RISE

There is no stopping the trend toward prefilled syringes. Countless new projects are based on pre-sterilised syringes – and not just for small batches, but also for high output lines. Yet other pre-sterilised packaging types are slowly but surely turning from niche products into appealing alternatives for pharmaceutical companies. Manufacturers of primary packaging made of glass – and in the meantime also plastic – are contributing to this change, for example by developing pre-sterilised, ready-to-fill vials and cartridges.

Here the greatest distinction is made between nest and tray systems: trays are



especially intended for use with classic bulk filling machines, whereas nests can normally be used with machines for syringe processing, including automated bag and tub opening, though some adjustments may be necessary, depending on the packaging geometry, material and structure (Figure 2). The broad range of resulting packing formats will confront machine manufacturers and pharmaceutical producers alike with major challenges. In this regard, initiatives akin to the ISO's standardisation work would be desirable.

### STILL NO STANDARD METHOD

Another aspect that is now being intensively discussed is the infeed of pre-sterilised

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packaging types. Though the e-beam has long been the standard solution for decontaminating tubs in high output lines with isolators, it is generally considered too large for smaller lines. Alternatives currently being explored include:

- Tunnels or locks used in combination with plasma
- UV light
- Nitrogen dioxide
- Hydrogen peroxide.

However, none has established itself as standard yet. Aseptic transfer is possible with restricted access barrier systems (RABS) or with isolator applications, provided a suitable, fully automatic bag opener is used, combined with spray disinfection of the bag. In this regard, double bagging for added safety is becoming more common.

The more packaging types that can be filled and closed on a single machine, the more space-saving it is for users. This is possible thanks to new combination (combi-) machines for flexibly processing various types of primary packaging. By integrating both filling and capping station in a single unit, there is no need for a second machine (Figure 3). Furthermore, compatibility with various filling systems is a prerequisite

for new filling and closing machines. In this regard, combi-filling stations, which can be easily reconfigured to accommodate a diverse array of filling systems without taking up more space, have quickly proven their value. They allow pharmaceutical manufacturers to adapt filling processes to their respective medications and packaging types, whilst ensuring that all filling systems are in the sterile area.

### HIGHER EFFICIENCY, MORE INDIVIDUALISATION

Given how costly biopharmaceutical drugs are, efficient filling methods are a priority. The key is to keep product loss to an absolute minimum, and the latest filling technologies deliver almost complete product yield. Here, above all, the focus is on the start-up and emptying process steps. A statistical or 100% IPC during production ensures that all containers leave the machine with exactly the desired amount of liquid.

In light of individualisation of products being the current industry trend, more customer specific, flexible solutions are also taking on a new importance. Clinical studies in particular require the highest possible flexibility in a very compact space, which can be achieved

