Pharmaceutical BIOPROCESSING

Flexible biomanufacturing for the production of biotherapeutics

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Inroduction

The biopharmaceutical market has become an important segment of the pharma industry. The coming years are also expected to bring further growth, which is ascribed to new products (such as monoclonal antibodies, hormones as well as enzymes for therapy and vaccines) and their biosimilars [1]. Production facilities in which biotherapeutics are manufactured with mammalian cell cultures are booming worldwide. In addition to large-scale facilities (with 20 m^3 bioreactors for products with titers up to 3 g L^{-1}), smaller, more flexible facilities (with 1 m^3 and 2 m^3 bioreactors for products with titers exceeding 5 g L^{-1}) are increasingly being built [2]. Whereas the large scale-facilities are primarily classic stainless steel facilities, single-use systems are utilised in the more flexible small-scale facilities whenever possible.

Single-use systems

The acceptance of single-use systems (whose cell-, medium- and product contacting surfaces are made from FDA-approved plastics and intended for single-use only) has increased in the production of biotherapeutics in the past 10 years [3]. This development may be explained by the advantages which single-use systems have in comparison with their reusable counterparts-when selected and applied correctly. Their usage is accompanied by lower contamination risk, and an increase in the facility flexibility is achieved by more rapid product and process changes. Furthermore, single-use systems contribute to savings in time and costs and allow for more sustainable production processes within smaller facility foot print [4,5]. The advantages outweigh the current limitations, the elimination of which is being worked on by suppliers of single-use systems and consortia consisting on both suppliers and users (such as BPOQ, BPSA, DECHEMA, ELSIE, ISPE, PDA). Materials (e.g. new films) and devices (e.g. leak test apparatus) to make the usage of single-use systems safer, and approaches for risk analyses as well as for standardized identification of leachables and extractables are the focus. Because they may migrate into the drug substance or drug product and may impair their quality under process conditions during manufacture, leachables are most dreaded [6].

There are a large number of single-use systems made by different manufacturers, which are mainly used in upstream processing (e.g. mixing, inoculum production, fermentation). In fact, upstream processing is carried out entirely with single-use systems in first modern biopharmaceutical production facilities. Moreover, single-use systems for downstream operations (e.g. biomass separation, clarification, virus separation and virus inactivation) as well as for fill & finish (e.g. storage, filtration, mixing, transport, filling) are available today too. Process platform technologies implemented by the key players of single-use technologies in the ReadyToProcess- or FlexFactory series (GE Healthcare), the Mobius series (Merck), the Allegro series (Pall Life Sciences) or FlexAct series (Sartorius Stedim Biotech) have proven themselves. These process platform technologies support the rational application of single-use

systems and the intensification of up- and downstream processing.

Process intensification by continuous processes

Although feeding procedures have been most prevalent in upstream processes of biopharmaceutical productions to date, a renaissance of perfusion is taking place [7]. Wave-mixed and stirred single-use bioreactors are periodically or continuously operated together with crossflow filtration systems in order to make cell production for cell banking and expression of the target product more efficient. The space-time yield linked with stable product quality is highest in continuous upstream processing, for which reason the bioreactors used are smaller than in feeding procedures. By extending the process, the space-time yield may be increased. It is worth mentioning that continuous perfusion processes have already been successfully performed in single-use bioreactors running between 30 and 90 days [8,9].

However, downstream processing is also under way for continuous solutions (e.g. continuous clarification, high performance resins, membrane adsorber technologies, continuous chromatography processes). The aim is downstream processing in less than 3 days with a minimum product yield of 75%. Because unlike upstream processing, downstream processing is not yet universally applicable to single-use systems in every case, a hybrid approach is often required. This means that single-use and reusable systems are combined. To keep the bioburden as low as possible, the facility components which come into contact with the product have to be suitable for irradiation [10].

The facility of the future

In the production of biotherapeutics, the trend is moving towards to the facility of the future, where work in continuous mode is increasing and where the drug substance and drug product are manufactured at one and the same site [10]. The facility of the future is characterized by a flexible facility design. Single-use systems are used in all stages of the biopharmaceutical production process from upstream processing until fill and finish. The modularization is an important factor for a versatile production facility, because time for planning and construction–as well as time for reconstruction in the event of product changes- may be shortened by applying modules and process platform technologies.

The priority aim of the facility of the future is sustainable production in a smaller space and at lower investment costs. The room concepts play a central role when realizing the facility of the future. Four main room concepts have gained acceptance: (1) The ballroom concept, (2) the dance floor concept, (3) the integration of modular cleanroom units into a ballroom, and (4) the assembly of modular, configurable units (e.g. KUBio-and FlexFactory modules). The latter are designed as so-called "blueprint facilities" and can be modified according to product- and process specific demands as well as national and international regulations.

Even though initial facilities of the future have already been built or are under way (e.g. from JHL in Wuhan and Pfizer in Hangzhou), there are still different challenges to be met. As example of this is the flexible configuration of the automatization systems. In this respect, a continuous integration from sensor to the production facility's management system is strongly required [10].

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