Review

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Single-use disposable technologies for biopharmaceutical manufacturing

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The manufacture of protein biopharmaceuticals is conducted under current good manufacturing practice (cGMP) and involves multiple unit operations for upstream production and downstream purification. Until recently, production facilities relied on the use of relatively inflexible, hard-piped equipment including large stainless steel bioreactors and tanks to hold product intermediates and buffers. However, there is an increasing trend towards the adoption of single-use technologies across the manufacturing process. Technical advances have now made an end-to-end single-use manufacturing facility possible, but several aspects of single-use technology require further improvement and are continually evolving. This article provides a perspective on the current state-of-the-art in single-use technologies and highlights trends that will improve performance and increase the market penetration of disposable manufacturing in the future.

The advent of single-use technologies

Many different factors have combined to encourage the current surge of interest in single-use or disposable technologies for biopharmaceutical manufacturing (Table 1). The production of all drugs is tightly controlled by cGMP guidelines to reduce or prevent bioburden, that is, contamination of the product stream with bacteria, viruses, and other potentially harmful adventitious agents [1]. A key aspect of cGMP manufacturing plants is the cleaning, between runs, of vessels and other equipment that comes into contact with the product [2]. This is a laborious and time-consuming requirement that means the manufacturing process must be taken off line, and the cleaning procedure must be extensively validated and documented [3] to demonstrate the elimination of bioburden and residual product, the latter to prevent cross-contamination in multiproduct manufacturing plants. Single-use technologies were first introduced as a means to avoid cleaning and validation requirements while simultaneously reducing the risk of contamination, particularly in cell culture processes. Single-use technologies also reduce the need for utilities such as the steam used to sterilize product contact equipment by steaming-in-place (SIP) before each use. The environmental benefits of the reduced energy demand can be said to outweigh the increase in solid waste generated by the disposal of single-use devices [4].

The economic benefits of single-use equipment are not restricted to the faster campaign turnaround times (for the same and different products) once a production facility is operating. Indeed, the cost benefits can be experienced at the beginning of clinical development for a product because single-use equipment reduces the time required to get a facility up and running, and the apparatus tends to be less expensive than stainless steel counterparts. It has been estimated that designing a new production facility based on single-use systems can reduce capital costs by up to 40% compared to a conventional hard-piped facility [5]. Even where major components such as fermenters and buffer tanks are stainless steel, the introduction of single-use buffer tanks can enhance operational flexibility and stretch production capability by removing bottlenecks caused by vessel capacity and changeover times. The five most common reasons cited for adopting disposable technologies are the elimination of cleaning requirements, the reduced risk of cross-contamination, the faster turnaround between campaigns, the increased convenience and flexibility of disposable technologies, and the reduced time for a new facility to become operational [6].

The economic benefits of disposable technologies are becoming more important because biopharmaceutical manufacturers are facing increasing pressure to reduce product costs while maintaining product quality. The costs of production received little attention in the early years of the industry because the profit margins on critical, life-saving biopharmaceuticals often exceeded 98%. But as the pace of drug discovery and commercialization slows and fewer blockbuster drugs reach the market [7], competition in the sector is getting hotter, particularly in key therapeutic areas. For example, biopharmaceuticals have significantly improved the standard of care in the rheumatoid arthritis market and now there are no fewer than seven such products indicated for this disease [7,8]. Another key driver of costs is the rising market for generics or biosimilars, which are supported by most regulatory health authorities because they reduce the costs placed on national health infrastructures [9]. Biosimilars are intended to be priced lower than the innovator product, thus creating a demand for more cost-effective production [10]. The growing share of emerging biopharmaceutical markets around the world has also squeezed manufacturing costs because of the demand to colocate manufacturing facilities with these markets and the trend towards legislation that requires locally-sourced analytical release testing (quality

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Table 1. Factors driving the growth of single-use systems in biopharmaceutical manufacturing

