Single-Use Technology from A to Z

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The mini encyclopedia “Single-Use Technology from A to Z” explains important and often-used technical terms from the application area of single-use systems. It is directed at students of biotechnology (Masters level) and related disciplines (e.g. pharmaceutical technology, pharmacy, medicinal biotechnology, biotechnological engineering and facility design), but also towards first-time users from the industry.

To the Glossary

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Preface

Single-use systems, often referred to as “disposables“, are indispensable in the development and commercial production of biopharmaceuticals such as antibodies and vaccines today. This mainly applies to upstream processing for which a huge variety of equipment (such as storage bags, filters, mixers, bioreactors, connectors, pumps etc.) from several suppliers is available. But also for downstream processing, filling and formulation users can rely on appropriate single-use process platforms. Reusable systems are increasingly being replaced by their single-use counterparts in running hybrid production facilities. Furthermore, market forecasts assume that the number of complete single-use production facilities for mammalian cell-based antibodies and biosimilars will increase worldwide in the future.

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The authors

Britta Badertscher, Regine Eibl, Dieter Eibl
Zurich University of Applied Sciences, Wädenswil (Switzerland)

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Glossary

A

Additives

are chemical substances that are, among others, used in the processing of polymers, for example of **bags**, in order to increase the stability of the plastic material or to facilitate their shaping and molding. **Antioxidants** capable of protecting plastics from oxygen or **slipping agents (lubricants)**, as well as color additives, are also counted as additives [2, 3].

Adherent animal cells

are cells that grow on a surface, e.g. in the form of a **monolayer**. They are cultivated either on (1) planar plastic surfaces, (2) **carriers** or (3) membranes (for example, in **hollow fiber bioreactors** or **two-compartment systems**) [4]. See **vaccines** or **animal cell culture**.

Aegis5-14 film

is a novel multilayer film developed by Thermo Fisher Scientific intended for **bags** used in cell culture technologies.

Aeration system

see **sparger**.

Air filter

are separators in the air in- and outlet (e.g. of **bioreactors**) that filter particles, suspended substances and aerosols from the air. In the aseptic area mainly **HEPA filter**s, sintered metal candles and **membrane filter**s are used [38].

Air inlet filter

see **air filter**.

Airlift bioreactors

are a special type of **bubble column bioreactors** (bubble column bioreactor with inner tube) and belong to the group of **pneumatically driven** bioreactors [5, 6]. Mass and heat transfer are provided by direct gassing with air or any other gas as the ascending air bubbles cause mixing.

Allegro bioreactors

are stirred (Allegro STR with a **working volume** up to 2000 L) and wave mixed (Allegro XRS with a working volume up to 20 L) **bag bioreactors** for animal cell cultures or microorganisms provided by Pall Life Sciences.

Alternating Tangential Flow (ATF)-modules

allows biomass and/or product to be restrained by alternating tangential flow technology (a special filtration technology developed by the company Repligen, formerly Refine) after being coupled to a bioreactor. The ATF-module uses a diaphragm pump to suck the cell containing culture broth from the bioreactor through a

hollow fiber module and back to the bioreactor using the same route. This leads to a varying direction of medium flow through the filter membrane, causing cells settled on the hollow fiber module to be washed off as cell-free medium passes through. The alternating tangential flow is responsible for a reduced deposition of material on the membrane (**fouling**) and blocking (**clogging**) of the membrane [11]. In recent years, ATF-modules have been applied with stirred or wave-mixed bag bioreactors when realizing **concentrated fed-batch processes** or **perfusion**. A single-use model of an AFT-module is commercially available. See **crossflow filtration**.

ambr15 und ambr250

are fully automated, stirred, instrumented single-use **microbioreactors** from the company Sartorius Stedim Biotech (formerly known as TAP Systems) for **screening** and process optimization with **animal cell culture**s and microorganisms. The cultivation vessel consists of a 15 or 250 mL synthetic container made from rigid plastic. See **stirred bioreactors**.

American Society for Testing and Materials (ASTM)

is an international organization based in the USA that publishes technical standards. Their group for bioprocessing equipment works in close cooperation with the **ASME**.

American Society of Mechanical Engineers (ASME)

is an American institution (professional association of mechanical engineers in the USA) that supports the implementation of **single-use systems** by elaborating recommendations concerning their standardization with special focus on **leachables** and **extractables**.

Animal cell culture

are mammalian and insect cell lines that are used for biotechnological production processes (see **biopharmaceuticals** and **antibodies**). They grow as **monolayers** (see **adherent animal cells**) or in suspension (see **suspension cells**).

Antibodies

are an important component of the immune system. The *in vitro* production of the up-to-date therapeutic **monoclonal antibodies** is currently achieved in **hybrid production facilities**, whereby the **USP** is increasingly performed with **single-use systems**. Mainly **fed-batch processes** with **temperature shifts** are applied, reaching antibody concentrations between 2 und 5 g L^{-1}. See **biopharmaceuticals**.

Antioxidants

protect the polymer film from oxidative degeneration during **extrusion** (see **film manufacture**), **gamma-sterilization** and storage. By deactivating hydroperoxides, however, oxidized molecules can arise which can disturb the biotechnological production process as **leachables** and/or **extractables** when chemically decomposed in further reactions [2, 9]. See **additives**.

AppliFlex bioreactors

are wave-mixed **bag bioreactors** for **animal cell culture**s and **plant cell cultures**, as well as algae for cultivations, with a **working volume** of up to 25 L provided by the company Applikon. Photobioreactor versions are available. See **illumination** and **wave-mixed bioreactors**.

Aseptic connections

are realized by **aseptic connectors** and/or **aseptic sealing (welding)** of tubes. See **tube welding machines** (welder) and **connectors**.

Aseptic connectors

are single-use connectors, such as the Lynx connectors from Merck Millipore, the Kleenpak connectors from Pall or the Opta SFT sterile connectors from Sartorius Stedim Biotech. They can be used easily, quickly and safely in a classified, non-sterile or sterile environment and allow the setting up of sterile connections. See **aseptic connections** and **connectors**.

