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Single-Use-Bioprocesses - Hype or Future Technology?

Rentschler expands its GMP production capacity with a 2000-liter single-use bioreactor as a result of the sustainable growing project business.

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Today, disposable or single-use technologies, and here, in particular, the single-use bioreactors, have become indispensable in biopharmaceutical development and production processes. Within a few years, they have prevailed for the flexible and cost-effective production of clinical test material. Single-use bioreactors are now used in approximately two thirds of all new bioprocesses. In general there is an optimistic growth market in the two-digit range in this sector [1].

Advantages of the disposable technologies

Compared to bioreactors made of stainless-steel, single-use production plants not only have a low contamination risk, but they are also more cost-effective and faster to implement. The initial investment costs are therefore approximately 40% lower. Since systems for cleaning and sterilization (CIP/SIP) are obsolete and the time-consuming piping is not required, the project lead time for implementation of single-use production plants is significantly reduced by at least eight months compared to stainless-steel reactors, which still have their place in commercial production.

Pharmaceutical customers also benefit from the lower costs of maintenance and energy. Of particular note, however, is the high flexibility. Thus it is possible to design processes modularly using single-use production systems and so to scale them easily; very rapid product changes are possible, and as a result an overall faster time to market can be realized.

Clean room plant with a 1,000 liter single-use production capacity

Single-use is environmentally compatible

Single-use systems with disposable components made of plastic are also far less damaging to the environment than widely believed – particularly when compared to stainless-steel reactors. Stainless-steel reactors need a continuous cleaning and sterilization which results in a high consumption of chemicals and ultrapure water. Single-use plants have a 46% lower total water consumption and a 35% more favorable CO_2 balance than stainless-steel reactors[2].

Due to the heating of large quantities of water for CIP and SIP, the energy consumption of stainless-steel reactors is even considerably higher than the production and disposal of plastic bags, the burning of which can also be used to feed back energy[3]. Rawlings and Pora have calculated that the total energy consumption of single-use systems is about half of that of stainless-steel reactors[4]. This means that the disadvantages of disposable systems – above all the higher costs for consumables – are more than offset by the high water, energy and chemicals saving.

Challenges of single-use bio processes

For demanding processes – particularly in the case of high cell densities and product titers – the classical production process in stainless-steel reactors is still superior, especially during product harvesting. During harvesting all cells and cell fragments are separated from

the process liquid normally using centrifugation and subsequent filtration. The centrifugation step in single-use processes, however, must be mapped with a cascade of deep-bed filtration steps, and low filtration capacities have to be accepted[5]. Single-use centrifuges have only recently become available, and Rentschler is working on the installation of such a centrifuge in order to bypass the bottleneck in harvesting.

The capacities of chromatography systems, which are still too low, are another challenge. For example, the titer of the 2000 l single-use bioreactor is limited to 3 g/l, because otherwise problems can occur during purification due to the small column sizes. Furthermore the manufacturers still work on the development of single-use sensors for measuring of pH-value and oxygen. As long as these disposable sensors are not sufficiently robust, optical sensors made of glass or steel still have to be used.

The possible release of so-called leachables and extractables from the plastic bags, which are normally gamma sterilized, represents a major challenge when polymer compounds are used in single-use systems. Leachables / extractables dissolve out of the bags and can migrate into the cell culture medium. For distinction: Extractables are defined as substances which are washed out from foils, bags and tubes under harsh conditions, such as antioxidants, plasticizier or their degradation products. In contrast, leachables are washed out in the ongoing process. They not only jeopardize patient safety, but they can also damage the entire manufacturing process.

Cytotoxic leachables are particularly undesirable under process conditions, because they adversely affect the growth of the cells, their vitality and consequently also the titer. For this reason, a screening with mammalian cell cultures in addition to the extractable studies established by the manufacturer makes sense. Critical films can be identified at an early stage using such a screening, the quality control of single-use bags can be improved and their implementation can be simplified. Rentschler and other users of single-use bags therefore regularly carry out appropriate cell culture tests using cell lines, culture media and instruction of their own. A standardized cell culture test was recently published from the Dechema working group “Single-use Technologien in der biopharmazeutischen Produktion”[6]. The further purification progresses the more risk arises from the leachables in terms of patient safety. For depletion of the leachables,

Virus filtration system for tangential filtration

Renschler follows a risk-based approach which incorporates both manufacturer’s data and process data. This guarantees that depletion is carried out within defined limits so that patient safety is ensured at all times.

No hype - a paradigm shift

By enabling high modularity and flexibility as well as feasible energy savings, single-use bioprocesses have long ago developed beyond hype and now represent a paradigm shift in the production of clinical material. Some products, however, are better suited for the production in stainless-steel reactors, and commercial production is also usually more cost-effective in reusable stainless-steel reactors. But here, too, rethinking is taking place. The pharmaceutical company Shire uses a single-use system for the market production of a niche product. Rentschler is one of the first toll manufacturers worldwide to establish a complete single-use plant for the upstream and downstream area. The company has a flexible disposable concept consisting of two multi-product single-use bioreactor systems with 2 x 1,000 l volume of work and an additional 1 x 2,000 l bioreactor coming soon. This allows an easy scale-up as well as the reduction of manufacturing costs and product cycle times. The disposable plant involves four independent all-purpose clean room plants for operating the to 100% mobile one-way production plant for the upstream processing (USP) and downstream processing (DSP) as well as an inoculum suite. All clean room suites are connected to plant-wide Data Logging System (DLS) which is preconfigured for “plug and play” of the mobile production equipment. In 2012, Rentschler received the Facility of the Year Award (FOYA) in the category “Equipment innovation” for its flexible plant concept. Incidentally, the company supplies its complete plastic waste to an incineration plant, thereby contributing to the recovery of a significant amount of heat energy.

Literature

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