Market factors	Advantages	Current limitations
Emphasis on production costs	Reduced capital costs for plant construction and commissioning	Leachables and extractables
Flexible, multiproduct manufacturing facilities	Reduced risk for product cross-contamination in a multiproduct facility	Prior investment in fixed equipment
Biosimilars	Rapid changeover	Scales limited by current 2000 liter cell culture bioreactor capacity
Multiple, smaller manufacturing plants colocated with markets	Lower utility costs due to reduced need for SIP	Limited number of vendors
Increasing number of low-volume biopharmaceutical products	Reduced need for cleaning validation	High cost of disposables
		Lack of universal standards for vendors
		Solid waste disposal

control testing). This favors pharmaceutical sellers that have a significant manufacturing and economic presence in the local market, but these markets are typically smaller than the traditional US and EU markets thus creating a demand for smaller-scale commercial launch facilities that have a lower capital cost base if they use disposable equipment. A final consideration is the progressive increase in product titers, with many proteins now produced in cell culture with a titer exceeding 5 g/l. This means that smaller bioreactors are sufficient for production scale. Whereas many commercial production facilities were installed with multiple 10 000–25 000 liter bioreactors, facilities may in the future be able to produce the same amounts of product with single-use 2000–5000 liter bioreactors [11].

History of single-use technologies

Disposable tissue culture flasks and roller bottles have been used in the laboratory for many years, and some early biopharmaceutical products were manufactured using roller bottle cell cultures. With these exceptions, single-use technologies in large-scale biopharmaceutical production facilities have traditionally been confined to the early inoculum stages of the cell expansion process, which involved the use of shake flasks or T-flasks. The first single-use systems for large-scale production came about with the introduction of the WAVE bioreactor in 1996 [12]. Disposables are now widely used for inoculum expansion processes, but they have also been employed as the production bioreactor when smaller cell culture volumes are sufficient [13]. The first single-use stirred-tank bioreactor was launched by Hyclone in 2004 and had a working volume of 250 l. This system used a self-contained plastic bag that was placed in a stainless steel shell. Larger single-use stirred-tank bioreactor systems have been developed more recently (1000 liters in 2006, 2000 liters in 2009) as well as various fermenters where mixing is achieved by rocking or orbital shaking [14–17]. Box 1 provides further details about cell cultivation in single-use bioreactor systems including some of the challenges faced when making the transition from conventional systems.

Cell cultures are usually harvested by centrifugation and/or depth filtration [18], and the convenience of disposable depth filters means they are the most widely used

Box 1. Cell culture in single-use bioreactors

Cell culture was one of the first areas of bioprocessing to benefit from single-use systems, starting with the WAVE bioreactor which eliminated the need for cleaning or sterilization and thus reduced contamination rates significantly. A variety of other disposable bioreactors have been developed based on the 'cell culture in a bag' concept.

WAVE bioreactors

WAVE bioreactors feature a bag partially filled with cell culture medium and mounted on a tray that can be rocked to provide agitation and gas transfer. Oxygen enters the culture from the headspace above the culture medium. Parameters such as the rocking angle, rocking rate, and bag fill ratio can also influence the mass transfer rates in WAVE systems, which are now available at volumes of up to 500 liters and have become established as part of the seed expansion steps for most cell culture-based production operations. They are compatible with a wide variety of mammalian, insect, and plant cell lines [13].

Orbitally shaken bioreactors

Orbitally shaken single-use bioreactors [40] rely on the rotating motion of the culture vessel around a central axial shaft to provide mixing and oxygen transfer from the head space into the culture. Orbitally shaken bioreactors are now available up to a 200 liter working volume developed by Kuhner AG in collaboration with Excellgene and comarketed by Sartorius-Stedim. This is the only bioreactor system in which oxygen supply occurs by air alone and has been shown to be operable without any oxygen probes owing to the high gas transfer rates [41].

Pneumatically mixed bioreactors

Another addition to single-use cell culture systems has been the combination of single-use with airlift bioreactors in which mixing and oxygen are supplied via air bubbles without a mechanical agitator [42]. Such systems are available from Cellexus (3–50 liter volumes) and from PBS Biotech (3–500 liter working volumes).