Aseptic disconnections

of **tubes** or bag units is carried out by thermal sealing (see **tube sealing machines** (sealer)), mechanical clamping (see **aseptic disconnector Clipster**) and/or sterile **disconnectors** [1].

Aseptic disconnector Clipster

is a single-use device produced by Sartorius Stedim Biotech that allows the sterile mechanical disconnection (see **aseptic disconnection**) of tubes and bags.

Aseptic disconnectors

See **aseptic disconnections** and **disconnectors**.

Aseptic sampling systems for single-use bioreactors

are gamma-sterilized (see **gamma-sterilization**) and preassembled sampling systems. The majority of single-use bioreactors is already equipped with one or multiple connections, valves or vessels for sampling, such as **bags**, **manifolds**, flasks or tubes. Sampling is generally conducted by needle-free **clave connectors** or single-use syringes with **Luer Lock** ports.

Aseptic Transfer Devices (ATDs)

are transfer devices (such as the Biosafe aseptic transfer devices from Sartorius Stedim Biotech) that are available for fluids, components or powder. ATDs allow these substances to be transferred between places of different classification and under aseptic conditions. For aseptic fluid transfer without spatial separation, **aseptic connectors** can be used. See **aseptic connections** and **connectors**.

Aseptic welding

is a thermal welding process in order to connect two thermoplastic tube ends of the same welding quality. The user can rely on fully-automated tube welders, such as the BioWelder produced by Sartorius Stedim Biotech or the Hot Lips Tube Sealer produced by GE Healthcare. See **aseptic connections** and **tube material**.

B

BactoVessel

is a stirred single-use bioreactor manufactured by the company CerCell for the cultivation of microorganisms with a **working volume** between 2 and 75 L. The lid and the fittings are produced with a 3D-printer. See **stirred bioreactor.**

Bag bioreactors

have a **bag** as a cultivation vessel, in which stirring and aeration devices (see **sparger**), as well as reusable single-use **sensors,** are integrated.

Bag handling systems

deal in the transport of bags. For the transport of 2D-bags, stackable tanks and boxes are used. Special **container systems** are preferred for the transport of 3D-bags [1]. Safe bag-handling systems also exist for the transport of frozen fluids and liquid products. See **freeze and thaw** and **storage and transport systems**.

Bag manufacture

takes place after the **film manufacture**. The films are cut according the bag specifications, welded and complemented with fittings, tested, confected and sterilized. The bag manufacture is done in cleanrooms. See **aseptic welding**, **bags** and **molding**.

Bag materials

are polymer films (see **film manufacture**) whose composition is dependent on the manufacturer. **Bags** for storage and transport partly consist of only one single layer. Bags for the cultivation are generally made of **multilayer**s [1].

Bag mixing systems

can be divided into **mechanically** and **hydraulically driven** versions according their power energy. While mechanically driven bag-mixing systems work with rotating or tumbling stirrers (see **tumbling stirrers**) and oscillating discs, hydraulic mixing systems are driven by pumps.

Bags

are flexible polymer bags that are used in nearly all steps of a biotechnological production process. Primarily, bags are used for cultivation, storage, sampling and transport, as well as freezing and thawing procedures. Bags can be derived from either two-dimensional pillow-like 2D-bags or three-dimensional bags (3D-bags) according their shape. The simplest bag system is the **tank liner**.

When handling small volumes between 50 mL and 50 L, 2D-bags are mainly used. Larger bags with a volume of up to 200 L are also available but are used only in exceptional cases. Bags are funnel-shaped and hold a large outlet if powder needs to be handled. See **powder transfer bag systems**.

3D-bags have been approved for more complex applications and larger volumes. They contain up to 2500 L and are more diverse in terms of shape and fittings compared to 2D-bags [1]. For better and more secure handling of the flexible bags, special **container systems** (see **bag handling system**) were developed [2, 13].

Ballroom concept

is a term from the cleanroom technology. It describes a cleanroom concept in which all steps of a process are performed in a cleanroom with uniform classification. (In the concept of normal practice the cleanroom is divided into different areas with different classifications depending on the individual process requirements; the criterion is the number of particles of a defined size per unit volume). In the ballroom concept the cleanroom is equipped flexibly with devices and equipment depending on the process. Thereby, process equipment is sometimes encapsulated. This concept is increasingly becoming evident in single-use **production facilities**. See **facility of the future**.

bDtBPP

or bis(2,4-di-*tert*-butylphenyl)phosphate is a degradation product of tris(2,4-di-*tert*-butylphenyl)phosphite, also known under the trade name **Irgafos 168**, which is present in many polyethylene-based films. For **CHO cells** bDtBPP is the first leachable component whose cytotoxicity in small concentrations of 0.1 mg L^{-1} was experimentally proven [2]. See **antioxidants**, **bags**, **film manufacture** and **leachables**.

Bio-Process Systems Alliance (BPSA)

is an organization founded in 2005 by the industry to support the implementation of the single-use

technology.

Bioburden

describes the biological pollution of a material and refers to the number of viable microorganisms per investigated object.

Biolector

is an instrumented and automated single-use microbioreactor (m2p-labs) for **animal cell culture**s and microorganisms. It works with orbitally shaken microtiter plates. See **microbioreactors** and **orbitally shaken bioreactors**.

Biopharmaceuticals

are active ingredients that are often produced biotechnologically using genetically engineered organisms (microorganisms, **plant cell culture**, **animal cell culture**). The development and production of protein-based therapeutics, such as **monoclonal antibodies** and **vaccines** as well as **cell therapeutics**, count as main applications of the single-use technology.

BioPhorum Operations Group (BPOG)

is a consortium of specialists from the industry aiming towards establishing best practices for the production of pharmaceutical active ingredients, ranging from the process development to the final filling. Together with the **BPSA**, the BPOG counts as leading institution working on the development of standardized tests for **leachables** and **extractables**.

Bioplastics

are biodegradable plastics, for example, poly-3-hydroxybutyrate.

Bioreactors (disposable)

have a cultivation vessel made from plastics which is disposed of after one or several usages. These bioreactors are available on a milliliter- to cubic meter scale.

