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1 INTRODUCTION

1 Introduction

The biopharmaceutical industry has experienced rapid development in the past few decades. Pharmaceuticals manufactured with biotechnology (first and foremost biopharmaceuticals, such as therapeutic antibodies and vaccines) are at the top both quantitatively (new authorisations/pipeline) and qualitatively (fields of application). As a result, this product sector is becoming increasingly interesting both for many established companies and for younger ones. Due to enormous development costs, it is expected that only the first three companies that enter the market for a field of application with a new biopharmaceutical product will be commercially successful (1).

Expiring patents also allow companies to introduce biosimilar biologic drugs (biosimilars). Biosimilars generally have a shorter development time, while the clinical test phase remains approximately the same, thus making them more cost effective. Emerging and developing countries, in particular, have a great need for biosimilars, because these countries are not able to pay the market price in industrialised nations. Therefore they have initiated programs for local production, which in recent years have resulted in a boom in new production facilities. In these production facilities, pharmaceuticals are produced under more economical conditions by local companies or under license agreement with the patent holders.

At the same time, the healthcare systems in industrialised nations are reaching maximum capacity and are exerting pressure on pharmaceutical companies to significantly lower the prices for new biotherapeutics and biosimilars. This has resulted in corresponding adaptations of the manufacturing procedures and capacities and has led to two production strategies in pharmaceutical companies. On the one hand, the pharmaceutical industry (e.g. Hoffmann-La Roche/Genentech, Biogen Idec, Samsung) is pursuing the strategy of production in large facilities so they can manufacture biotherapeutics in large quantities (6 x 20,000 L at up to 3 g/L product titre) and at low cost (<100 \$/g). On the other hand, pharmaceutical companies like MSD, Sanofi and Bayer have established more flexible factories, particularly so they can master the wide range of new product candidates during product development. Here high product titres >5 g/L make production in smaller facilities possible while market demand remains the same. The idea of these “Facilities of the Future” (FoF) is not new and has already been tried for a few years in so-called sandbox facilities (2) (e.g. Shire and MSD). However, the solutions developed here (new technologies, the flow of materials and personnel, lean procedures and the need for cleanrooms are optimised) are also becoming more and more established in GMP production (e.g. at Amgen).

Our status paper on the “Facility of the Future (FoF)” is directed at newcomers and interested parties who are at the initial stage of designing an FoF. We would like to provide readers with a guidebook that takes up the most important aspects on the topic and refers to more indepth literature (e.g. the “Biomanufacturing Technology Roadmap” of the BioPhorum Operations Group). In the process the current state of the art is represented without any claim to completeness.

2 TRADITIONAL BIOPHARMACEUTICAL PRODUCTION PLANTS VS. FOF: AN OVER-VIEW OF THE MAIN DIFFERENCES

2 Traditional biopharmaceutical production plants vs. FoF: an overview of the main differences

Biopharmaceutical production processes can be subdivided into active pharmaceutical ingredient (API) manufacturing with upstream and downstream operation and pharmaceutical manufacturing. The latter includes end formulation and filling as well as labelling and packaging (see Figure 1). The product of active pharmaceutical ingredient manufacturing is the drug substance (DS) and the product of pharmaceutical manufacturing is the drug product (DP). Generally the DS only undergoes further processing after approval by quality assurance and after the stipulated quality characteristics have been confirmed. DS and DP can be produced in one production location, but also in spatially separated production locations.

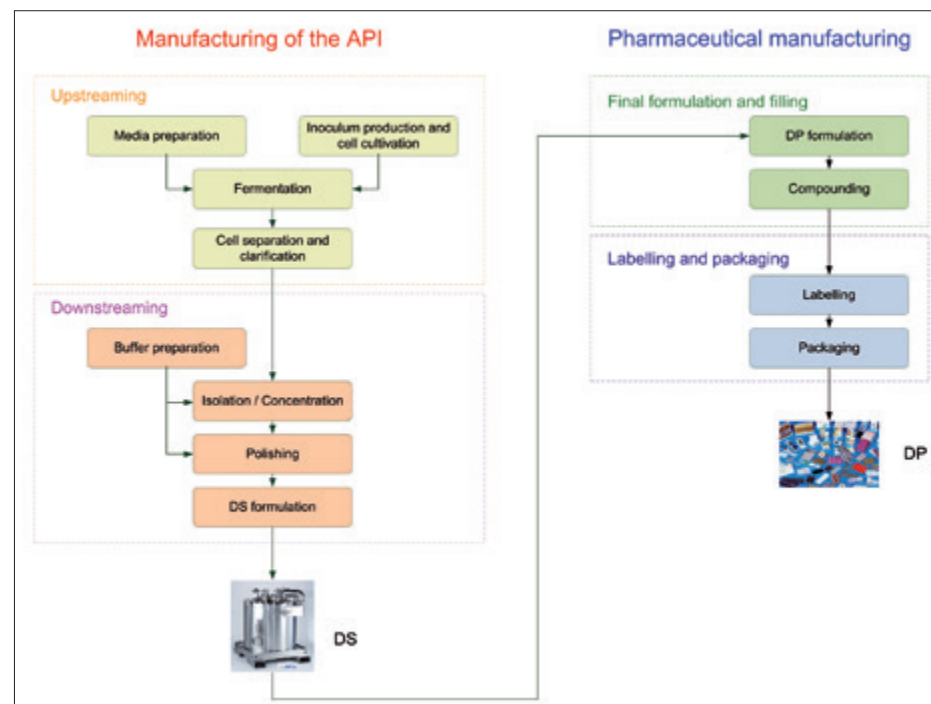


Figure 1: Schematic illustration of a typical biopharmaceutical production process (modified according to (2)).

2 TRADITIONAL BIOPHARMACEUTICAL PRODUCTION PLANTS VS. FOF: AN OVER-VIEW OF THE MAIN DIFFERENCES

Today, biopharmaceutical production facilities are either traditional facilities made of stainless steel, hybrid production plants (stainless-steel plants combined with single-use systems (3)) or single-use production plants. Single-use production plants are production facilities in which the substance conversion, the transport and the storage of initial materials, interim products and end products occur in single-use systems either completely or to a large extent.

Traditional stainless-steel facilities are primarily found in biopharmaceutical production processes with older authorisation dates, i.e. in processes with product titres up to 3 g/L and medium and larger production volumes. Hybrid production plants, which currently account for 75% of biopharmaceutical production facilities, are currently the most widespread (2). Single-use production plants, which currently exist worldwide in various stages of expansion, are still rare. They are primarily used in the American and Asian regions at large pharmaceutical producers, but also at smaller and medium-sized contract manufacturing operations. Single-use systems are used for upstreaming in particular, although solutions for downstreaming, filling and formulation (fill & finish) also exist (2). This affects both development and production on a small and medium scale, where the primary focus is on cultivating mammalian cells and, more seldom, microorganisms and insect cells. In biopharmaceutical production, the process steps are executed according to their sequence. The main process steps of a procedure based on mammalian cells with secreted product are shown in Figure 2. In processes with an intracellular target product, cell disruption, extraction and – for inclusion bodies that can occur in microbial processes – refolding processes must be executed.

