SINGLE-USE TECHNOLOGY IN BIOPHARMACEUTICAL MANUFACTURE

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EDITED BY
REGINE EIBL | DIETER EIBL

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Single-Use Technology in Biopharmaceutical Manufacture

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Second Edition

Edited by

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Preface

Single-use devices have become a major part of the biopharmaceutical production process. They now make up 85% of the equipment in preclinical bioprocessing and are increasingly being employed in the commercial manufacture of biopharmaceuticals. It is in upstream processing, which can be accomplished entirely with single-use technology, where they are used with greatest diversity, for example, in the manufacturing of modern antibodies and vaccines. Single-use solutions are also, however, available for downstream processing and for Fill & Finish which are accepted by users. Today, the first fully single-use production facilities have already become a reality.

It seems that users have more confidence in single-use technology, which can be explained by the further development and the improved design of such devices. The new generations of single-use devices are more robust and easier to handle than their predecessors. Possible problems, such as leakage and integrity, have already been addressed by the suppliers during the manufacturing process. Moreover, progress has been made in film technologies, bioreactor design, sensor techniques, and automation.

The second edition of the book *Single-Use Technology in Biopharmaceutical Manufacture* consists of an introduction section for beginners and a case-study collection for advanced-level readers. It summarizes the latest developments in single-use technologies. In addition to a presentation of single-use systems as applied to different unit operations and to platform technologies, their selection, implementation, and level of trouble-free usage are discussed. This includes approaches to intensify bioprocesses and to realize continuous processes but also to aspects of quality assurance and standardization, the influence of single-use technology on the environment, and the importance of risk analysis.

We would like to thank all authors for their valuable contributions to the new edition of this book. We would also like to extend our special thanks to the management of the Department for Life Sciences and Facility Management of the Zurich University of Applied Sciences for their support in realizing this book. We hope that the new edition of *Single-Use Technology in Biopharmaceutical Manufacture* will be helpful for bachelor and master students of biotechnology and related fields, for experienced practitioners who are developing as well as producing biopharmaceuticals and designing production facilities, and, finally, for those who intend to begin using disposables.

Regine and Dieter Eibl

Part I

Basics

1

Single-Use Equipment in Biopharmaceutical Manufacture

A Brief Introduction

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1.1 Background

The term "biopharmaceutical" was first used in the early 1980s [1] when recombinant, commercially manufactured insulin, a therapeutic protein for diabetes patients, was introduced. In the United States and Europe, the most frequently used definition is that of a pharmaceutical manufactured by biotechnological methods with organisms, or their functional components, which have a biological origin. Following this definition, all recombinant proteins, monoclonal antibodies (mAbs), vaccines, blood/plasma-derived products, nonrecombinant culture-derived proteins, and cultured cells, in addition to tissues from human or animal origin and nucleic acids, are considered to be biopharmaceuticals [2–4]. The majority of the above are classified as biologicals (or biologics) by regulatory agencies [5]. Traditional pharmaceutical products, such as chemical compounds extracted from plants, secondary metabolites from microbial and plant cell cultures, and synthetic peptides, which may not comply with the above definition, are more often regarded as non-biopharmaceuticals. Irrespective of differences in definition, recombinant protein pharmaceuticals constitute an important category of biopharmaceuticals.

The most significant protein pharmaceuticals available include hormones such as erythropoietin, enzymes such as the human plasminogen activator, vaccines such as Flucelvax, and mAbs such as bevacizumab. It is worth mentioning that the top 10 best-selling drugs are dominated by therapeutic mAbs today [5].

In most cases, protein pharmaceuticals are produced with mammalian cell lines. During the last few years, Chinese hamster ovary cell lines have increasingly displaced earlier mammalian cell production systems such as hybridomas or embryonic feline lung fibroblast cell lines [6, 7]. Further production organisms of choice for protein pharmaceuticals are microbial cells [8] (see also Chapter 21), plant cells [9] (see also Chapter 28), and insect cells cultivated in conjunction with the baculovirus expression vector system [10].

The worldwide demand for protein pharmaceuticals (and, in particular, protein therapeutics) has resulted in increased efforts to expand the process efficiency over the past 10 years. It is undoubtedly the case that the huge growth in knowledge in molecular and cell biology has led to high-productivity cell lines and improved culture media. These cell lines provide product titers exceeding 3 g/l in fed batch mode and contribute to shrinking bioreactor size, which is associated with cost savings [11]. Further cost savings can be achieved by replacing stainless steel with single-use equipment in the production process [12, 13].