The cultivation vessel of disposable bioreactors for animal and human cells as well as microorganisms was designed for only one single usage. For this reason, disposable bioreactors for animal and human cells or microorganisms are named single-use (disposable) bioreactors. The vessels are mainly made either as rigid plastic vessel from polysulfon or polycarbonate, or from flexible **bags** with contact layers made of polyethylene- or ethylene vinyl acetate. If a bag is used, a suitable holding device (container systems) becomes necessary which holds and fixes the bag. In addition, the container system supports the heat transfer if necessary and holds peripheral elements such as probes or the power unit. Depending on the power input type, single-use disposable bioreactors on the market can be divided into **mechanically**, **pneumatically** and **hydraulically driven** versions. The mechanically driven ones form the largest group.

For plant cell cultivations disposable bioreactors that can be used multiple times, so-called multi-use disposable bioreactors were developed. These are primarily pneumatically driven bubble-column bioreactors and hydraulically driven spray or mist bioreactors [15] (see **bubble column bioreactors**, **spray bioreactors** and **mist bioreactors**). Compared to the single-use disposable bioreactors, multi-use disposable bioreactors are low-cost bioreactors whose cultivation vessel needs to be sterilized with steam or another gas but which are generally less expensive to manufacture. However, the advantages generally seen for single-use disposable bioreactors (higher flexibility, increased process security, time- and cost reduction, “greener” process) cannot be applied to multi-use disposable bioreactors.

Biosensors

are analytical sensors that are composed of immobilized biological material such as enzymes, antibodies,

cells or cellular organs. The biological detectors convert the biochemical signal into a measurable and quantifiable electrical signal [6]. It has to be considered that biosensors cannot be heat-sterilized as the detectors would otherwise become inactive and destroyed [1]. See **instrumentation**.

Biosimilars

are subsequent products or generics of **biopharmaceuticals**. First single-use **production facilities** for biosimilars, such as the ones from Alvotech in Iceland, are currently under construction.

BIOSTAT bioreactors

manufactured by Sartorius Stedim Biotech are available as wave-mixed (BIOSTAT RM with a **working volume** of up to 100 L) and stirred (BIOSTAT STR with a working volume of up to 2 m^3) bag bioreactors. The references include successful applications with animal and plant cell cultures, algae, microorganisms and human cells. The BIOSTAT RM is also available as a photobioreactor version. See **illumination**, **stirred bioreactors** and **wave-mixed bioreactors**.

biotechnet Switzerland

is a national network of competence founded in 1998 by universities of applied sciences active in biotechnology, the EMPA St. Gallen, and associated members and partners from academia and the industry. It is active nationally and internationally in the areas of research, service and further education, whereby a platform of biotechnet Switzerland also works on the development and application of single-use technologies in biopharmaceutical production. Together with the Swiss Biotech Association, biotechnet Switzerland forms the National Theme Network (NTN) Swiss Biotech.

Bubble column bioreactors

see **airlift bioreactors**.

C

Capacity sensors

are **sensors** whose electrodes form an electric capacitor. They measure the capacity, or accordingly the change in capacity, between the electrodes. Capacity sensors that directly measure the concentration of living cells [41] and that belong to the chemical sensors are available for single-use bioreactors. See **conductivity sensors**.

Carbon dioxide sensors

are made as single-use **sensors**, measure contact-free and belong to the optical sensors [20]. The sensors have a gas-permeable membrane and are based on a pH-sensitive dye in a HCO_3^--buffer solution. If CO_2 is present in the culture broth, it diffuses through the gas-permeable membrane into the HCO_3^--buffer solution and changes its pH value. This is detected with the sensor and allows the pCO_2 concentration to be determined afterwards using the Henderson-Hasselbach equation [20].

Carriers

are particles with a smooth or porous surface made from different materials and divided into **micro**- or **macrocarriers** depending on their size [4, 16]. Their surface is either electrostatic or covered with cell-adhering molecules (fibronectin, collagen, laminin), both support the cell growth on the carrier and in its

pores [16]. See **adherent animal cells**.

Cell banks

consist of long-term stored cells (see **cryoconservation**) of the Master Cell Bank (MCB) and the Working Cell Bank (WCB) [80]. They are a precondition for patenting cells and processes regulated by **GMP**. Thereby, one single vial of the MCB (consisting of 10 to 20 **vials**) is used to generate the WCB with approximately 100 vials.

Cell cultures

see **animal cell culture** and **plant cell culture**.

Cell retention

see **macrocarriers**, **microcarriers** and **perfusion**.

Cell therapeutics

for example, Laviv, Cartistem or Prochymal, are commercial pharmaceuticals for the therapy of diseases. Here, cells (as, for example, **stem cells** or **T-cells**) are the product. More than 300 cell therapeutics are currently undergoing clinical research [18, 81, 82].

Cell-tainer bioreactors

are wave-mixed bioreactors for animal cell cultures and microorganisms. They are distributed by Cell Tainer Biotech (formerly known as Cellution) with bag sizes of 20 L and 200 L. See **wave-mixed bioreactors**.

CellFactory

is a non-instrumented plastic layer system from the company Nunc. CellFactories exist with one or several (max. 40) layers. For many vaccine and cell therapeutic productions, the CellFactory is the preferred cultivation system and has replaced the productions with roller flasks (see **roller bottles**). See **adherent animal cells**, **CellSTACKs** and **multi-tray systems**.

CelliGen BLU bioreactors

are single-use bioreactors with a cultivation vessel made from rigid plastics (up to a **working volume** of 40 L) from Eppendorf. Besides **stirred bioreactors** for microorganisms, stirred and **fixed-bed bioreactors** for **animal cell culture**s and human cells are available.

CELLine

is a small-volume (15 mL **working volume**), non-instrumented, two-compartment system (see **two-compartment systems**) manufactured by Integra Biosciences which is used for routine cell production and preclinical antibody production on a milligram-scale. Versions for adherent animal cells and for suspension cells exist. Cell densities of more than $1x10^7$ cells mL^{-1} can be achieved with the CELLine. See **HCD** and **high cell density**.