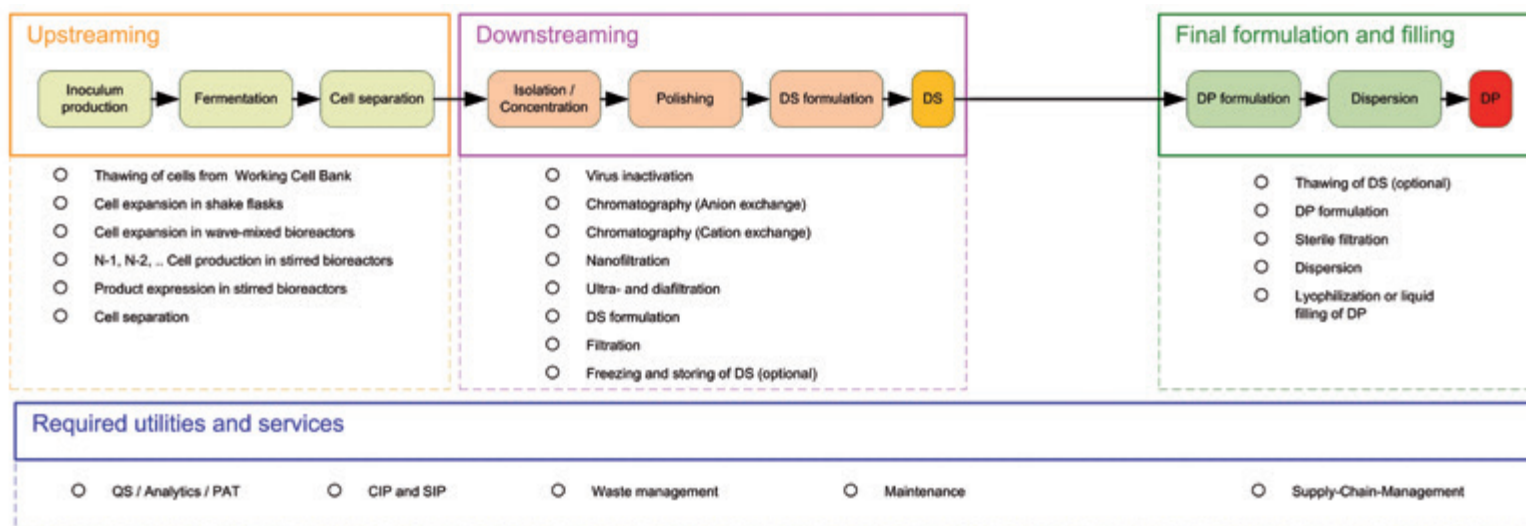


Figure 2: Main process steps of a biopharmaceutical production process based on mammalian cells

2 TRADITIONAL BIOPHARMACEUTICAL PRODUCTION PLANTS VS. FOF: AN OVER-VIEW OF THE MAIN DIFFERENCES

If necessary, raw materials, intermediate products and end products are cooled and stored temporarily. In contrast to downstreaming, which is carried out in batch mode in traditional production plants, upstreaming uses all forms of the operating modes (batch, fed batch, continuous perfusion). Fedbatch procedures for cultivation and product formation still remain predominant today, while so far continuous processes are only seen in isolated cases.

FoF is characterised by new, flexible plant concepts, in which it is possible to work with single-use systems from upstreaming to fill & finish, i.e. all process stages. This forward-looking production concept requires highly productive cell lines (production titre >5 g/L), for which the small and medium scale (max. 1 m³ or 2 m³ production bioreactor) is sufficient. Such production plants allow for complete biopharmaceutical production with short timelines. At the end of the product chain the DP is available in liquid or freeze-dried form and in a deliverable state (tested, labelled and packaged). However, this makes the appropriate process analytical technology (PAT) (see Section 5) and the prompt approval of the DS and DP mandatory. So-called “blueprint facilities” (3) have been designed to allow for rapid reaction to market changes. Here sizes and special features can be adjusted according to needs and national and international regulations.

3 Process-intensification options for the FoF

In addition to optimised media and high-performance cell lines, highly productive procedures for biopharmaceutical products require efficient upstream and downstream processes. Thus, in the production of therapeutic antibodies (mAbs), until today the three approaches for the intensification of upstreaming compared in Table 1 have proven themselves: the fed-batch process, the intensive process, which is based on XD technology (3), and the continuous perfusion process.

Table 1: Comparison of the product yield in mAb production runs depending on upstreaming

Process	Reactor volume	Product titre/ productivity	Process duration	Number of batches per year	Yield per batch ¹	Yield (75%) per batch ²	Yield per year
Fed-batch	2000 L	8 g/L	15 d	22	>16 kg	>12 kg	>264 kg
XD technology	2000 L	25 g/L	20 d	16	>47 kg	>37.5 kg	>600 kg
Continuous perfusion	500 L	2 g/L ³	50 d	6	>50 kg	>37.5 kg	>225 kg

¹ before downstreaming, ² after downstreaming, ³ per day

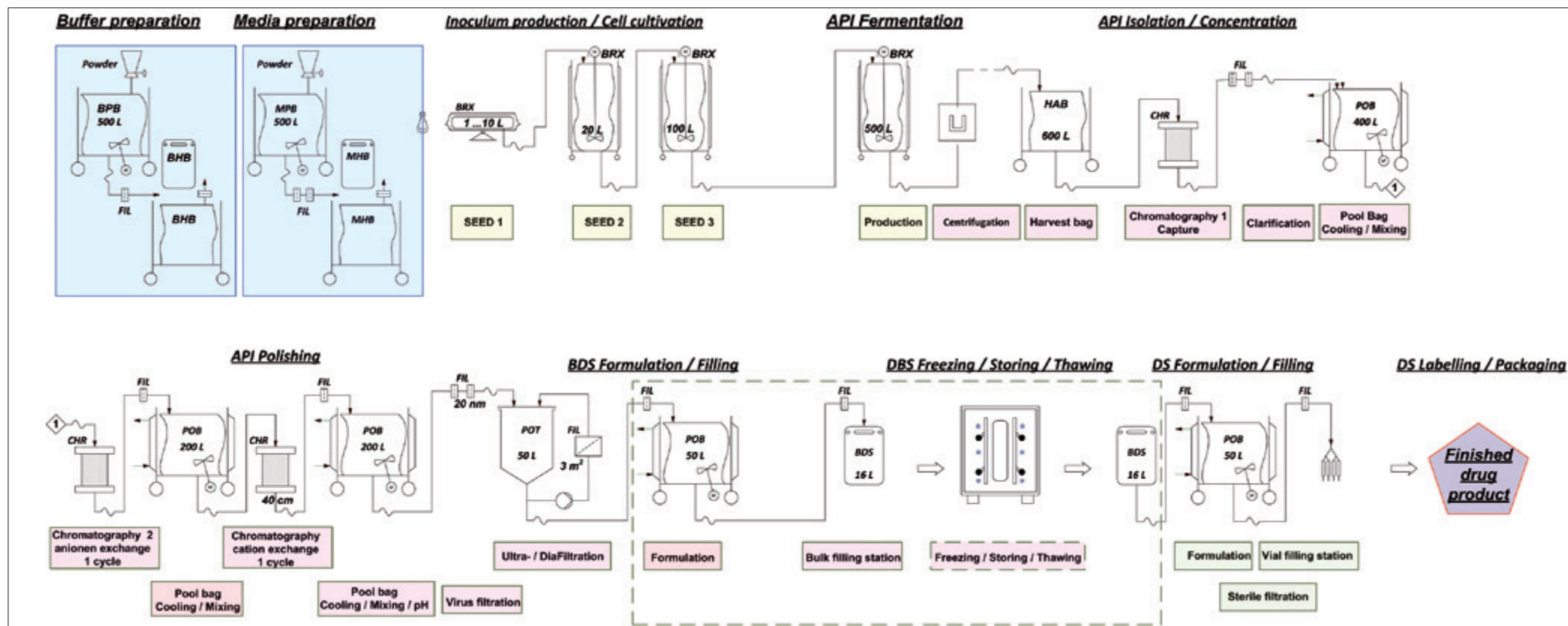


Figure 3: FoF working in fed-batch operation for production of mAbs.

3 PROCESS-INTENSIFICATION OPTIONS FOR THE FOF

Assuming a maximum reactor volume of 2000 L, a product titre of 8 g/L and a yield of 75% in downstreaming with 22 cultivations per year, mAb quantities >264 kg can be produced in fed-batch mode (see Table 1 and Figure 3).

For a process management by means of biomass enrichment (XD technology), with the same reactor volume and product titres of 25 g/L mAb, quantities of > 600 kg can be realised with 16 cultivations (see Table 1). It should be noted that the XD process is patent-protected by DSM.