The present chapter introduces the reader to the area of single-use technology. In addition to terminology, advantages and disadvantages of existing single-use devices will be described. Based on a schematic of a typical production process for a protein therapeutic, an overview of currently available single-use devices and a categorization approach will be presented. Moreover, the main criteria for implementing single-use systems in biopharmaceutical production processes are summarized, and current concepts concerning single-use production facilities are briefly explained.

1.2 Terminology and Features

As the term "single-use" (or "disposable") implies, such systems are only ever used once. Disposables currently in use originated in the fields of medical care (e.g. rubber gloves, sterile swabs, and the technology for intravenous applications) and infant care (e.g. paper towels and disposable diapers). With the exception of special

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protective clothing and consumables (e.g. swabs and paper towels), single-use products are typically fabricated from plastics approved by the Food and Drug Administration (see also Chapter 8), such as polyethylene, polystyrene, polytetrafluoroethylene, polypropylene, or ethylene vinyl acetate. These materials are typically supplemented with additives to aid performance and/or prolong usable life [14, 15], thereby ensuring their suitability in biopharmaceutical manufacturing applications. In all cases, the product contact surfaces are free of animal-derived components.

Disposables can be rigid (molded systems) or flexible (bags made from multilayer films) and are often supplied presterilized, having been gamma irradiated at dose levels between 25 and 50 kGy [16, 17], although some are autoclaved or sterilized with gas. This eliminates the need for subsequent sterilization of the equipment, such as the steam sterilization normally required for stainless-steel components. Disposables can, therefore, quickly be brought into operation. On completion of the process operations, the disposables used are decontaminated and discarded. Thus, time-consuming and expensive cleaning procedures which may require the use of corrosive chemicals (which could potentially pose a health hazard to the operator) and water-for-injection, often considered as a bottleneck in traditional biopharmaceutical facilities, are no longer required.

Disposable technology is often regarded as greener, due to the reduced requirements for cleaning and sterilization (see also Chapter 13). Furthermore, equipment turnaround time is reduced, and process and product changes can be more easily accommodated (a particular advantage in the manufacture of multiple products) when neither cleaning nor sterilization is required [17]. Similarly, the potential for product cross contamination and microbial contamination is reduced, and the requirements for validation and in-process documentation are minimized [15, 18, 19]. Further benefits of disposables include savings in time (e.g. development time, manufacturing time, and time to market), cost reductions (e.g. capital investment and cost of goods sold), and a reduction of the facility's footprint. It can be concluded that disposables may offer distinct advantages compared to their reusable counterparts when selected and used correctly. To summarize, they can be smaller, safer, greener, faster, and more flexible, while offering savings both in terms of capital outlay and operating costs (see Table 1.1).

Yet, there are still limitations to the use of disposables due to the chemical, biological, and physical properties of the plastic material. Besides leakage (see also Chapter 2), the primary risk associated with the use of disposables is the potential migration of undesired components from the plastic material (see also Chapters 8, 11, 17, and 18). Main undesired contaminants may either be leachables (which may migrate under process conditions over time) or extractables (which may migrate when exposed to aggressive process conditions such as high temperatures) [20, 21]. Another topic that has been raised by the increasing implementation of single-use devices for final Fill & Finish is the detection of particulate contamination over the past years (see also Chapter 18) [22, 23]. Additional issues which limit the use of disposables are restricted scalability (due to the mechanical strength of the material), the limited availability of single-use sensors (see also Chapter 6), and the lack of advanced automation techniques (see also Chapter 7).

So far, the replacement of disposable components constitutes an increase in operating costs and contributes to the increased cost of solid waste disposal and consumables. Another weakness of single-use systems is the dependence on suppliers (see also Section 1.4) resulting from lack of standardization (see also Chapter 13). Furthermore, it is worth noting that extra training of staff may be necessary as the scale of a manufacturing facility incorporating disposables increases. A challenge that should also not be underestimated is the packaging of single-use systems which covers the system integrity at the supplier level as well as in manufacturing and the maintenance of sterility. Thus, a thorough investigation

Table 1.1 Summary of advantages and limitations of single-use equipment.

Pros	Cons
Safer: High bio- and process safety • Sterilized • Preassembled • Decreased risk of microbial contamination and cross contamination • Facilitates qualification and validation *Greener* • Reduced requirements for cleaning and sterilization *Faster and more flexible* • Easier process and product change *Cheaper: Saving of time and cost* • Reduction of cultivation, cleaning, sterilization, qualification, and maintenance requirements • Lower capital investment, reduced infrastructure and maintenance costs *Smaller* • Reduced facility footprint	*Material properties* • Breakage and leakage • Leachables and extractables, particulates *Scalability* • Limited by the properties and fabrication of the polymer materials *Running costs and wastes* • Increased operating costs (costs of solid waste disposal and consumables) • Ongoing replacement of the disposables *Automation level, sensors* • No high-level automation solutions • Restricted availability of disposable sensors *Lack of standardization* • Supplier dependence *Training of staff* • Increasing requirement with rising culture volume

is recommended to determine whether the benefits of disposable systems are sufficient to overcome their disadvantages in any particular manufacturing scenario.