CellMaker bioreactors

are bioreactors produced by the company Cellxus intended for **animal cell culture**s and microorganisms with a maximum **working volume** of 50 L. CellMaker bioreactors are pneumatically-driven **bag bioreactors**. See **airlift bioreactors**.

CellSTACKs

are planar non-instrumented single-use systems manufactured by Corning with a maximum of 40 layers. See **CellFactory** and **multi-tray systems**.

CellTumbler

are **wave-mixed bioreactors** (from CerCell) with bags of up to 10 L **working volume** for the cultivation of **animal cell culture**s.

Centrifugal pumps

such as the magnetically bedded and driven single-use centrifugal pumps of the PuraLev series are distributed by the company Levitronix GmbH. Compared to conventional centrifugal pumps, the impeller is held in balance magnetically and, in addition, driven contact-free via rotating magnetic induction. This new technology allows a very steady, particle-free and gentle transportation [45].

Centrifugation

is an operation of the **DSP** that aims towards separating the cells from the culture medium. Currently, single-use centrifuges from KBI Biopharma (the kSep single-use centrifuge) and from CARR Centritech Separation Systems (Carr Centritech, Carr UniFuge) are on the market [83].

Chemically defined medium

is a culture medium by which all media components are defined. It allows a reproducible production procedure and facilitates product purification. Especially the chemically-defined minimal culture media are in line with the trend, due to their cost-saving potential for modern antibody production processes. The difficulties of **leachables** in single-use bioreactors were so far only described in combination with chemically-defined minimal culture media for the cultivation of **CHO cells** and polyethylene contact layers. See **bDtBPP**, **CHOMaster medium**, **CHO XM 111-10 cells**, **Irgafos 168** and **multilayer**.

CHO cells

originate from the ovaries of the Chinese hamster. They are ranked among the most frequently used production cell lines for the production of **biopharmaceuticals**. Several subtypes exist, including CHO DUXB11, CHO DG44, CHO K1 and CHO S cells.

CHO XM 111-10 cells

secrete the alcaline phosphatase from the placenta. The model cell line was established by Prof. Dr. Martin Fussenegger's section (ETH Zurich). The cells can be obtained from the Culture Collection of Switzerland, CCOS, and were recommended by **DECHEMA** for the early identification of **leachables** in **bags** [17].

CHOMaster medium

is a chemically-defined, minimal culture medium (Cell Culture Technologies) for **CHO cells**. See **chemically defined medium** and **CHO XM 111-10 cells**.

Chromatography

is used for **downstream processing (DSP)** and can be divided into adsorption, distribution-, ion-exchange-, exclusion-, affinity-, and chiral chromatography based on the separation principle. The chromatographic steps include isolation (capture) and several purification steps (polishing).

The single-use gel chromatography columns on the market are already packed, sterilized, qualified and, thus, ready to use. Nevertheless, their performance and scalability is limited. A promising alternative is single-use membrane absorbers. See **membrane chromatography**.

Clave connectors

are valve membrane systems that allow needle-free docking. They originate from the clinical area. See **aseptic sampling systems for single-use bioreactors**.

Cleaning In Place (CIP)

describes *in situ* cleaning. This step becomes superfluous with single-use systems, resulting in a reduced water and energy consumption and a decrease in the **CO_2-footprints** [1]. See **Life Cycle Analysis** and **environmental burden**.

Clogging

describes the blocking of a membrane (for example at **filtration units** or **hollow fibre bioreactors**).

CO_2 footprint

is a unit for the totality of CO_2 emissions that are built directly or indirectly into a process. The environmental impact of a bioprocess can be estimated using the CO_2 footprint. See **Life Cycle Analysis**.

Concentrated fed-batch processes

are biotechnological procedures in which not only the cells but also the target product are retained in the bioreactor (via **micro-** and **ultrafiltration** membranes) [44]. The pore size or the **MWCO** is 2 to 3 times smaller than the product. With this cultivation mode, **antibody** productions with mammalian cells reached cell densities of more than 10^8 cells mL^{-1} and product titers larger than 10 g L^{-1}. See **ATF-modules**, **crossflow filtration**, **TFF** and **XD-technology**.

Conductivity sensors

serve to detect electric conductibility, which is also termed as conductivity. They function by applying an AC power source to one electrode which is placed in the solution to measure. The electricity runs through the solution and to a second electrode. By determining the currency and the voltage drop between the electrodes, the resistance of the solution can be calculated using Ohm's law. As the resistance and the conductivity directly correlate, the latter can be deducted from the first. The system needs calibration before it can be used as geometry, surface and material of the electrodes play an essential role. Measuring cells consisting of 2 and 4 electrodes are available, whereby 4-electrode measuring cells are able to cover a larger measuring range. In contrast to the 2-electrode cells, the measurement is not disturbed by polarization effects or impurities at the electrodes [41].

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Connectors

are elements for the coupling of systems. **Aseptic connections** can be established after previous sterilization of connectors and under the laminar flow of a sterile workbench. In addition, a connection can be achieved outside of a sterile area with **aseptic connectors**. See **SIP connectors**.

Container systems

are available for cubic or cylindric bags and are made of stainless steel or rigid plastic. The containers are equipped with rolls or can be transported with the help of a forklift or a trolley. The containers can be optionally equipped with a balance. If bags with sterile liquids need to be transported over long distances, transport-containers with adjustable or fixable lids are recommendable. This allows oscillation of the liquid to occur during transportation [1]. See **bag handling systems** and **storage and transport systems**.

Continuous processes

are generally characterized by a continuous supply of fresh culture medium and the discharge of culture broth (in the same proportion) during cultivation in a bioreactor. Continuous processes are most commonly realized in perfusion mode. See **cultivation mode** and **perfusion**.

Contract Manufacturing Organizations (CMOs)

are companies that work as contract manufacturers in the pharmaceutical industry. They have increasingly invested in single-use technologies in recent years.