Stirred tank bioreactors

The majority of cell culture operations for large-scale biopharmaceutical production involve the use of stirred-tank bioreactors. The key development in this area was the concept of culturing cells in an integral plastic bag that could be mounted within a cylindrical frame to support the bag. Hyclone was the first market entrant with its Single Use Bioreactor (SUB) system, which used a top driven impeller for mixing and agitation. Xcellerex followed with the XDR disposable stirred tank bioreactors featuring magnetically-coupled bottom-driven agitators. A wide variety of small-volume and large-volume single-use stirred-tank bioreactors are now available (see Table 2 in main text). Early challenges with efficient mixing and aeration have been addressed and the disposable systems now appear to be equivalent to stainless steel stirred-tank systems for CHO cell cultures [20,43].

disposable devices in the industry, along with tubing and connectors (used in 54% of all commercial processes [6]). Centrifugation has proved to be more difficult to convert into a single-use setup because of the complexity of the devices compared to filters. However, two disposable centrifuges are now commercially available. KSep Systems has a technology based on revolving chambers that are fitted with a single-use bag to enable closed system processing, whereas Carr Centrifuges has launched the Unifuge system that is essentially a tubular bowl centrifuge lined with a bag.

Disposable systems have also been developed to handle downstream processing operations. The first single-use systems were in-process microfilters for bioburden control between process steps [19]. These filters are typically housed in a plastic capsule that can be discarded after the process intermediate is filtered. Membrane chromatography was first introduced as a process step in the late 1990s and constituted the first single-use technology that was intended to replace a conventional option (preparative chromatography on columns). Although membrane chromatography has the lowest take-up of all disposable devices, currently featuring in 19% of commercial processes [6], it is also the most recent addition to the family of disposable concepts and has the strongest market growth, with a compound annual growth rate of nearly 27% between 2006 and 2012 [6]. Column chromatography has also entered the single-use market, with the development of mixing and storage tanks that feature a plastic liner inside a stainless steel frame, and the GE Healthcare Akta Ready chromatography skid with a fully-disposable fluid flow path so that the buffers and product do not come in contact with any fixed parts that require subsequent cleaning. Completely disposable chromatography columns have also been introduced and several companies offer pre-packed, pre-validated disposable columns in a range of sizes containing any resin chosen by the customer. Other disposable unit operations such as ultrafiltration/diafiltration (UF/DF) and drug substance storage (liquid or frozen) have also been introduced into the marketplace. We list some examples of current single-use equipment and their vendors in Table 2. The current state-of-the-art has enabled the setup of several manufacturing production trains that feature end-to-end disposable technologies [20–22].

An integrated single-use drug substance production process

Figure 1 shows a schematic representation of a typical biopharmaceutical manufacturing process with single-use technologies for all unit operations [23]. This highlights the diverse range of unit operations that go into producing a biopharmaceutical product. The production process typically begins by thawing a single vial of cells and increasing cell counts through the inoculum expansion process. The early inoculum process typically uses shake flasks or spinner flasks and then progressively larger volumes in WAVE or small stirred-tank bioreactors. A combination of WAVE and seed bioreactors is typically used in the seed train for mammalian cell culture processes. The seed bioreactor is used to inoculate the production bioreactor during which the cells shift from the growth phase to the product expression phase, resulting in the secretion of the product into the culture medium. Cell harvest and clarification removes whole cells and cell debris from the culture broth to provide clarified feed that can be loaded onto chromatography columns for downstream purification. In large-scale processes, harvest and clarification typically involve centrifugation followed by depth filtration and membrane filtration to remove cells and cell debris. For smaller bioreactors, depth filtration may be used as the primary harvest and clarification step without centrifugation.