However, the greatest potential lies in continuous process control. This offers the best space-time yield and improves as long as the process can be operated stably. Continuous perfusion processes in single-use bioreactors have already been performed successfully for over 70 years (4,5). Assuming a reduced bio-reactor volume of 500 L, a specific product performance of 2 g/L/d and a yield of 75% after downstream-

3 PROCESS-INTENSIFICATION OPTIONS FOR THE FOF

ing, the annual mAb quantity in continuous perfusion mode is > 203 kg. 6 cultivations are sufficient for this. If a reactor volume of 2000 L with continuous perfusion is assumed, this would result in an annual mAb yield as high as > 900 kg. In continuous perfusion processes, the high space-time yield is associated with consistent product quality, which also allows for new approaches for product assurance in real time.

In downstreaming greater emphasis is also put on single-use systems. In this process, a minimum yield of 75% and product reprocessing within an extremely short timeframe (i.e. less than three days) is the aim. Virus depletion or removal must be proven. To ensure downstreaming for processes with high product titres, there is an increased use of high-performance resin. In addition, continuous chromatography procedures (multi-column processes or simulated moving bed technology) and membrane adsorber technologies for the removal of DNA and host cell protein are used (see also (3)).

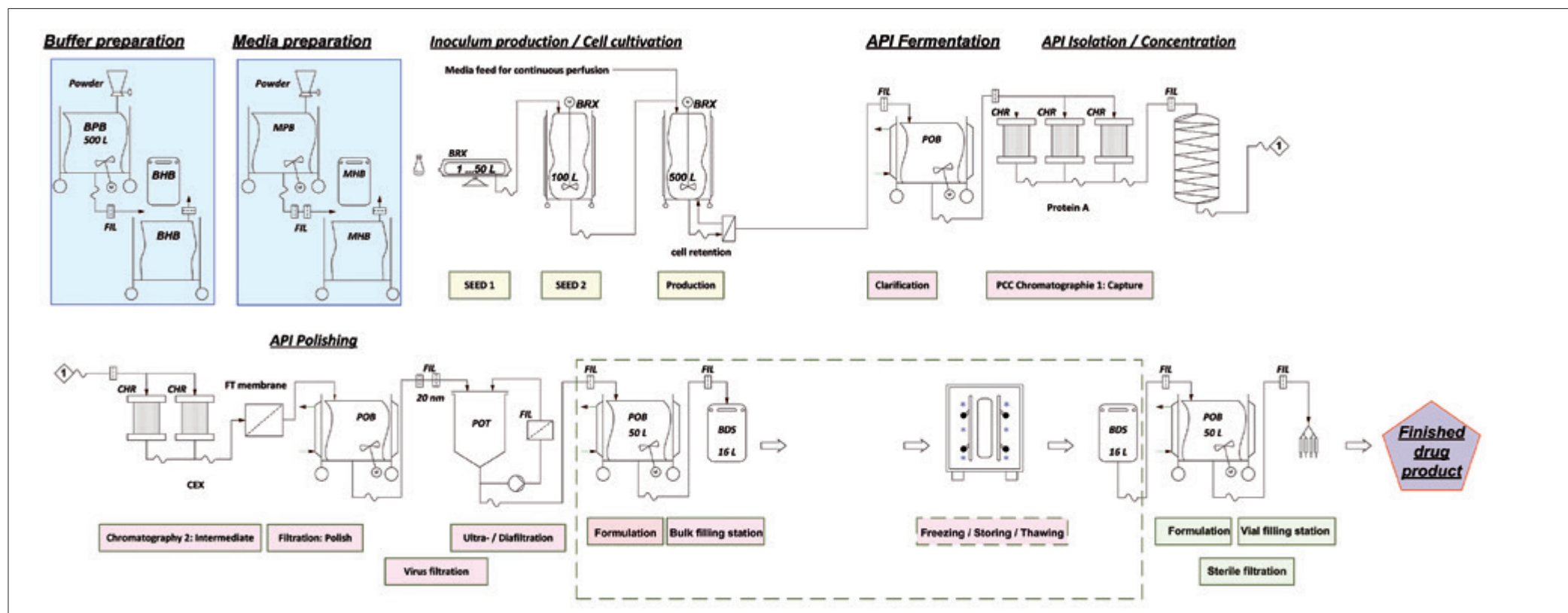


Figure 4: Continuous FoF for production of mAbs.

4 Equipment and infrastructure for FoF setup

4.1 Product and process-based selection criteria for the equipment and infrastructure

In addition to the planned input and output, product and process-based requirements play a significant role in determining the necessary equipment and the infrastructure of the FoF. In addition to the process media and the IT system, rooms (classified and unclassified cleanrooms) are assigned to the FoF infrastructure in which the sub-processes described in section 3 are carried out. The product and process-based requirements of the FoF are closely linked together and cannot always be distinguished from each other (Table 2).

Table 2: The product and process-side requirements of the FoF that must be considered

Product-based requirements	Process-based requirement
<ul style="list-style-type: none"> » The complexity of the process corresponds to the target product (e.g. intra- or extracellular protein, enzyme, vaccine, antibody-drug conjugate, cell therapy) » Presentation: DS or DP, liquid, solid, trade and packaging unit » Purity » Toxicity » Virulence » Product analysis 	<ul style="list-style-type: none"> » Operating modes corresponding to the complexity of the process » Complexity of the process according to the number and type of the process steps as well as biosecurity » SIP/CIP: Hybrid facility and single-use production plant » Media and buffer » Need for dry and cold storage » Waste product elimination » Process analysis » Product change on a facility

4.2 Options for FoF infrastructure

4.2.1 Conversion of a traditional biopharmaceutical production facility into an FoF

The planning and establishment of an FoF is pursued with the priority objective of more sustainable production, with a reduced need for space and lower investment costs and shortened development and time to market (6–11). This puts high demands on the analysis and approval systems in the quality departments, since the interim and end products must be analysed *on line* or *in line* during the process and lead to an IT system that records data reliably and makes the quality systems available without any errors for “just-in-time” approvals. The first approaches using electronic batch records, manufacturing execution systems, laboratory information systems and direct digital control systems have already been realised (7).

The rooms, which the producer of biopharmaceutical agent will implement either by converting an existing traditional facility or building a new facility, play an equally important role for the FoF. Whether conversion or new construction is necessary and which design makes the most sense must be analysed specifically for each case.

Various biopharmaceutical manufacturers are currently reviewing the options for converting their existing facilities into FoF. This task often consists of making rooms that have been constructed for large, permanently installed stainless steel facilities usable for smaller, mobile and flexible single-use equipment. For example, in the cleanrooms for upstreaming, the floor heights and stainless steel bioreactors have been set up to extend over several floors, and are supplied with medium, sterilisation steam, correction agents, etc., via stainless steel tanks and components. In contrast, the smaller single-use bioreactors need a small cleanroom that has sufficient space and the necessary ceiling height for single-use bioreactors. Ideally, the bioreactor spaces are supplied with electricity, gases, etc. via supply modules installed on the ceiling. The bioreactors can be connected to the modules with a “plug-and-play” system. The supply lines represent another difference between stainless steel and single-use facilities: while rigidly connected supply lines from stainless steel storage tanks are used in the stainless steel process, in single-use systems fluid is transferred flexibly beyond the containment limit of the cleanroom. The mobile media and buffer bags are connected in the wall via qualified connections, and in the cleanroom they are transported to the process by a linked hose. This makes it possible to reduce the need for expensive cleanroom space. Because media and buffer and transported in closed rollable bags, the bags can also be handled in cleanrooms with a lower classification.

Adapting the infrastructure of an existing facility to an FoF based on single-use-equipment will accordingly be associated with corresponding structural adaptations to the process rooms. These include removing unused stainless steel components and adapting the cleanrooms to the process-specific single-use systems. Additionally, adequate storage rooms and disposal paths for the single-use components must be created.