Cross-contamination

is contamination from a certain source to another non-contaminated property. If, for example, a product in a cleaned **multipurpose facility** is contaminated by residual substances from a previous production process (media, product, microorganisms, cells, cleaning solutions et cetera), cross-contamination occurs. Single-use equipment reduces the danger of cross-contamination [45].

Crossflow filtration

is a filtration method. The liquid that needs filtering is pumped parallel to a membrane with high velocity and the permeate is derived across the direction of flow. Due to the high velocity, the membrane surface is constantly cleaned and the build-up of a filter layer (see **fouling**) on the membrane is reduced. See **ATF modules**, **filtrations**, **perfusion** and **tangential flow filtration**.

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Cryobags

are **bags** (e.g. Kryosure Cryopreservation Bags from American Fluoroseal) that are resistant to low temperatures (> -80 °C) and suitable for the establishment of **cell banks** [46]. See **cryoconservation**.

Cryoconservation

serves to freeze and store cells or tissue at a temperature range often below -80 °C. Thereby, most cells are stored in the gas phase of liquid nitrogen in **cryovials** (**vials**) or **cryobags** [6], whereby the metabolic activity stops. After thawing, the cells can once again take up their typical physiological processes, presuming that the cells were not damaged through ice crystals thanks to fast freezing. Important factors for successful cryoconservation are, furthermore, extremely vital cells at the time of freezing, optimal freezing and thawing rates (generally -1 °C per minute when freezing and as fast as possible when thawing), a sufficient amount of cells, the suitable culture medium and the use of **cryoprotectants**. See **cell banks**.

Cryoprotectants

are substances that avoid crystallization during the freezing process. They are especially important when using a serum-free medium and interact, for example, with water molecules or increase the solubility of salts

which also avoids cellular damage [47, 48]. The protectants themselves, however, are harmful to the cells. Cell damage increases with increased time of contact. For this reason **freeze and thaw** should be conducted as quickly as possible in order to minimize the contact time of protectant and cells. See **cryoconservation**.

Cryovials

see **cryoconservation**, **vials** and **cell banks**.

Cultivation mode

is the method of running a bioreactor. With single-use systems, **fed-batch procecces** (**feeding**) are dominant. Lately, also **concentrated fed-batch processes** and **perfusion** are trending.

Current bioreactors

are orbitally shaken single-use bioreactors provided by Hangzhou Amprotein Bioengineering and intended for **animal cell culture**s for a maximum **working volume** of 300 L. See **orbitally shaken bioreactors**.

Current Good Manufacturing Practice (cGMP)

is the current good manufacturing practice whose guidelines are updated on a yearly basis in the USA. See **GMP**.

D

DASGIP parallel bioreactors

are single-use stirred bioreactors for animal and human cell cultures and microorganisms with a **working volume** of up to 1.25 L marketed by Eppendorf. See **stirred bioreactors**.

DECHEMA

is the Society for Chemical Engineering and Biotechnology based in Frankfurt am Main (Germany). Within the DECHEMA, a group of experts focuses on problem-solving strategies for single-use technologies.

Depth filtration

is characterized by separation within the filter medium which is why the fluid medium represents the valuable substance. See **filtrations**.

Diafiltration

is a membrane separation process in which the solvent and part of the ingredients of a solution or a suspension are exchanged. Thereby, the product is held back. For diafiltration, crossflow filtration systems are used. The membrane is selected according the molecule-size of the substance to be exchanged in the process. See **crossflow filtration**, **filtrations** and **TFF**.

Disconnectors

exist from the same suppliers that market single-use connectors. Disconnectors allow a sterile disconnection of tube-connections. See **aseptic disconnections**.

Disposable

describes a system which is decontaminated and discarded after one (single-use) or several (multi-use) usages. See **bioreactors** and **single-use systems**.

Double jacket

serves in heating and cooling the bioreactor content and is filled with water in reusable bioreactors. **Disposable bioreactors** with rigid plastic vessels are generally equipped with a **heater mat** (which makes a cooling of the bioreactor impossible). However, **bag bioreactors** as well as **storage and transport systems,** can be instrumented with heating- or cooling coils or double jackets.

DSP

includes all steps of purifying a product. It consists of three steps: (1) the separation, (2) the **enrichment** and (3) the **purification**. In the first step, the crude product is separated from the biomass or cellular mass and other solids. Thereby, it has to be considered that the product can be present either intra- or extracellular. An intracellular product requires a previous disruption of the cells. The separation can then be carried out via **centrifugation**, precipitation or filtration (see **filtrations**). This is followed by water removal in order to enrich the product. Common procedures to eliminate water are reverse osmosis, adsorption and extraction methods. For subsequent product purification, chromatographic methods (see **chromatography**) are used. **Virus removal,** as well as the final **formulation and filling** of the purified product, also belong to the area of DSP.

Dynamic bioreactors and mixing systems

are systems in the single, double or triple-digit liter-scale in which power is inputted in order to secure the mass and energy transfer [20]. See **bioreactors**, **power input** and **bag mixing systems**.

E

Ecobalance

includes the whole life cycle of a defined system from the raw material with its extraction and processing, the manufacture and use, up to disposal or recycling. Studies covering the ecobalance of **antibody** productions show a higher environmental sustainability for plants using **single-use systems** compared to reusable stainless-steel production plants. Using single-use systems causes reduced water (87 %) and energy consumption (30 %) and less CO_2 (25 %) emission [29, 57, 58]. See **CO_2-footprint** and **LCA**.

Energy input

is the type of power or energy input of a bioreactor or a mixer. It can be hydraulic (see **hydraulically driven**), mechanic (see **mechanically driven**), or pneumatic (see **pneumatically driven**). See **bag mixing systems**, **dynamic bioreactors and mixing systems**.

Enrichment

see **DSP**.

Environmental burden

see **ecobalance** and **CO_2-footprint**.

Equilibration

marks the preparation and adjustment of a sensor (regardless of being single-use or reusable) that needs to take place before implementation. Equilibration is generally compromised of holding the sensor in medium or buffer solution for a defined duration of time in order to activate the sensor surface for the measuring process [12]. See **sensors**.