After harvest and clarification, downstream purification aims to produce a pure protein suitable for clinical dosing into humans. This is generally achieved through a combination of column chromatography and/or membrane chromatography, buffer exchange using UF/DF, and viral filtration/inactivation steps. Several chromatography steps are often involved using orthogonal separation principles to achieve high resolution and peak separation, traditionally involving a mixture of capture chromatography (where the product binds to the resin allowing contaminants to be washed through) and flow-through chromatography, which is used for polishing, that is, the product flows through and contaminants are retained on the resin. Large, reusable steel chromatography columns have been the key enabling technology at the heart of most bioprocess separations because disposable solutions have not been available at a comparable scale and the cost of resins means that regeneration and reuse has been required to make processes economically viable. As discussed above, the trend more recently has been to use product-dedicated fixed columns and fully disposable columns where this proves cost-effective (Table 2). Whereas large columns remain the best solution for most bind-and-elute steps, disposable membrane cassettes are becoming more popular for flow-through chromatography steps. Membrane chromatography involves the use of synthetic porous membranes containing the same functional groups as packed resins, which is advantageous for polishing steps because there is much less mass transfer resistance and therefore more efficient hydrodynamic behavior, which means the membranes can be operated at higher flow rates with a lower overall buffer consumption and a much shorter processing cycle [24]. Disposable membranes are therefore becoming established as a platform for the removal of host cell DNA by anion exchange, which can be performed with a membrane bed height of 4 mm at flow rates of more than 600 cm/h [25,26]. The availability of disposables in a variety of sizes and functionalities also facilitates scaling up, particularly given that parameters such as frontal surface area, bed volume, flow rate, and static binding capacity scale in a linear fashion, whereas the normalized dynamic capacity remains constant at 10% or complete breakthrough.

Throughout the process, several ancillary unit operations are used for buffer and media batching in mixing vessels, the storage/hold of process intermediates between steps, and membrane filtration to augment bioburden control. The entire process must be connected to allow the transfer of process intermediates from one unit operation to the next. Appropriate sensors and detectors must also be integrated to ensure that the production process

Table 2. Single-use bioprocessing technologies: current scales and vendors[a]

Unit operation	Examples of single-use technology on the market
Bag cultures	20–300 liter Wave™ Bioreactors (GE Healthcare) <300 liter Biostat Cultibag (Sartorius Stedim) <500 liter BioWave (Sartorius Stedim) <25 liter Appliflex (Applicon) <160 liter Tsunami Bioreactor (Tsunami Bio)
Production bioreactors	Single Use Bioreactor (SUB) < 2000 liter (Hyclone/ThermoFisher Scientific) XDR Disposable Stirred Tank Reactor < 2000 liter (Xcellerex) Biostat Cultibag STR Plus < 200 liter (Sartorius Stedim Biotech)
Bench-top bioreactors (laboratory scale, but could also be used for seed train)	CelligenBLU Single Use Bioreactor (New Brunswick) < 14 liter CELLtainer Single Use Microbial Bioreactor (Lonza) < 15 liter Mobius Cellready (Applikon and Millipore) < 2.4 liter XDR-10 (Xcellerex) 4.5–10 liter
Centrifugation	kSep® 400 and 6000 (for 1–6000 liters) (kSep Systems) Unifuge (Carr Centritech) for up to 1000 liters
Depth filtration	POD (Millipore) Stax (Pall) Zeta Plus (Cuno) Sartoclear P (Sartorius-Stedim)
Chromatography columns	ReadyToProcess (GE) Opus (Repligen) GoPure (Life Technologies) Uno monolith (BioRad) CIM® monolithic columns (BIA Separations)
Membrane chromatography	Mustang (Pall) Sartobind (Sartorius) Chromasorb (Millipore)
Chromatography skids	Akta Ready (GE)
In-process microfiltration	ReadyToProcess HF (GE) KrosFlo (Spectrum)
UF/DF membranes	Pellicon (Millipore) Omega (Pall) (Sartorius)
UF/DF skids	Sciflex (Scilog) Mobius FlexReady (Millipore) Allegro (Pall) Cadence single pass (Pall)
Viral filtration	Planova 15N and 20N (Asahi) Viresolve Vpro (Millipore) Virosart CPV (Sartorius) DV20 (Pall)
Mixing (bag mixing with rotating stirrer)	6–2000 liter Levmixer™ (ATMI Life Sciences) 6–2000 liter Magnetic Mixer (ATMI Life Sciences) 100–1000 liter Mobius™ (Millipore) 100–1000 liter XDM Quad™ (Xcellerex) 50–1000 liter Flexel® 3D LevMix (Sartorius-Stedim Biotech) 50–2000 liter Single Use Mixer (Hyclone/ThermoFisher Scientific)
Mixing (bag mixing with rocking)	20–1000 liter Wave™ (GE Healthcare) 30–5000 liter HyNetics (HyNetics Corp) 5–2000 liter SALTUS (Meissner)
Connections/tubing	C-flex weldable tubing Bioquate DAC (Bioquate) Ready-mate DAC (GE) KleenPak (Pall) Quick-connect, MPC, Saniquik, AseptiQuik, sanitary TC (Colder)
Bulk drug substance cold storage	CX5-14 HDPE Labtainer (Hyclone) Bioeaze PE (SAFC) Flexel (Sartorius)
Bulk drug substance freeze-thaw	CelsiusPak (Sartorius) Platinum UltraPak (Lonza) PETG or polycarbonate bottles (Nalgene)