Ultimately a conversion of an existing production facility into an FoF remains a case-by-case decision, which must be made by means of an analysis of the production process and with consideration of the expense associated with changing the infrastructure. Furthermore, the time of the facility conversion plays a crucial role for the biopharmaceutical manufacturer. It is difficult to imagine converting a running production facility that delivers products for market supply without capacities in alternative facilities to ensure the market supply. In contrast, it is more likely that facilities will be converted to new production processes with adaptations to infrastructure in the pre-clinical stage, between clinical phase 1 and 2, or during the preparation of a facility that is not in use.

4.2.2 New construction of an FoF: “ballroom” vs. “dance floor”

The first room concept that can be used as basis during the new construction of an FoF is the “ballroom” concept (12,13). Here in a small room with a low cleanroom classification, partial areas with the corresponding heating, ventilation and airconditioning (HVAC) are raised to the cleanroom class required for the respective process step. For optimal setup and operation and for testing and training purposes, it is

4 EQUIPMENT AND INFRASTRUCTURE FOR FOF SETUP

recommended that the sandbox facilities mentioned in the introductory section be realised in advance or in parallel. In these sandbox facilities all process units are tested before or parallel to construction and operation of the actual production facility. The functionality and process performance of the units are also checked, and personnel are trained and used for troubleshooting in case of problems while production operation is running.

With the “ballroom” concept, changes such as an increase of production capacity, the integration of new sub-processes and parallel operation of different productions are easy to implement. For example, a scale-up in upstreaming would be easy to realise by upscaling the bioreactor or via a scale-out approach, which would involve adapting the upstreaming to the new situation within the “ballroom”. On the basis of a “ballroom” concept, a creative planner can develop various production scenarios and design the required “ballroom” in this way.

The second concept is characterised by small, dedicated process-step units (Figure 5 b) in the required cleanroom class and is referred to as the “dance floor” concept (13). At first glance, this concept offers an optimal environment for the planned production process because it represents the required space exactly, thus keeping the costs for surface area and cleanroom operation low. However, the flexibility of this variant is limited. The “ballroom” concept (Figure 5 a) requires a larger surface area than the “dance floor” concept (Figure 5 b), but offers the advantage of higher flexibility. A “dance floor” FoF is appropriate when processes are going to be performed with the same facilities/equipment/platform technologies in a different location or when only a single process is going to be performed. Examples of an FoF with a “dance floor” concept are facilities from Amgen and JHL. These are facilities that can be constructed any time and anywhere identically without a fundamental replanning (e.g. to supply other markets, to ensure production capacities in a second location or to expand production capabilities).

4.2.3 New construction of an FoF: modular constructions

Another approach that is used for the new construction of an FoF is based on modular cleanroom units, which are either introduced in a ballroom or are put together as modular, configurable units. Systems with pre-installed supply units (e.g. from G-CON Manufacturing, SmartFit Modular, GE Healthcare) and those without such utilities (e.g. from Daldrop, AES, Plascore) are suitable for this (14). The KUBio System (Figure 6) from GE Healthcare currently offers the most comprehensive and best-known example of this modular design.

It is comprised of configurable units that become a biopharmaceutical factory when all of them are put together. Each of these units are 80 to 90% pre-installed. This means that heating, ventilation, a cleanroom, and most supply units for the equipment and piping systems are already included. The units can be assembled quickly and efficiently at the facility construction site. A time savings of 18 months is expected for the construction of a KUBio facility compared to traditional stainless steel facilities. The production site is prepared for the introduction of the modular units, and the actual production rooms including their infrastructure are produced simultaneously in another location. JHL has already realised a facility of this kind in Wuhan, China (15). Pfizer has started to build a KUBio-based facility in Hangzhou, China (16).

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Figure 5: Schematic representation of the “ballroom” concept (A) and the “dance floor” concept (B).

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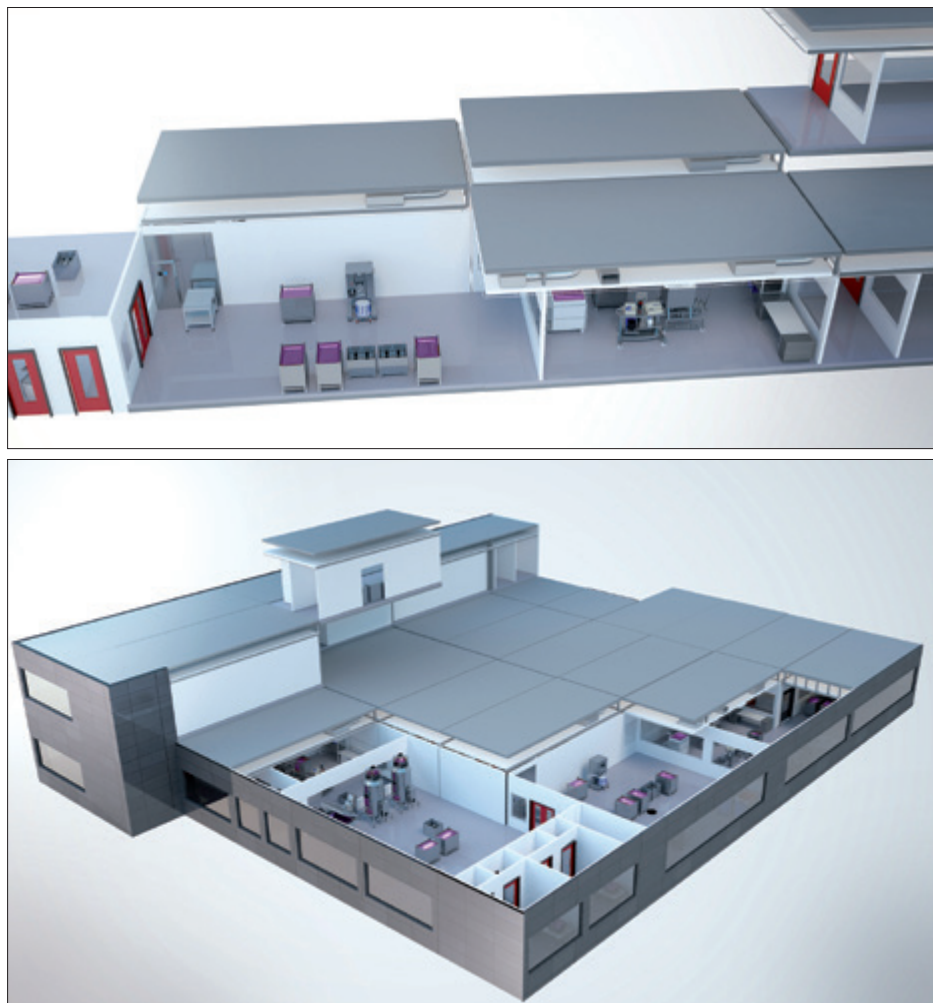


Figure 6: KUBio facility (courtesy of GE Healthcare).

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4.2.4 Infrastructure elements

Infrastructure elements that are important for biopharmaceutical production in an FoF are listed below. For select areas (e.g. regulatory support and analysis) it may be interesting to contract external partners and to reduce costs via outsourcing.

Infrastructure for services

- » Analytical areas
- » Regulatory support
- » Storage, logistics
- » Personnel areas (offices, conference rooms, lounges, relaxation rooms, changing rooms, etc.)
- » Facility administration and maintenance
- » Training

Infrastructure for production areas

- » General
 - Production and distribution of operating gases
 - Production and distribution of coolants
 - Production and distribution of water for injections
 - Production and distribution of process water
 - Production and distribution of energy for room heating or cooling
 - Storage (drying, cooling and freezing rooms) for:
 - Raw materials
 - Single-use products
 - Equipment
 - Intermediate products
 - Finished products
 - Cleaning and correction agents
 - Quarantine or approval storage
 - Containment
 - Waste water
 - Waste product disposal
 - Safety devices
- » Unclassified area
- » Cleanroom concepts
 - Cleanroom infrastructure (air filter, air conditioning, etc.)