Erlenmeyer flasks

see **shake flasks**.

Ex situ

describes something outside or out of a system.

Exhaust air condensors

are heat exchangers built in the exhaust air flow of **bioreactors**. They avoid the **fouling** of **exhaust air filters** caused by volatile substances and ensure the condensation, cooling, as well as the recirculation of volatile substances [1]. Even though single-use versions of exhaust air condensers are present on the market, the simpler filter heater is generally sufficient for cell culture applications.

Exhaust air filter

See **air filter**.

Extractables

are components that can migrate from plastic materials if solvents are applied or at high temperature or over long time spans [2, 13, 20, 27]. See **bag materials** and **multilayer**.

Extractables and Leachables Information Exchange (ELSIE)

is a consortium of companies that have developed a data bank in order to collect secure information about **extractables** and **leachables** from different materials.

Extrusion

is a process in which individual components of a film, often present as granulate, are melted and homogenized in an extruder. The extruder consists of a heated spiral conveyor that is built in a cylinder. The granulate is filled in via a funnel on one side of the cylinder, from where it is transported through the cylinder by the rotating spiral. The granulate then melts due to the heating elements on the cylinder and the friction. While the melting granulate is transported, the geometry of the auger narrows which builds up pressure. After the compression zone, the granulate is fully molten and can be fully homogenized with additional mixing elements at the auger. The liquid polymer is now pressed through a filter whereby gels and degraded or non-melted material is separated. Afterwards, the polymer is compression or injection molded [1] and proceeded to further **molding** steps.

F

Facility footprint

is the area which is needed for the totality of a facility (including the resources such as steam etc.). With the implementation of single-use technologies it is possible to save up to 40 % of space [7]. Reasons for this reduction are the easier and more flexible installation of hardware with a more efficient use of the space

available [8]. It has to be considered, however, that production facilities using **single-use systems** are generally in need of larger storage compartments for warehousing (e.g. of consumables).

Facility of the Future

is a collective term describing future production concepts that include the full application of single-use technologies. See **ballroom concept**, **production facilities**, **process platforms** and **flexible single-use biomanufacturing**.

Fed-batch processes

describe a cultivation process in which the **bioreactor** is started with a smaller volume (20 % to 50 % of the maximum **working volume**). As soon as the key components are depleted or growth-limiting concentrations of metabolites are reached, fresh medium or a specially formulated solution (consisting of diverse components) is periodically or continuously added until the maximum working volume is reached. With a fed-batch strategy, the growth phase can be elongated and cell and product concentrations can be increased [28]. See **feeding**, **concentrated fed-batch processes** and **repeated fed-batch processes**.

Feeding

is a cultivation procedure during which medium components or complete medium are added to a running cultivation. Thereby, substrates can be replaced and metabolites are diluted [4]. See **fed-batch processes**.

Filling

see **final filling**.

Film

see **bag materials**.

Film manufacture

includes melting the granulate in an extruder and pressing it to an appropriate form (**extrusion**). Afterwards, the plastic film is cooled on rolls whereby sterile-filtered air is used for cooling. Thus, the produced film is already protected from contamination during its production, as foreign substances can be locked in the still soft plastic material. If several film layers should be combined to create a **multilayer**, a coextrusion (rare) or a **lamination** can be performed.

Film quality

is assessed after **gamma-sterilization** as the polymer can change due to the radiation. The films are subjected to sterility testing, mechanical (stretchability, tensibility, resistance), physical (oxygen and carbon dioxide transfer through the film materials), chemical and biological tests (reaction of cell cultures to the film). Studies of **extractables** and **leachables** are an important component of the chemical and biological tests.

Filter integrity testing

is a test to confirm the performance of a sterile filter and the aspired quality of the filtrate from sterile filters used in **GMP** processes.

Filtration unit

belongs to the oldest single-use systems and is used for pre-filtrations, **diafiltration**, **microfiltration**, **nanofiltration**, **depth filtration** and **ultrafiltration** [29].

Filtrations

are operations of the **USP** and **DSP**. They belong to the classical separation techniques and serve the clearance, **sterile filtration** and **virus removal**. Static and dynamic filtration processes can be differentiated. See **crossflow filtration**, **diafiltration**, **microfiltration**, **nanofiltration**, **depth filtration**, **TFF** and **ultrafiltration**.

Final filling

is the **filling** of a final formulation into primary drug containments such as flasks or syringes [23, 24]. The final filling has specific requirements in order to guarantee sterility, integrity, the operational security and efficiency, as well as the correctness of the filling volumes [25]. The trend in final filling systems also moves towards **single-use systems** [25].

A single-use final filling system for medication usually consists of **bags** for storage and intermediate buffers, sterile filters with corresponding bags for the integrity testing, as well as a manifold system (see **manifolds**) with filling needles [26].

Fixed-bed bioreactors

include static carrier material that forms the bioreactor bed and is circulated by medium. **Adherent animal cells** and **suspension cells** can be immobilized on the carrier material. The media flow can be led from bottom to top or reversed, while the media circulation is done internally or externally. Fixed-bed bioreactors (such as **CelliGen BLU bioreactors** or **iCELLis bioreactors**) are available as single-use systems from different suppliers and allow **high-cell density** productions [4]. See **HCD**.

FlexFactory

is a single-use production concept for **biopharmaceuticals** from GE Healthcare. It conforms to **cGMP** and is based on single-use process platforms. See **flexible single-use biomanufacturing** and **production facilities**.

Flexible single-use biomanufacturing

describes flexible single-use production concepts for the manufacture of **biopharmaceuticals**. Such production concepts allow fast and world-wide realization of **GMP-production sites** (see **FlexFactory**, **KUBio**, **POD facility platform**), as well as the modification and extension of existing production facilities. See **ballroom concept**, **Facility of the Future** and **process platforms**.

Flexsafe S80 film

is an optimized polyethylene film for **bags** (Sartorius Stedim Biotech) for which the concentration of **Irgafos 168** was minimized. As studies based on recommendations of the **DECHEMA** show, cell growth inhibiting effects through **leachables** could be excluded beyond **CHO cells** [30, 31]. See **bag materials** and **film**.