[a]Although every effort has been made to provide up-to-date examples of single-use products currently on the market, the authors cannot be held accountable for any omissions or errors.

remains within specified tolerances. Finally, the purified drug substance must be transferred to appropriate containers for storage and shipping. In a single-use facility, all of the main and ancillary unit operations, the connections between them, and the monitoring devices need to be developed with disposable product contact surfaces. This can become a challenge when developing an end-to-end single-use facility because although several vendors offer

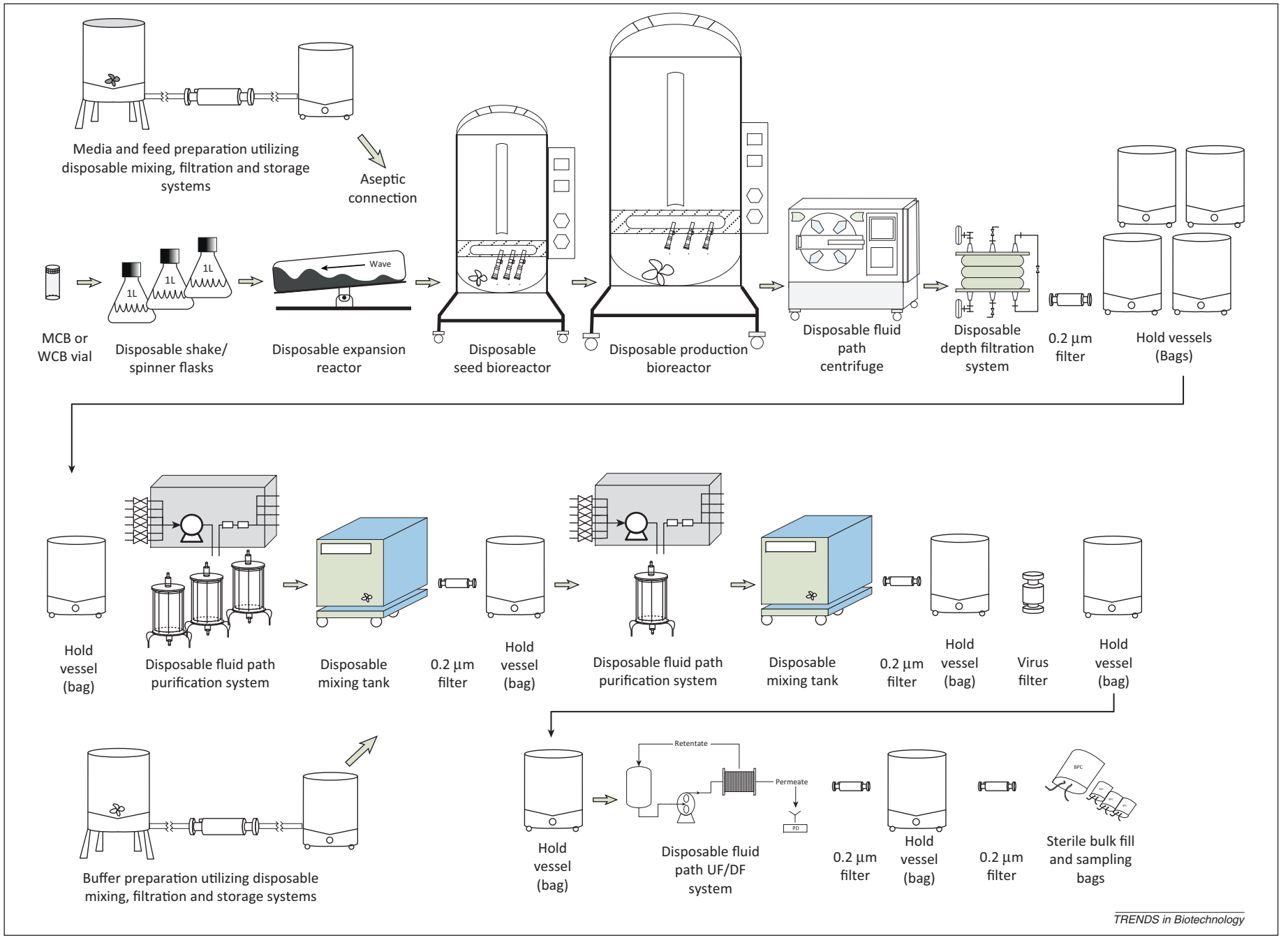

Figure 1. A biopharmaceutical drug substance production process. Reproduced, with permission, from [19].

off-the-shelf bags, fluid path designs, and configurations with reasonable lead times, the use of too many different platforms creates a requirement to build, sterilize, and stock a large number of different tubing and connector sets in order to bridge the gap between systems. To avoid this issue, several vendors now offer custom connector sets, although it is important to ensure the size of the connectors is appropriate to maintain the intended flow rate. Depending on requirements, a connection can be made open, for example with Luer Lok fittings (Value Plastics), sanitary tri-clamps, or quick-connects (Colder Products), or closed if an aseptic connection is required, for example, for bulk filling. In the latter case, it is appropriate