4.3 Equipment

4.3.1 Fundamentals for selecting the appropriate facility components

In principle, the procedure for selecting the system components for an FoF does not differ from the one used for a traditional biopharmaceutical production facility. First, the client must create a detailed specification. The specification combines the basic product ideas and transfers them into a concept that can be implemented. The specification also helps to define milestones. It is the foundation for initial discussions with potential suppliers and planning offices. The service provider will use the specification to create a performance specification. In accordance with DIN 69905, it will contain the “realisation requirements worked out by the contractor” and describe the “implementation of the specification provided by the client”. The performance specification forms the basis for the tender preparation by the service provider and therefore must be prepared and reviewed very precisely. The batch size is defined by the process data (titre, ...), the process operation (batch, fed batch, continuous, ...) and the market data. Process simulation tools offered by suppliers or independent consultants and universities (e.g. (17)) can support the operator when making the decision.

In principle, single-use systems offer the user less flexibility than traditional stainless steel systems (2). This primarily affects the scale, which can be seen in the design of the system. The DECHEMA Working Group “Single-Use Technology in Biopharmaceutical Manufacturing” has published a recommendation to characterise the biotechnological process of single-use mixers and bioreactors (18), which should contribute to a standardisation of the design parameters. Many manufacturers already use this guideline to characterise their single-use equipment.

It is important to note that the equipment and process type that are used during the clinical phase (up to phase 2) are similar to that of the final production process, since they can save time during the process validation and during the scale-up. Generally, all devices used must be chosen with an awareness that they may be used in a GMP environment, which is why they must comply with national and/or international regulations (e.g. national machine guidelines, software CFR21 Part 11, etc.). This in turn requires the qualifications represented in Figure 7, in addition to creating the risk analysis and the validation master plan.

Initial recommendations are available from various organisations (e.g. ASTM, BPOQ, BPSA, DECHEMA, ELSIE, ISPE, PDA) both for the selection and the application of single-use systems in the biopharmaceuti-

Before shipment		At the place of installation			
User:	Supplier:	Supplier/User: Functional qualification			Supplier/User: Maintenance
URS User Requirements Specification based on the GXP	DQ Design Qualification	IQ Installation Qualification	OQ Operation Qualification	PQ Performance Qualification	OQ/PQ Operation/Performance Qualification

Figure 7: Temporal and regional progression of the qualification tasks.

cal industry. In addition to questions about standardisation, the focus is on the material of the single-use systems, because this influences the selection of the manufacturer and therefore the selection of the equipment. Device manufacturers are also often the producers of the single-use components that fit their devices, such as bags or filters. Because different manufacturers use different materials and the material can influence the product quality, preliminary examinations of these influences on a small scale are absolutely necessary. Particular critical are leachables and extractables (19–21) in increasing proximity to the end product or patient.

If the device manufacturer has the appropriate single-use equipment, the 6 points listed below should also be complied with:

1. Knowledge of GMP fundamentals
2. IQ/OQ protocols for the equipment
3. Calibration protocols and certified testing equipment
4. The upstream and downstream devices should be compatible with each other (e.g. connector).
5. If a global process software is going to be used, it must be possible to integrate all devices easily.
6. Connection of online measuring techniques (PAT/QbD)

Furthermore, it must be kept in mind that when an FoF is implemented with single-use equipment, the user is entering long-term partnerships with the device manufacturers. Single-use components must constantly be resupplied later, which is why it is absolutely necessary to qualify the manufacturer and set up a change control system. Another option, although it is difficult to implement, is constructing a second supply source for the single-use components to prevent production outages due to missing components.

4.3.2 Equipment for fluid management and unit operations

For the single-use system components, a distinction is made between equipment for fluid management (Table 3) and equipment for unit operations (Table 4).

Because single-use systems generally cannot be changed after they have been produced (e.g. adding an additional port) and can only be manufactured economically above a certain ordered quantity, today an increasing number of so-called single-use process platform technologies are in use. Single-use process platform technologies are technically implemented, well-defined sequences of processes or process steps and allow for the rational use of single-use systems in a modular design. Typical single-use process platform technologies exist for applications in the areas storage, transportation and mixing, inoculum production and fermentation, downstreaming and fill & finish. Because single-use systems are not yet fully available in downstreaming as well and fill & finish, hybrid systems are expected in the future.

A sufficient reduction of the bioburden load is a problem for continuous long-term processes, which can be solved by irradiating the single-use systems. This cannot be guaranteed by conventional sterilisation procedures of traditional steel and glass systems. For this reason, it should be possible to irradiate all system components of hybrid production facilities that come into contact with products.

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Table 3: Examples of equipment for fluid management

Equipment for fluid management	Examples of manufacturers
» Connection systems <ul style="list-style-type: none"> • Tubes • Y-pieces, T-pieces, etc. • Couplings • Laminar flow • Steamable systems • Aseptic connectors • Aseptic transfer systems • Welding systems • Identification systems (RFID tags) 	Colder Products Company, GE Healthcare, JM BioConnect, Merck, NewAge Industries, Pall Life Sciences, Parker, RFID Solutions, Saint-Gobain, Sartorius Stedim Biotech, Thermo Fisher Scientific
» Valves	Crane, GEMÜ, Parker
» Storage <ul style="list-style-type: none"> • Bags <ul style="list-style-type: none"> – 2D and 3D bags – Tank liners • Manifolds • Sampling systems 	GE Healthcare, JM BioConnect, Meissner Filtration Products, Merck, Pall Life Sciences, Sartorius Stedim Biotech, Thermo Fisher Scientific
» Mixing <ul style="list-style-type: none"> • Stirred systems • Tumbling systems • Oscillating systems <ul style="list-style-type: none"> – Wave-mixed systems – Vibrating discs • Hydraulically driven systems 	GE Healthcare, Merck, Pall Life Sciences, Sartorius Stedim Biotech, Thermo Fisher Scientific
» Transportation <ul style="list-style-type: none"> • Bag-handling systems <ul style="list-style-type: none"> – Shells – Trays – Racks – Transport containers 	GE Healthcare, Meissner Filtration Products, Merck, Pall Life Sciences, Sartorius Stedim Biotech, Schulte bagtainer systems, Thermo Fisher Scientific
» Pumps <ul style="list-style-type: none"> • Peristaltic pumps • Piston diaphragm pumps • Centrifugal pumps 	Watson Marlow Fluid, Technology Group, Quattro Flow Systems, Levitronix

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Table 4: Examples of equipment for unit operations

Equipment for fluid management	Examples of manufacturers
» Cultivation <ul style="list-style-type: none"> • Static systems • Hydraulically driven systems • Pneumatically driven systems • Orbitally shaken systems • Wave-mixed systems • Stirred systems 	CerCell ApS, Celltainer Biotech BV, Eppendorf, GE Healthcare, Adolf Kühner, Merck, Pall Life Sciences, PBS Biotech, Sartorius Stedim Biotech, Thermo Fisher Scientific, TPP Techno Plastic Products
» Cell harvesting and clarification <ul style="list-style-type: none"> • Depth filtration systems • Microfiltration systems • Ultrafiltration systems • Nanofiltration systems • Centrifuges 	3M, Barry-Wehmler, GE Healthcare, JM BioConnect, Merck, Pall Life Sciences, Repligen, Sartorius Stedim Biotech, Spectrum Lab, Thermo Fisher Scientific
» Buffer exchange <ul style="list-style-type: none"> • Diafiltration systems 	GE Healthcare, JM BioConnect, Merck, Pall Life Sciences, Sartorius Stedim Biotech, Thermo Fisher Scientific
» Concentration and cleaning <ul style="list-style-type: none"> • Ultrafiltration systems • Membrane adsorber • Chromatography systems 	GE Healthcare, JM BioConnect, Merck, Pall Life Sciences, Repligen, Sartorius Stedim Biotech, Thermo Fisher Scientific
» Freeze Thaw systems	Sartorius Stedim Biotech, Thermo Fisher Scientific
» Filling systems	Bosch Packaging Technology, Merck, Pall Life Sciences, PDC Aseptic Filling Systems, Sartorius Stedim Biotech, Thermo Fisher Scientific

5 Automation concepts and sensors in the FoF

5.1 Process analytical technology (PAT): single-use technology requirements for process sensors

New market requirements in the pharmaceutical industry make it necessary to reconsider traditional automatic concepts and to develop new approaches. The trend toward using more and more single-use systems in process facilities also requires new process-analysis technologies. A central requirement for automation here is a flexible design of process functionality to react to changing market demands. At the same time, the time to market must be shortened, because an earlier market entry represents a crucial factor in a product's commercial success.