Flotation

describes the floating of cells in the bioreactor and can occur as a consequence of aeration of a bioreactor. Cells can attach to bubbles and get carried to the top and into the foam [6]. The cells do not swim freely in suspension anymore, are not provided with nutrients and die [4]. Flotation is also used as separation technique to isolate cells or substances from a culture broth. See **bioreactors**.

Formulation and filling

include process steps that are necessary to get a purified active component into the final dosage form. The active ingredient is often stored in a frozen state and is first brought in the correct concentration using buffers. After the active component is ready, it is mixed with the inactive components of the drug. Thereby, it

is especially important to follow and document the temperature and mixing time (see **mixing**) as an optimal environment (e.g. pH or ion concentration) for the active ingredient should be reached in which it is stable and functional [1]. If the parameters are not met, inhomogeneity can occur which can impair the quality and quantity of the final product [1]. Afterwards, the mixture must be transported from the formulation tank to the filling. After transportation the final sterilization, normally a **sterile filtration**, and the subsequent **final filling** take place [1].

Fouling

is the overgrowing of a surface (including membranes) with biomass, polysaccharides and proteins.

Freeze and thaw

are processing steps within the manufacture of biopharmaceutical intermediates and finished products. In a frozen state, biopharmaceutical products are stable over a longer period of time and can be more easily transported and stored [1]. Furthermore, the danger of an unwanted reaction or contamination can be minimized in this state [21]. The choice of a suitable freezing and storage container is dependent on the properties and quantities of the product. While both plastic tubes (see **vials**) and **bags** are used for milliliter-scale applications, only bags are used in liter-scales. Larger quantities between 50 L and 500 L are frozen in transportable stainless steel containers. Bags are recommended for the freezing of biological products in combination with **bag handling systems** and **manifolds**.

For a defined process control of freezing and thawing bags, specially designed freeze and thaw systems can be used, such as the Celsius freeze and thaw system (Sartorius Stedim Biotech). A potential disadvantage of using bags for freeze and thaw application is their integrity testing. Damaged bags can often only be detected after thawing if the user does not apply integrity testing systems to bags such as the Sartocheck 4 plus Bag Tester (Sartorius Stedim Biotech).

G

Gamma-sterilization

is the most frequently used sterilization method for plastics. The ionizing radiation amounts are between 12 and 50 kGy. The radiation penetrates the material and destroys the **bioburden** there [32]. Thereby, a sterility security value of at least 10^{-6} must be reached according to ISO-standard [33]. During gamma-sterilization the material further polymerizes. Protecting **additives** are necessary to avoid too strong oxidation or damage to the material [9]. Cytotoxically active **leachables** and **extractables** can be built during gamma-sterilization [20]. See **bags** and **bDtBPP**.

Good Manufacturing Practice (GMP)

is a synonym for guidelines that need to be considered during the production of certain products such as drugs. The aim is to produce these products in a reliable and reproducible way and of the desired quality. See **cGMP**.

H

HCD

is an often-used abbreviation for **high cell density**.

HCD cell bank

is a cell bank (see **cell banks**) of animal cells in which the cells are stored in **vials** (1 mL to 10 mL) and with a high cell density of around $10x10^7$ cells mL^{-1} [34]. See **high cell density** and **perfusion**.

Heater mat

see **double jacket**.

HEPA filter

(High Efficiency Particulate Air Filter) separate particles to a size of 0.3 µm. See **air filter**.

High cell density

describes cell densities of > 10 million cells mL^{-1} for animal cells. Microbial high cell densities arise from a dry biomass of > 100 g L^{-1} culture medium. See **HCD**.

High seed (HS) inoculation

is a novel approach that has established itself with the development of the single-use technology, and that aims towards producing the inoculum for mammalian cell-based antibody production processes in a **continuous process** via **perfusion**. The bioreactor is inoculated with an initial cell density of at least $1x10^6$ cells mL^{-1} in order to reach the desired product concentration with a high product quality within a short time [35].

Hollow fiber bioreactors

such as the **Quantum Cell Expansion Bioreactor** consist of a bundle of porous membrane capillaries that are integrated in a plastic cartidge. The cells are thereby expanded in the extracapillary space (around the capillaries) and are able to grow three-dimensionally. With the hollow fibers, nutrients from the aerated medium can reach the cells (intracapillary space) and waste products can be removed. This allows the generation of **high cell densities** (**HCD**) and the continuous secretion of protein-based products in the extracapillary space where the shear forces are low. The main disadvantages of the hollow fiber bioreactor are the limited oxygen transport and the limited **scale-up** capability [1].

Hose clamps

are used to regulate or interrupt the flow rate of solid, liquid or gaseous substances in a single-use transfer line.

Hybrid

describes the combination of two methods.

Hydraulically driven

means that the **energy input** is realized with a pump in the inner or external circulation. See **fixed-bed bioreactors**, **hollow fiber bioreactors**, **mixing systems**, **mist bioreactors** and **spray bioreactors**.

HyPerforma S.U.B.

are stirred **bag bioreactors** from Thermo Scientific that are available for **animal cell culture**s with working volumes between 25 L and 2000 L. See **stirred bioreactors**.

HyPerforma S.U.F.

are stirred **bag bioreactors** from Thermo Scientific that were brought to the market for microbial cultures with **working volumes** between 6 L and 300 L. See **stirred bioreactors**.

I

iCELLis bioreactors

from Pall Life Sciences are based on a fixed-bed with **macrocarriers** made from polyester fiber that currently guarantee a growth surface of up to 500 m^2 at 25 L fixed-bed volume. They are suitable for the development and production of biopharmaceuticals with **adherent animal cells**. See **fixed-bed bioreactors**.

Illumination

of a bioreactor is necessary if photosynthetically active organisms such as algae or certain plant cells are cultivated. In recent years, photobioreactor versions of **wave-mixed bioreactors** have been developed that host an LED illumination or fluorescent tubes [14]. In addition, reusable LED plug-in probes for rigid cultivation containers can be obtained from the company DASGIP or the LAMBDA LUMO light modul can be implemented. See **AppliFlex bioreactors**, **BIOSTAT** RM **Bioreactors** and **plant cell culture**.