1.3 Single-Use Systems in Production Processes for Therapeutic Proteins such as mAbs: Product Overview and Classification

As illustrated in Figure 1.1, a typical process for the manufacture of a drug product (DP) such as therapeutic proteins (mAbs) includes four main processing stages: (i) upstream processing, (ii) downstream processing, (iii) final formulation and filling, and (iv) labeling and packaging. In the upstream processing stage, culture media and buffers are prepared (mixed, sterilized by 0.1 and 0.2 µm filters, stored, and transported), seed and inoculum train are produced, and a so-called active pharmaceutical ingredient (API) is expressed in the production bioreactor (see Figure 1.1). The API which is, with only a few exceptions such as membrane proteins, normally secreted into the culture broth has to be separated from cells and clarified after harvesting. The subsequent downstream procedures [24–30] (see also Chapters 9, 10, 23, and 24), which produce a drug substance (DS), ensure the reduction of product impurities (e.g. protein A, host cell proteins, desoxyribonucleic acid, and aggregates) to an acceptably low level and include virus clearing (inactivation and removal by filtration). Consequently, the API must be further concentrated, separated, and purified, requiring chromatography processes (affinity chromatography, anion-exchange chromatography, cation-exchange chromatography, and hydrophobic interaction chromatography) and crossflow filtration (ultra and diafiltrations). Liquid storage and transportation, and buffer preparation also form part of the downstream processing stage. The liquid DS solution is formulated through the addition of stabilizers prior to being sterilized by filtration and/or aseptically poured into sterile containers. The DS may also be stored or transported when it is deep frozen prior to the Fill & Finish operations. The DS is then labeled and packaged to become the commercially available DP.

Nowadays, the developer and manufacturer of a therapeutic protein can choose among a multitude of single-use devices from different suppliers for all stages of the production process. Figure 1.2 provides an overview of the primary disposables currently utilizable in therapeutic protein manufacturing.

Single-use devices can be classified into three groups: expendable laboratory items, simple peripheral elements

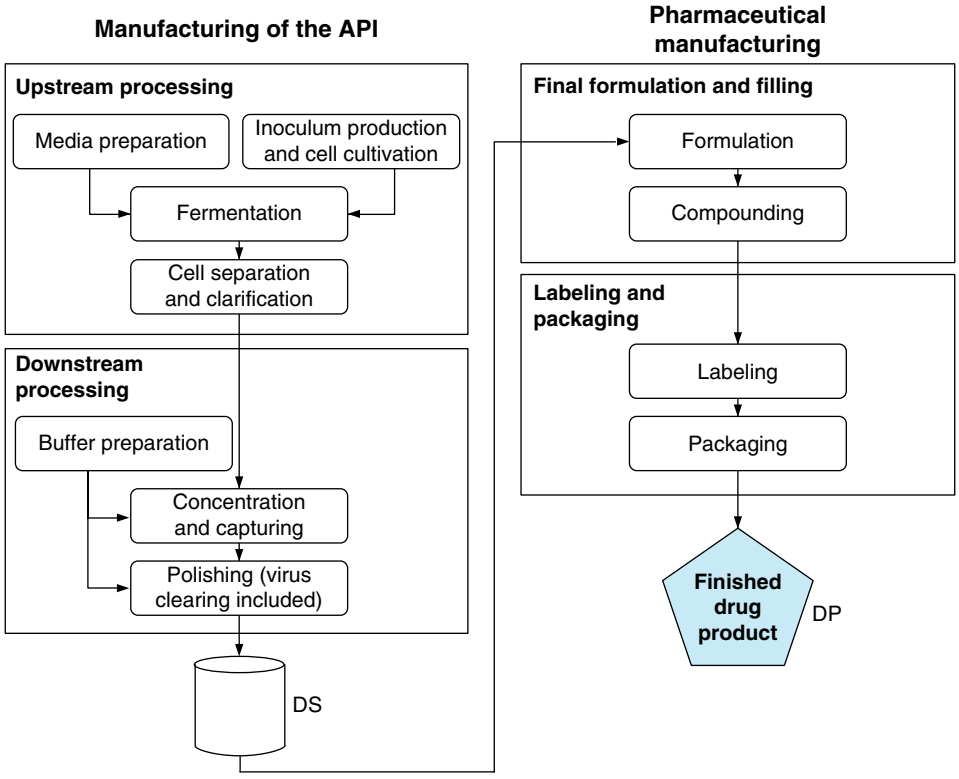

Figure 1.1 Schematic of a typical manufacturing process for therapeutic proteins such as mAbs.