The modularisation of the process facilities is an opportunity to meet these new challenges, and is considered a crucial factor for a flexible production facility that is able to change (22). Furthermore, the reusability of modules makes it possible to shorten the planning and construction time significantly. A central challenge when realising an FoF is the flexible configuration of the automation system (23). In the process, thorough networking from the sensor to the factory management system is of critical importance. Figure 8 classifies the various systems and technologies of the automation technology on the basis of a pyramid.

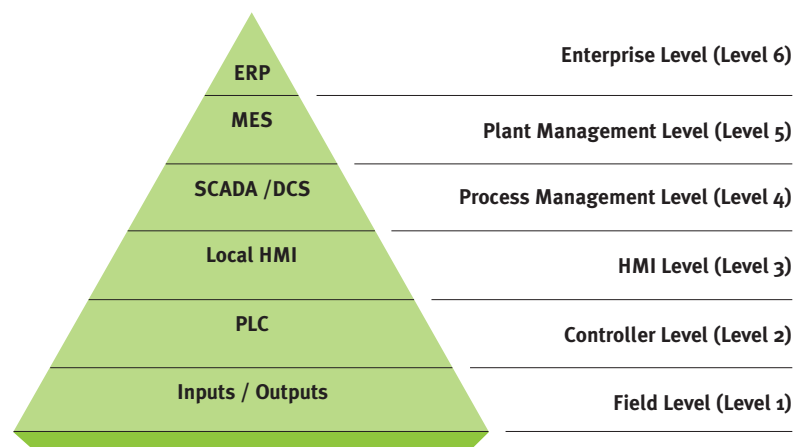


Figure 8: The automation pyramid.

For single-use bioreactors, sensors are needed that are pre-calibrated and can also be used without breaking the sterile barrier. Considering the central parameters pH and oxygen, chemical-optical systems are widespread in the area of single-use sensors. They typically consist of a single-use part that comes into contact with the product and has a polymer coated with an analyte-sensitive fluorescence dye (or mixture), and a reusable sensor head, which carries the optoelectronics. This construction has proven itself to be advantageous, because the connection between the two parts is realised purely optically, without breaking sterile barriers. While oxygen in single-use bioreactors is measured almost exclusively in this form, traditional glass electrodes or single-use electrodes are still used for the pH measurements. The disadvantages of both pH electrode types in terms of handling or costs are primarily their larger measurement range and their insensitivity to optical disturbances. The developers of chemical-optical pH sensors are therefore trying to shift the fluorescence stimulation of the pH sensors into the longer-wave range so they are more robust in response to fluorescent media components.

Although they are well suited to this application in principle, other optical sensors (turbidity, fluorescence) currently play practically no role in single-use bioreactors. In contrast, the detection of biomass by capacitive single-use electrodes is already a reality. While the measured cell capacity is celltype dependent, it is proportional to the living cell count, which makes it possible to monitor cell viability.

5 AUTOMATION CONCEPTS AND SENSORS IN THE FOF

5.2 From the package unit to the overall process: modular integration in process control engineering

Modular process facilities consist of individual package units that represent parts of the overall process. For the control of the individual package units that interact in the overall process, essentially two integration approaches are available on the process-control level: monolithic process automation and modular DCS integration. In the monolithic process automation the overall control logic is elevated to the process-management level. Here the individual package units are connected via remote I/O. In the second concept, the process logic is mapped on the local unit PLC at least up to the unit phase, but at most up to the unit-operation level (see procedural model of the ISA-88). The recipe procedure including the batch control is then mapped on the process management level. Figure 9 provides examples of both concepts in an automation lay-out.

The advantage of a modular integration into the process control system is the significantly simplified engineering on the process-control level. The data flow is limited to the information required for the recipe system. A combination of both approaches is also possible.

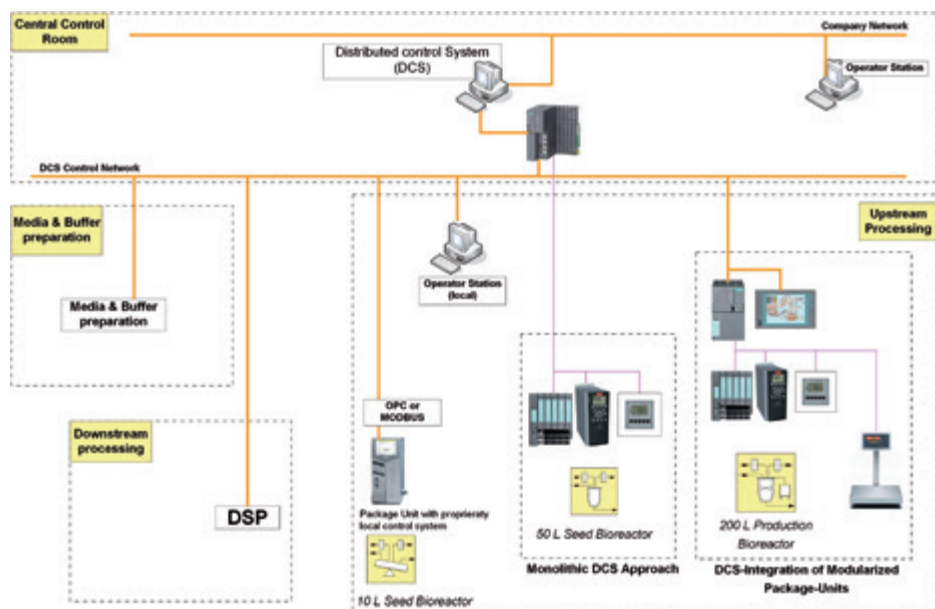


Figure 9: Exemplary automation layout of a biopharmaceutical production process (courtesy of Sartorius Stedim Biotech).

6 QUALITY CONTROL FOR RAPID BATCH APPROVAL

6 Quality control for rapid batch approval

As in the traditional biopharmaceutical manufacturing processes, rapid batch approval also has a key role in FoF. Due to the accelerated batch approval at the end of the manufacturing process, the time required to produce a batch is significantly reduced, because the batch does not need to be temporarily stored in a quarantine area for an extended period. In the past few years various regulatory initiatives have been developed and published that include concepts for faster batch approval. They are:

- » FDA Process Validation Guidance
- » ICH Q8(R2) Pharmaceutical Development Guidance
- » Process Analytical Technology (PAT) – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Both the ICH Q8 and the PAT guideline currently represent the basis for the development of new biopharmaceutical manufacturing processes, and introduce a series of new concepts and terms (design space, control strategy, quality target product profile (QTPP), critical quality attributes (CQAs), critical process parameters (CPPs), quality by design (QbD), real time release testing (RTRT)). A central component of both guidelines is the concept of influencing product quality by means of the process design. Here the QbD approach and the risk assessment during the overall process or during the process development