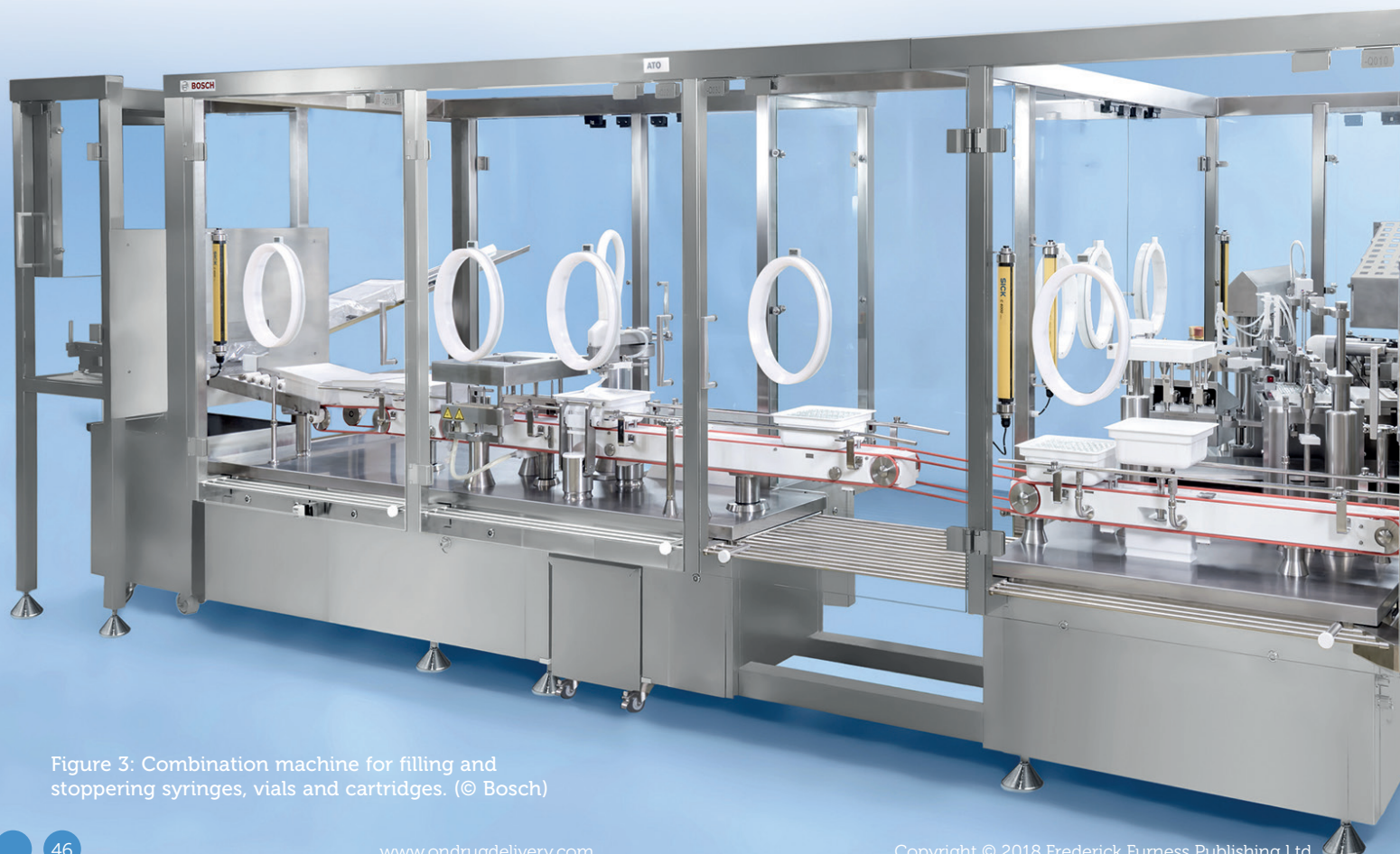


Figure 3: Combination machine for filling and stoppering syringes, vials and cartridges. (© Bosch)

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by combining manual, partly and fully automated processes, together with different packaging types. In this case, the infeed can be either manual or semi-automated so as to accommodate the new variety of packaging types, especially with regard to the outer packaging, and in turn the filling would be fully automated. To ensure that the individual work steps can be adapted to future types of packaging, the use of robots is advisable, be it for transporting packages from one station to the next or even for filling (Figure 4). Adding a reserve station at some point in the future is also worth considering.



Figure 4: Fully automated robotic filling of syringes. (© Bosch/AbbVie)

### COMPLETE LINE CONCEPTS

What pharmaceutical producers expect from their systems or lines can vary considerably, depending on their respective therapeutic area, region or company size. Yet they all share a focus on ensuring the best possible protection for the product and their machine operators. Accordingly, new filling and closing machines are, as a rule, characterised by a high degree of automation and equipped with either RABS or isolators. When they are used with upstream automatic tub and bag openers, and in combination with downstream process steps like inspection, plunger-rod insertion and labelling, the result is a complete filling and closing line – and in the near future, not just for prefilled syringes, but increasingly for other pre-sterilised containers too.

### ABOUT THE COMPANY

Bosch Packaging Technology – product division Pharma is one of the leading providers of process technology and packaging solutions for the pharmaceutical industry. The company’s portfolio includes single units, complete lines and integrated systems for the manufacturing and processing of liquid and solid pharmaceuticals. It also includes process technology, primary packaging and inspection technology for different application fields and packaging types. Secondary packaging with qualification and

validation, software solutions for “track and trace” and technical customer service are also available. The following product brands are part of the Bosch portfolio for the pharmaceutical industry: Hüttlin, Klenzaid, Manesty, Moeller & Devicon, Pharmatec, SBM Schoeller-Bleckmann Medizintechnik, Sigpack and Valicare.

### ABOUT THE AUTHOR

Klaus Ullherr holds a degree in electrical engineering. After university he worked for several years as a project manager in the electrical industry before joining Bosch Packaging Technology in March 2000. During his first two years there, he was project manager responsible for handling complex customer orders. Since 2002 he has been product manager for the business field’s syringes and cartridges with global product responsibility. Mr Ullherr’s main functions are market analysis, initiating new product developments, business development and resident expert for syringe processing. He is a member of the PDA Interest Group “Prefilled Syringes” and works as an expert in the DIN/ISO group for primary packaging. He is also a speaker at many conferences covering trends and solutions for fill/finish equipment, especially for prefilled syringes.