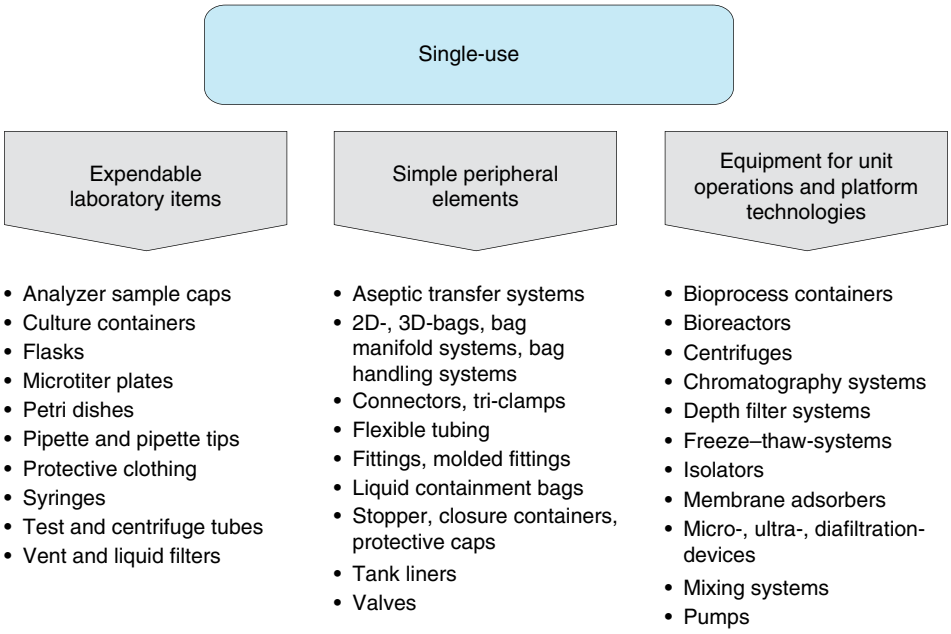

Figure 1.2 Primary categories of disposables utilizable for the development and manufacture of therapeutic proteins [31].
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(stand-alone components), and multi-component systems for unit operations and platform technologies. Thanks to single-use bioreactors (Chapter 4) together with bags for storage as well as transportation (Chapter 2), single-use mixers (Chapter 3), single-use plastic hoses, single-use plastic fittings, single-use connectors and sampling systems, and single-use pumps (Chapter 5), upstream processing carried out entirely with single-use technology up to the mid-volume scale has become possible. Leak test systems (Chapter 2) and novel connectors (multi-utilizable, hybrid, and neutral versions) have additionally improved safety in both upstream and downstream processing. Single-use systems preferably applied in downstream processing (Chapters 9 and 10) include those for centrifugation and filtration (micro-, ultra-, and tangential flow filtration), when biomass has to be separated, culture broth has to be clarified, or a virus has to be separated or inactivated. In addition, single-use membrane adsorbers and prepacked single-use chromatography systems have become increasingly common. Finally, the formulation and filling process steps are already able to be executed with single-use systems such as single-use storage systems, single-use filters, single-use mixers, single-use isolators, single-use dosage systems, single-use needles, etc. (Chapter 25).

Each and every key player in single-use technology now offers single-use process platform technologies (for media preparation, inoculum production, fermentation and biomass separation, virus separation and virus inactivation, formulation, and filling). Product examples include the ReadyToProcess and the FlexFactory series (GE Healthcare), the Mobius series (Merck), the Allegro series (Pall), the FlexAct series (Sartorius Stedim Biotech), and the HyPerforma series (Thermo Scientific). These process platforms support the rational implementation of disposables and process intensification (Chapters 14 and 16).

Disposables may be used in the same manner as their stainless-steel counterparts, provided due consideration is given to their specific characteristics. The user's requirements constitute the primary criteria in the decision-making process, while the projected product demand and the optimized usage of the asset must also be taken into account. The performance of the disposable, the associated costs, and the security of the supply chain must also be considered, while the risk of using a disposable must be minimized. Disposables pose a particular challenge in terms of assessing the technical risk associated with their use and the security of their supply chain. The majority of products have not been standardized, and therefore the security of supply, outlined in Figure 1.3, is of paramount importance when considering the utilization of disposables [32]. The essential prerequisite for the implementation of disposables in biopharmaceutical manufacturing is a thorough understanding of the associated risks and the appropriate management thereof. As described by Pora and Rowlings [33], and Sinclair and Monge [34–37], numerous factors must be considered. A risk analysis has to be done as shown by Merseburger et al. [38, 39] or Merck [40].