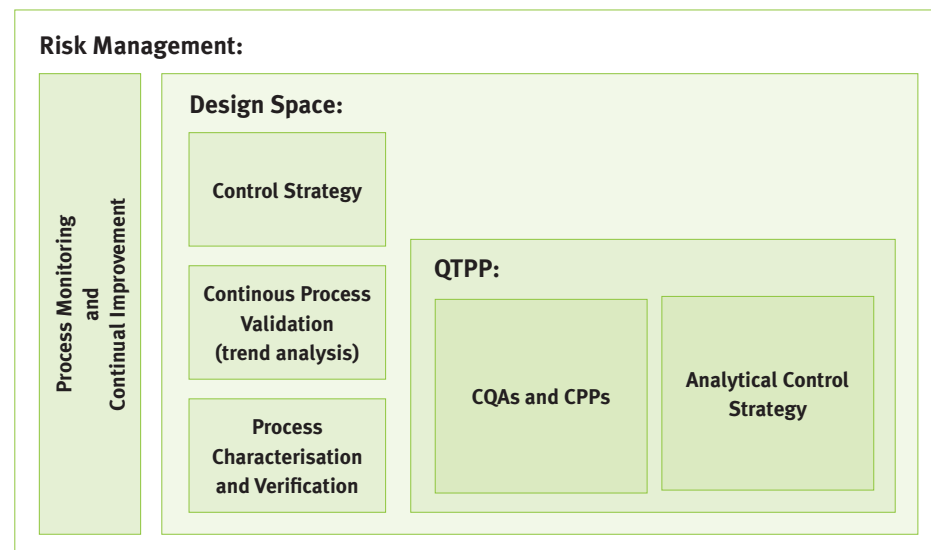


Figure 10: Schematic representation of the main points for the risk assessment and rapid batch approval in biopharmaceutical production processes.

6 QUALITY CONTROL FOR RAPID BATCH APPROVAL

become especially important. The systematic use of QbD for process development and the inclusion of existing knowledge, the results of DoE-based development studies to define the design space, process improvement within the design space and upstream risk assessment all make it possible to design processes more flexibly. A better understanding with regard to the materials used, the manufacturing options and the process parameters can be achieved by incorporating PAT approaches (see Section 5).

Figure 10 provides a schematic illustration of the points that should be included in the risk assessment and faster batch approval when developing new biopharmaceutical processes. Thus the development of new manufacturing processes always includes the characterisation of the QTPP and the identification and definition of possible CQAs and CPPs, which influence the quality of the end product. For this purpose, the CQAs and CPPs must be examined and established in detail in an appropriate scale-down model. The product quality within the design space can be guaranteed by controlling the CQAs and CPPs using a selected control strategy (in-process controls, raw-material controls, intermediate-product controls). Here, however, to compensate for the variability of individual processes, the risk assessment becomes extremely important. As a result of guaranteeing the process flow within the design space and due to the improved understanding of product performance, in the future it will also be possible to apply alternative approaches to batch approval such as RTRT. The RTRT can replace the testing of the end product, but not the testing and quality-control steps for batch approval required under GMP conditions.

7 THE DEVIL IS IN THE DETAIL: PROJECT MANAGEMENT FOR REALISATION OF FoF

7 The devil is in the detail: project management for realisation of FoF

The industry is currently in a transition phase from traditional biopharmaceutical production in large stainless steel facilities to modular and flexible production in FoF. Modular concepts are also currently being discussed in the chemical industry, issues in this sector are addressed, among others, by the temporary ProcessNet working group “Modular Systems” (24).

Figure 11 summarises the requirements for an FoF for biopharmaceutical production. To satisfy these requirements, an interdisciplinary project management system must be ensured. New approaches are particularly helpful during the implementation and production planning of single-use systems and technologies associated with them. Because suppliers of consumable materials (disposables) are now an essential component of the value-creation chain, risks arising from this should be evaluated in advance (25).

However, this new constellation can also give rise to areas of expanded cooperation. Securing the supply chain and quality assurance represent important interfaces between the “new” partners. Another area of work, however, is defining future standards on both a technical and a regulatory level. The objective for both sides should be to permanently question and continuously improve the current situation, and as a result lower both the investment and the running costs (total cost of ownership). This can be realised if single-use systems are used to the greatest possible extent in all manufacturing areas (upstreaming, downstreaming and fill & finish) (26). From a technical perspective, it is important to identify current limitations and to find solutions to them.

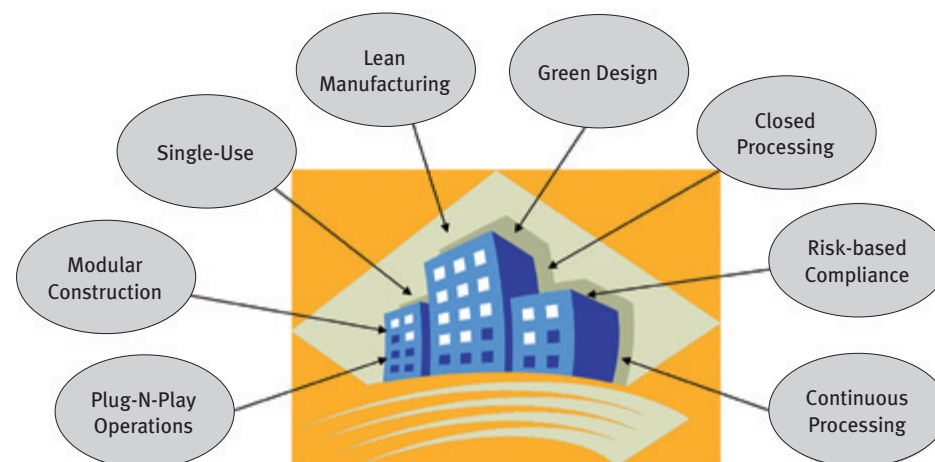


Figure 11: Requirements for the FoF.

Cooperation between operators and suppliers is the central requirement. Experience shows that a sequential approach in line with “good engineering practice” (GEP) recognisably leads to success (27). GEP should be subdivided into seven phases that are coordinated with each other. The first three phases are used to determine technical and economic requirements and to specify conditions in writing. The objective of the subsequent phases 4 and 5 is detail planning and technical implementation. Phase 6 involves commissioning and qualification, as well as monitoring during the initial engineering runs. In the final phase 7, supplier and operator remain in constant contact. This is not only important to ensure the supply chain, but also for services that allow for the flawless production of active substances.

Phase 1: Early integration is essential so that suppliers can understand the needs of the operators. In what is known as the “**pre-conceptual design**” phase, requirements can be specified and processes can be simulated, which allows economic assessments to be performed. This activity is often outsourced to third parties, e.g. engineering service providers. In the process it must be kept in mind that these third parties do not understand the process in detail, and do not have deep knowledge of the planned single-use systems or their limitations and possible alternatives.

Phase 2: The **conceptual design** builds on the results of phase 1. Here, if necessary, feasibility studies should be carried out for critical process steps or certain technologies. A process flow chart helps provide an overview of the entire manufacturing process and its interfaces. In addition to the automation concept, in this phase the cleanroom layout is drafted and the energy requirement is determined. After these steps have been performed, an initial cost estimate is possible.

Phase 3: Here the **basic design** is carried out, which determines all the requirements. For this purpose the documents from phase 2 are specified and detailed. On this basis, a description of the single-use systems (hardware and software) can be created in the form of an equipment list and a description of the disposables (wetware) can be prepared as a “bill of materials” (BOM). The process flow chart and the process automation (HDS/SDS) are also specified. When all needs have been clearly specified, a so-called “project execution plan” (PEP) and a qualification model are created. The PEP defines the responsibilities and contacts and describes the further procedure until takeover by the operator. At this point the design is frozen and a hold point is fixed.

Phase 4: In the **detail engineering** the required documents (e.g. drawings) for the production are prepared (2D/3D CAD). This affects both the hardware and software as well as the wetware components (e.g. bags and transfer sets). If necessary, in this phase the extractables/leachables studies are performed as part of the validation. These include but are not limited to compatibility tests, adsorption tests, bacteria ingress test, challenge test, product-specific integrity tests, bag integrity tests, particle-release tests, product & process safety testing and shipping validation. The “project quality plan” (PQP) ensures that all quality-relevant tests are described and their criteria are specified. These documents are reviewed and approved by the operator.