to use Kleenpak sterile connectors (Pall), ReadyMate DAC (GE Healthcare), Opta SFT (Sartorius Stedim), Lynx ST (Millipore), or Pure-Fit SC connectors (Holland Applied Technologies). Tube welding can also be used to make sterile connections, and several tube welders are available commercially from companies such as GE Healthcare (Sterile Tube Fuser), Sartorius (BioWelder), and Terumo. The tubing can be selected from several different vendors, for example, C-Flex (Cole Parmer), PharmaPure (Saint Gobain), Advantaflex heat sealable tubing (AdvantaPure), and SaniPure 60 (Saint Gobain) heat sealable tubing (Table 2).

End-to-end drug substance manufacturing using single-use systems are now becoming more widely established. Indeed, the benefit of single-use technologies are fully realized when they are used throughout the production process. This concept is now being extended to mobile manufacturing facilities that can be set up and operated within a very short time period. Vendors are now increasingly cognizant of this market and are starting to offer integrated solutions for biopharmaceutical manufacturers, which makes it easier to source and combine various unit operations together.

Current challenges facing single-use technologies

Key challenges facing the developers and end-users of single-use bioprocessing technologies include their limited scale, the restricted diversity of options, the lack of standardization, and some remaining performance issues that can be addressed by further research and development [6].

