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Reliable and Efficient Processing of Small Batches with Flexible Production Systems

To launch important medicine such as vaccines or insulin on the market both reliably and at low cost and thus make it affordable to the greatest possible number of patients have been the challenges for the pharmaceutical industry over the past decades. Manufacturers of filling and packaging lines made their contribution by developing more efficient lines providing an increasingly higher degree of automation and increasing - at the same time - the number of units to be processed with more and more enhanced inspection systems.

It goes without saying that high-speed production lines that are able to fill and close 60,000 syringes per hour are still in high demand on the market. But the current challenges the future manufacturers of pharmaceutical products and production lines are facing are different: Nowadays, it is all about producing high-grade medicine in small numbers tailor-made for special patient groups – or even only for one individual patient – in such a way that their production is both reliable and cost-efficient. A high output is important in this context, too. In this case, however, not only the number of units matters, but also the number of consecutive batches manufactured.

Biotechnologically produced pharmaceutical products are in the focus

In particular, the manufacture of biotechnologically produced pharmaceutical products requires different framework conditions. The strict requirements, especially when it comes to sterile production, are laid down in Annex 1 of the European Guidelines for Good Manufacturing Practice (GMP). The increasing significance of so-called biologics is also reflected by the repeated revision of Annex 1 to live up to the rising production volumes and the quality requirements [1].

Originally, the term biotechnology was used to describe the sum of all procedures by means of which products were generated from raw materials with the aid of microorganisms. Modern biotechnology makes also use of cell cultures obtained from animals or plants. Their genetic material has been modified by genetic engineering in such a way that proteins (e.g. insulin) can be produced [2]. In light of the rising number of products getting marketing approval biosimilars (successors of the original biologics) will also bring about additional growth in this section.

23 out of the 45 drugs newly approved within the EU in the year 2017 were biopharmaceuticals already, 10 of them biosimilars. 10 years ago, 10 out of the 40 drugs approved had been produced, using biotechnological processes, 2 of them being biosimilars. This means that the percentage share of newly approved biopharmaceuticals has doubled within a decade [3].

Furthermore, a clear trend towards individualized products has manifested itself in the research field. In extreme cases, the batch size comes down to 1 – as with Kymriah, a product approved for Novartis for the treatment of blood cancer. The body's own cells are trained to detect cancer and infused into the patient as a therapeutic agent after they have been reproduced. Many pharmaceutical companies fall back on the principle of using (modified) body's own cells as a cure and test it in clinical studies.

In the past, the preparation of the requested target cells from cell compounds of biopsies or blood donations and the subsequent identification and/or characterization of specific cell types had been in the focus of the production process, e.g. of cell therapies.

The manipulation of cells with growth factors or genes to generate specific surface molecules so that they can be used as potent drugs is gaining importance at a tearing pace. Verification processes are lengthy for the time being and reduce the product yield to some extent.

Especially in this field, methods which will not cause damage to the cells are in the upswing and allow for an automated and also digitalized faster approval of the cell preparations with simplified documentation. Currently, manual or semi-automatic solutions are still prevailing in the production and/or filling of this type of drugs – entailing all the disadvantages inherent in this method.

It is now up to the equipment manufacturers to make the processing of biopharmaceuticals more reliable, faster and more cost-efficient by a higher degree of automation and further technical answers to the specific challenges presented by the production of biopharmaceuticals.

Special dosing systems for lossless start-up and low-loss running empty

To begin with, a great variety of dosing systems is available – matching the respective requirements. Dosing systems, for example, with lossless start-up and low-loss running empty are important in this context. In contrast with low-cost pharmaceutical products (where the fact that incorrectly filled containers occur during start-up and running-empty and must be rejected is of less significance), such a situation must be avoided to the maximal possible extent with small batches and personalized medicine in particular. Multidosing directly on a scale makes sure that product loss is minimized.

Another important item: It must be possible to combine all dosing systems with single-use-systems. Improvements in this field bring about higher process reliability and easier handling. The single-hose peristaltic pump is a good example in this context. This peristaltic pump of the new generation uses one hose only instead of two: Only one product hose is running from the product vessel to the dosing needle for each dosing position. It is therefore perfectly suitable for disposable systems. Without Y-connector, the product flow is clearly arranged and simple, thereby further enhancing process reliability. Insertion of the hose is easy and can be carried out without problems using glove ports which is especially important for handling in the isolator.

Economic use of isolator technology

As a general rule, biopharmaceuticals are sensitive products that are subject to an increased risk of contamination with microorganisms during the entire production process, which might entail the rejection of the complete batch and thus an enormous financial loss. Very specific requirements to clean room production are valid in this field and, as a consequence, isolator technology is increasingly used for this application in spite of high investment costs [4].

Special modular system, consisting of isolator and machine component

Normally, the isolator and the filling machine are firmly attached to each other – a good solution for medium and big batches. Standardized isolators are meanwhile available on the market to reduce costs and make sure that the acquisition of isolator technology pays off for small batch processing. But as far as flexibility is concerned, technology has now moved one step further. Nowadays, it is even possible to use a standardized isolator for different packaging material and processes. With this system, the special production modules can be very easily moved out of the isolator like a workbench and replaced by a different one.

Especially the unproblematic extension of the production line plays an important part for pharmaceutical manufacturers. Currently, new drugs are often produced by start-ups; the issue of investment costs is a central factor in this context. Depending on the area of application, machine modules with different degrees of automation are therefore available for manual, semi-automatic or fully automatic processing. It is even possible at any time to upgrade a module for laboratory use involving manual handling steps into a fully automatic production line or vice versa.