Phase 5: Now **all components of the production facility requested by the operator are produced**. For the wetware components a distinction is made regarding whether standard solutions or customer-specific solutions are involved. If the customer requires a special design, a prototype is produced first, which is examined by application specialists during the test phase and then approved for series production.

Phase 6: In the **test phase**, which is subdivided into the factory acceptance test (FAT) and the site acceptance test (SAT), the needs-based functionality of the production facility is tested and the results are documented. Between the FAT and the SAT the facility is transported to the place of use and commissioned. Based on the BOM, which has been finalised and approved by the operator, now a supply-chain concept can be prepared that regulates the provision and storage of the consumable materials. In this phase intensive training on the facilities also becomes possible. This training should enable operators to work with the single-use systems safely and professionally. Regulatory aspects are also considered. When all the tests have been performed successfully, the operator can enter the formal validation phase. Generally, a successful process validation is verified by three identical process runs. However, PAT approaches increasingly allow for verification by means of a so-called “design space”, which describes the bandwidth of the previously determined critical process parameters (CPPs/CQAs).

Phase 7: This phase describes the **monitoring of production by the suppliers**. In this phase, the provision of the single-use systems is an essential component of the production process. For this the supplier must present the operator with a reliable concept and ensure that all components are available *in time* and *in quality* and also over a longer period of several years. Technical support and preventative maintenance tasks round out the support.

A higher-ranking project management authority coordinates the complex tasks. This includes the coordination of the individual sub-projects, the exchange of relevant information between the various project participants, the prioritisation of available resources, the handling of operator requirements and the processing of a requirement analysis for the consumable material.

8 New competencies: education and training of employees as a basis for the efficient operation of the FoF

The increasing implementation of single-use systems in biopharmaceutical production plants has resulted in a series of changes relating to process technology (including the associated quality assurance), the planning and implementation of production plants, supply-chain management and product authorisation. As a result, continuous processes both in upstreaming and in downstreaming are becoming increasingly important (4,5). Perfusion technology has evolved and is being used more and more often for inoculum production (high-cell density and large-volume cell banks) (28–30) and continuous product expression (31). This makes it possible to work with production bioreactors that are 5 to 10 times smaller than in the previously dominant feeding mode (fed batch). Work is being done on equipment and procedures for continuous clarification and chromatography. This is laying the foundations for complete, continuous production processes for biopharmaceutical products.

On the other hand, the greater problem of extractables and leachables that arises if single-use systems are utilised requires the early involvement of the manufacturers of the single-use systems and their suppliers. Toxicologists must be included to determine the limit values for the extractables and leachables for the active substance or the drug. The manufacturer must create a corresponding risk profile for every process step, with the process steps that are closest to the end product and the patient being the most critical (32–34). Furthermore, the constant replacement of parts of the single-use systems that come into contact with cells, process media and product requires corresponding storage capacity, and the lower degree of automation of the single-use systems requires more manual work and therefore higher training expenses for the user. Ultimately, advantages (faster, safer and more flexible, more environmentally friendly, smaller) only arise from utilising single-use systems if they are chosen and used correctly.

Consequently, training programs are needed for biotechnology students, but also special continuing education programmes for the operators in the biopharmaceutical industry, the manufacturers of single-use systems, the production plant planners and builders as well as the experts on the drug approval side. Here practical aspects for dealing with single-use systems under GMP conditions should definitely be integrated. The current offering from universities and technical colleges as well as for-profit conference organisations, international and national non-profit organisations does not cover the entire range of topics that is required. For the implementation and the efficient operation of the FoF, the 11 main topics listed below are relevant, which can be summarised in tailor-made courses.

Topic 1: Characteristics of plastics and their manufacture

- » Main materials and characteristics
- » Plastic manufacturing processes
- » Sterilisation procedures
- » Quality control

Topic 2: Single-use systems for upstreaming, downstreaming and fill & finish

- » Characteristics
- » Reconstitution
- » Selection and design
- » Best practice
- » Plastic vs. glass and steel

Topic 3: Correct handling of single-use systems

- » Coupling/decoupling
- » Inserting a bag
- » Implementation of sensors, calibration and recalibration
- » Leak test

Topic 4: Training simulators

- » Conveying the fundamentals of bioprocessing
- » Improving training quality by action-oriented learning – conveying additional content and competencies
- » Minimising training costs by
 - saving on operating costs for experiments
 - minimising the preparation expense
- » Realistic illustration of all important procedural and biological effects
- » Simulation of the process in real time (and accelerated)
- » Visualisation of the complex system behaviour
- » Intuitive operation
- » Functionalities according to a process control system, e.g. alarms, operating functions, etc.

Topic 5: Planning and realisation of single-use production plants

- » Facility layouts
- » Fundamentals/requirements of flexible production
- » Dynamic operation and building planning
- » Personnel and material flow planning
- » Modelling and training simulators
- » Life cycle assessment

8 NEW COMPETENCIES: EDUCATION AND TRAINING OF EMPLOYEES AS A BASIS FOR THE EFFICIENT OPERATION OF THE FOF

Topic 6: Product approval when utilising single-use systems

- » Risk analysis (e.g. failure mode and effects analysis)
- » Leachables/extractables
- » Qualification and validation
- » PAT

Topic 7: New work techniques in the production of biotherapeutics and cell therapies

- » Perfusion and continuous process management
- » Vaccine production
- » Processing of cells for cell therapies
- » Microbial processes

Topic 8: Occupational safety/the environment/biosafety

- » Fundamentals
- » Principles
- » Examples
- » Description

Topic 9: Transport (hazardous material aspect and recyclable material)

- » Fundamentals
- » Principles
- » Examples
- » Description

Topic 10: Handling of single-use equipment

- » Delivery
- » Storage
- » Unpacking/bringing in
- » Insertion/installation
- » Assembly/integrity test
- » Use of corresponding instructions from supplier
- » Connection of reusable components
- » Dismantling
- » Disposal/decontamination
- » Description

Topic 11: Automation

- » Fundamentals: from process automation to logistics
- » Principles
- » Examples
- » Description

ABBREVIATIONS

API	Active Pharmaceutical Ingredient	IPC	In-Process Control
ASTM	American Society of Testing and Materials	ISPE	International Society for Pharmaceutical Engineering
ATF	Alternating Tangential Flow	MAL	Material Air Lock
BDS	Bulk Drug Substance	MHB	Media Hold Bag
BHB	Buffer Hold Bag	MPB	Media Preparation Bag
BOMs	Bill of Materials	mAb	Monoclonal antibody
BPB	Buffer Preparation Bag	mAbs	Monoclonal antibodies
BPOQ	BioPhorum Operations Group	QbD	Quality by Design
BPSA	Bio-Process Systems Alliance	OQ	Operation Qualification
BRX	Bioreactor	QTPP	Quality Target Product Profile
CHR	Chromatography	PAL	Personnel Air Lock
CIP	Cleaning In Place	PAT	Process Analytical Technology
CPPs	Critical Process Parameters	PCC	Periodic Counter Current Technology
CQAs	Critical Quality Attributes	PDA	Parenteral Drug Association
DCS	Digital Combat Simulator	PEP	Project Execution Plan
DECHEMA	Gesellschaft für Chemische Technik und Biotechnologie (Society for Chemical Engineering and Biotechnology)	POB	Pool Bag
DP	Drug Product	POT	Pool Tank
DQ	Design Qualification	PQ	Performance Qualification
DS	Drug Substance	PQP	Project Quality Plan
ELSIE	Extractables and Leachables Safety Information Exchange	QS	Quality Safety
FAT	Factory Acceptance Test	RTRT	Real Time Release Testing
FDA	Food and Drug Administration	SAT	Site Acceptance Test
FIL	Filtration	SIP	Sterilization In Place
FoF	Facility of the Future	URS	User Requirements Specification
GEP	Good Engineering Practice	XD	Xcellerated
GMP	Good Manufacturing Practice		
HAB	Harvest Bag		
HVAC	Heating Ventilation and Air Conditioning		
IQ	Installation Qualification		

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