Most disposable technologies have been developed for a maximum upstream production scale of 2000 liters cell culture. Table 2 provides examples of the single-use components available for different unit operations and the scales that are currently offered. It seems clear that the scales are limited compared to conventional technologies but it should be emphasized that these restrictions are not technological but are based on demand, thus larger systems will probably be introduced as the demand for them grows. The adoption of single-use technologies has been growing year on year since 2004 and disposables are predicted to reach a 20% share of the bioprocess technologies market within the next 3–5 years. Already, up to 90% of manufacturers and contract research organizations use disposable filters and tubing at some stage of the development pipeline, whereas 77% use disposable bioreactors and 58% use disposable membrane adsorbers [6].

The diversity of options is another current limitation of disposable technologies. This is less apparent for laboratory equipment but increasingly prevalent as we move towards process scale manufacturing and it correlates with the number of vendors offering particular categories of equipment. For example, many different vendors offer disposable filters and tubing, a handful offer disposable bioreactors, and two supply disposable centrifuges. Competition between vendors often drives innovation so the diversity of disposable devices is bound to increase as more vendors enter the market. This may be stimulated by the interest in single-use technology now shown by larger suppliers, a key example being the recent acquisition of Xcellerex Systems by GE Healthcare.

Another challenge that affects all disruptive technologies is the absence of standardization and regulation of the quality of materials used. One of the key reasons cited by manufacturers for not taking up disposable technologies is the lack of a validation process to determine the nature, quantity and risk associated with leachables and extractables from the disposable plastics, which could potentially contaminate product intermediates.

Cell culture is the most sensitive aspect of a biomanufacturing process in terms of operability in a single-use system. The plastic bags used for cell culture have the potential to either bind media components [27,28] or to contribute leachables that could adversely impact cell growth. The greatest challenge appears to occur when cultivating cholesterol-dependent NS0 cell lines, because the lipid components of the media are depleted by binding to the plastic bioreactor surfaces. However, this issue has been addressed by the development of a novel cholesterol supplementation strategy for these cells [29]. In our experience, most CHO cell lines do not have any issues in being operated in single-use bioreactor systems.

The issue of organic compounds leaching from plastic surfaces is often cited as a concern for the use of single-use technologies because the leachables could interfere with cell growth and activity. Leachables are chemicals that migrate from the product contact surface into the process fluid (e.g., buffer, water, or process intermediate) under normal exposure conditions, whereas extractables are chemicals that can be removed from the product contact surfaces using appropriate solvents under extreme exposure conditions to facilitate their identification and quantitation. The extractable profiles released from bioreactor bags under extreme temperature and solvent conditions are typically characterized by vendors. Leachables are typically a subset of the extractables and are expected to be released at very low levels under normal conditions. For example, certain bags used to formulate and weigh out media powders for feeds could impact cell culture due to the presence of anti-static agents. The evaluation of cell culture in single-use bioreactors is a prudent step when setting up a new cell culture platform for the first time. A key area for future advancement is to arrive at a common standard set of conditions or analytical techniques to quantify extractables across different vendors and product types. The Bioprocess Systems Alliance (BPSA) is currently working towards a set of standards but more work needs to be done to meet the requirements of end-users [30].

The advent of fully integrated bioprocessing using single-use systems creates the need to source multiple parts

and systems from a variety of vendors. In addition to integrating systems from different vendors into a single process, supply of parts and disposables has to be carefully mapped and synchronized. From a supply chain perspective, it is often suitable to treat these as long lead items and conduct facility fit exercises prior to process transfer to plan for these items.

Future directions for single-use technologies

The coming decade is likely to see the increased acceptance of single-use technologies as a standard component of the biopharmaceutical manufacturing process. This has already occurred with disposable tubing and filters, and to a certain extent buffer and media storage bags, where market growth has slowed to less than 10%. Other types of disposable equipment are still becoming established and benefitting from innovative developments to create more diverse end-user choices. Mixing systems, bioreactors, and membrane adsorbers are in this category and the growth rate in each sector is 20–30% [6]. There is less activity in other equipment categories and market options are limited, for example, centrifuges and UF/DF skids. Therefore, although single-use technologies are finding significant mainstream applications in bioprocess operations with many new production trains already starting to employ these systems, further research is needed to increase the diversity available for the unit operations, which have yet to fully embrace the disposables revolution.