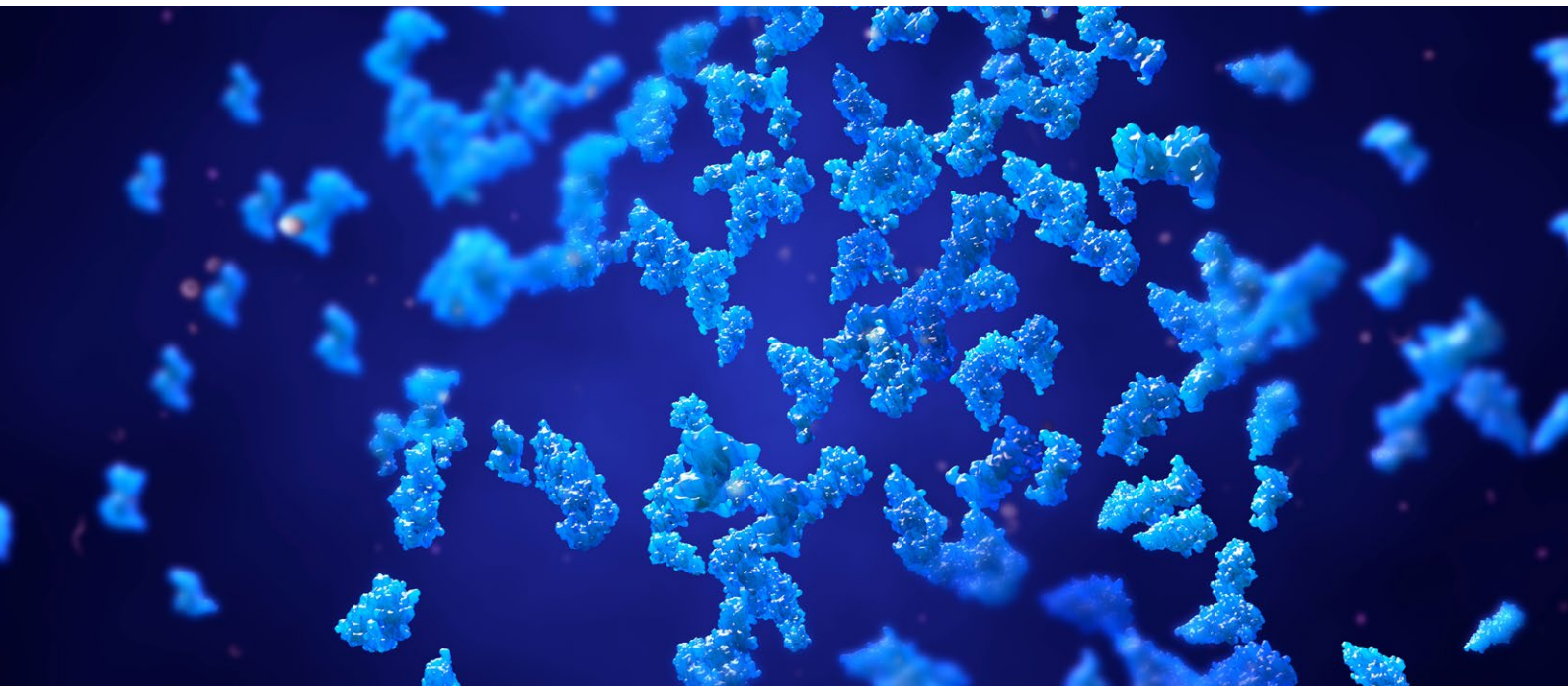
Without any doubt, clean room robots will in future open up even wider fields of application. Currently, their use is limited to the handling and the provision and/or transfer of packaging material. It is also possible, however, to use them for other processes – for biomonitoring, for cleaning and for size change, for instance.

Modular solutions for the medium capacity range

Production line manufacturers prefer a different approach when it comes to the next higher capacity range. To provide higher flexibility and enhanced reactiveness for pharmaceutical companies, especially in the medium capacity range, they rely on lines consisting of modules. Due to the modular design, the line can be quickly and easily adapted to the special requirements of the customer – thus considerably accelerating project lead times for a line, without the need for the user to do without adaptations tailor-made for his process.

Further development of the lines and adaptation to new processes and requirements

All flexible systems designed by the production line manufacturers are subject to continuous further development on the basis of new processes applied in the pharmaceutical companies. The requirement contained in Annex 1 to use modern verification procedures in future to detect microbiological contaminations on the production lines can be mentioned as an example in this respect. For by now, it would be possible both to detect in real time viables in air samples using laser detection systems and to quicker identify any particles found in a more cost-efficient way using modern analysing equipment such as for example Next Generation Sequencing. Flexibility is therefore by far not limited to the actual filling and closing process, but goes well beyond that.



As far as service and maintenance of a production line are concerned, digital tools such as Virtual Reality and Augmented Reality provide interesting fields of application already today, for example in supporting maintenance work. Open modular platforms which bundle, evaluate and thus put to use the data of the individual line components and which have especially been designed for pharmaceutical applications represent another important cornerstone in this context. Using a central interface, machine and process parameters of all machines integrated in the production line can permanently be recorded and made available worldwide via a cloud or the company's network.

These data and their processing form the base for the so-called Predictive Maintenance. The predictive maintenance of production lines may lead to a further increase in efficiency and productivity. Thanks to the real-time-processing of the underlying data, it is possible to make predictions forming the basis for a requirements-oriented maintenance and allowing the reduction of downtimes. In future, the customer will thus be in a position to give a service technician the order to eliminate a problem even before it occurs. By knowing which devices need maintenance and when, planning resources for maintenance work such as spare parts or persons can be improved. In addition, the line availability can be enhanced by replacing unexpected stops by increasingly shorter and more frequent stops. This also marks an important cornerstone in terms of flexible production.

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Questions? Let's talk!

If you would like more information about this topic please feel free to contact us.

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