Although scalability is one of the current challenges for vendors of disposable technologies, future commercial production will likely be carried out at the 5000 liter scale because of the increasing titers of cell cultures. Therefore, we anticipate that the next frontier for single-use bioreactors will be an expansion to the 5000 liter production scale, making single-use technologies a viable replacement for stainless steel in a wider segment of the production space. This increase in scale will drive an increase in throughput and/or scale for other single-use technologies, particularly centrifugation, depth filtration, UF/DF, and the flow rates achievable using disposable skids.

In the future it will also be necessary to develop sensor and monitoring technologies that are compatible with single-use facilities, in order to facilitate the integration of process analytical technologies (PAT). The PAT initiative was introduced by the US FDA to improve the online monitoring of manufacturing processes and facilitate control and (if necessary) correction during a campaign rather than testing the product against specifications after manufacture [31,32]. PAT was aligned with the quality by design (QbD) initiative, which aimed to prevent production errors as far as possible by building quality control into process development [33,34]. Examples of recent PAT applications include the use of Raman spectroscopy to examine the lot-to-lot variability of cell culture media [35], the use of chromatographic profiles to predict chromatography bed stability and decay in binding capacity [36], and the use of liquid chromatography/mass spectroscopy (LC/MS) to evaluate glycan heterogeneity in monoclonal antibodies [37]. These analytical technologies are not exclusive to the single-use market, but the trend towards single-use production systems highlights the need to align the development of sensing technologies with innovations in processing systems. Therefore, single-use sensor technologies are likely to be another key area that sees significant development in the next decade. There is an urgent need for non-invasive sensor technologies that can monitor the health and performance of cell cultures [38]. These can include novel chemicals that are added to the cultures to indicate changes in cell metabolism as well as wave-based technologies that can monitor processes by taking external measurements through a site window. The development of these techniques is certainly the next step towards achieving the goal of PAT for cell culture technologies.

Another key area for the expansion of single-use technologies is microbial fermentation. Traditionally the challenge here has been to provide adequate mass transfer required for fermentation and also to cope with the heat generated by microbial cultures [39]. Current single-use microbial fermenters are therefore limited to the 50 liter scale, and the absence of higher-volume fermenters for the production of biopharmaceuticals on the clinical scale is an area of critical unmet need.

Concluding remarks

Single-use technologies began as an innovative alternative to fixed equipment for the production of biopharmaceutical proteins, but they have since become established as a strong competitive technology for many parts of the production and processing chain, outcompeting conventional hard-piped stainless steel components in terms of economy, convenience, and quality. The increasing pressure on capital and operating costs, the risk of product cross-contamination, and the cost of cleaning validation all conspire to push manufacturers away from fixed equipment and to embrace the significant advantages of disposable processes for an expanding network of cGMP manufacturing facilities. The growth of single-use manufacturing technologies are anticipated to reduce biopharmaceutical manufacturing costs thus aiding the launch of biosimilars, facilitating clinical entry for a wider range of innovative products and an expansion of biomanufacturing activities closer to markets for products manufactured in these facilities. For these reasons, we feel that these technologies have the potential to significantly alter the biopharmaceutical landscape in the years to come.

Several recent innovations have facilitated the implementation of integrated manufacturing facilities based entirely on single-use technologies. Nevertheless, further innovation is required to increase the number of suppliers, the diversity of platforms, the capacity of disposable bioreactors, standardization of vendor support packages, and the integration of biosensor technologies for non-invasive process control. We anticipate that all these areas will expand significantly in the years to come, bringing disposable technologies to the forefront of biopharmaceutical manufacturing in both clinical and commercial manufacturing settings.

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