In situ

means that a processing step (e.g. measuring, sterilization, cleaning) of a biotechnological production process is performed directly in place [6, 40].

In-line analysis

describes a reliable method for process control where the measuring probe is in direct contact with the product and is able to measure continuously and without previous probing. The terms in-line analysis and **on-line analysis** are often used as synonyms.

Incubators

ensure a controlled environment for cell cultivation and allow the control and regulation of temperature, gas atmosphere, humidity and/or the **illumination** [38]. Incubators are mandatory if the used **single-use system** does not possess measuring, controlling or monitoring devices of its own.

Inoculum production

aims towards producing the inoculum for a bioreactor in sufficient amounts and high vitality (> 95 %). Starting point are **vials** or **bags** from which the cells are expanded via **shake flasks** or **spinner flasks** to **wave-mixed bioreactors** [36, 39]. Nowadays, inoculum is produced in **single-use systems** with almost no exception.

Instrumentation

describes the equipment of a container (e.g. mixer, storage tank) or a bioreactor with **sensors**. Single-use **bioreactors** are not as highly instrumented and automated as their reusable counterparts. Standard parameters for process control in single-use bioreactors are temperature, pH value, flow rate, dissolved oxygen concentration, shaking frequency, filling volume, foam height or pressure. In addition, the weight of the reactor, conductivity, viscosity, as well as substrate and metabolite concentrations, can be recorded [15].

Thereby, single-use bioreactors can be equipped with single-use or reusable ***in situ*** or ***ex situ*** sensors [40]. The number of available single-use sensors, however, is still relatively small compared to the number of reusable sensors. Furthermore, the type of sensor is predetermined by the manufacturer of the single-use bioreactor [15].

International Society for Pharmaceutical Engineering (ISPE)

is an international society whose specialist group “Disposables Community of Practice“ is composed of manufacturers and uses elaborates standards (e.g. for **extractables** studies) in relation to single-use technology.

Irgafos 168

see **bDtBPP** and **leachables**.

K

k_La value

see **oxygen input** and **volumetric oxygen transfer coefficient**.

KUBio

is a pre-assembled, scalable production facility with a single-use process solution for the production of **biopharmaceuticals** from GE Healthcare. It conforms to **cGMP**. See **flexible single-use biomanufacturing**, **production facilities** and **process platforms**.

L

Lamination

is the grouting of two finished **films** with the help of a warm freshly extruded binding layer during the manufacture of a **multilayer** film [33]. See **film manufacture**.

Leachables

are components that can migrate from primary (e.g. storage **bag**) or secondary containment (e.g. label) under normal process conditions (see **bDtBPP**). Together with the **extractables** they belong to the substances that can contaminate culture broth, intermediate or final product. Thereby, leachables are regarded as more dangerous as they can occur under normal process conditions. The sources of leachables are **additives**, especially **antioxidants**, which arise during the extrusion in **bag manufacture** (see **film manufacture**) or the **gamma-sterilization**, and leak as water-soluble components from the plastic material. Leachables can disturb cell cultivation, increase protein aggregation and are a risk for patients due to their toxic effect when administered parenterally [2, 3, 50, 51]. Therefore, it is important to detect the development of leachables at an early stage. This can be done with specific chemical-analytical methods such as the GC-MS or the LC-MS (gas or liquid chromatography mass spectroscopy), or with general tests such as the determination of TOC (total organic carbon, total amount of organic carbon), the pH value, or the conductivity. In addition, cell culture tests (such as the test with **CHO XM 111-10 cells** recently suggested by **DECHEMA**) where the vitality and proliferation of cells after cultivation in incubated medium and water for

injection is determined [3, 52]. It is very important to not only identify **films** or **bags** that do not excrete leachables for cultivations, but also for the storage of starting material and products. At present, bags made from films with an improved composition of additives and that are tested for the absence of leachables are available [9]. See **Aegis5-14 film** and **Flexsafe S80 film**.

Life Cycle Analysis (LCA)

stands for an **ecobalance**.

LifeReactor

is a prominent representative of the multi-use **disposable bioreactors** from the type of bubble column bioreactors. Its advanced version is used by the Israeli company Protalix for the commercial production of ELELYSO (the recombinant glycocerebrosidase against the Gaucher disease) with genetically modified carrot cells. See **airlift bioreactors**, **bubble column bioreactors** and **plant cell culture**.

Lubricants

are used for the manufacturing and processing of **films** for **bags** (see **bag materials**) and belong to the group of **additives**. These are amides of fatty acids that avoid the agglutination of the films during **film manufacture** [9]. Alternatively, chemically inert additives can be used, as is the case in the **Flexsafe S80 film** produced by Sartorius Stedim Biotech.

Luer Lock

is a normed connecting piece for tubes originating from medicinal technology that is used in combination with cannulas, syringes, catheters, three-way valves and infusion tubes. See **aseptic sampling systems for single-use bioreactors**.

LV cell bank

is a large volume **cell bank** in **cryobags** with a **working volume** of around 100 mL. See **one-step inoculation**.

M

Macrocarriers

are porous carrier materials with a size of between 0.6 and 5 mm. They are mainly used for **adherent animal cells** in combination with single-use **fixed-bed bioreactors** [4]. They allow the realization of a perfusion mode. See **carriers** and **perfusion**.

Manifolds

are **single-use systems** that connect different elements (**bags**, filter, **tubes** etc.) and are used for media distribution, sampling, as well as **filling** processes. They can be connected with **aseptic connections**. See **aseptic connectors**, **aseptic sampling systems for single-use bioreactors** and **aseptic welding**.

Mechanically driven

describes the input of energy (**energy input** or **power input**) in **bioreactors** or **mixing systems** through stirrers, rockers, vibrating discs or shakers.

Membrane aeration

is the bubble-free aeration of cells with gases or mixtures of gases, whereby membranes with open pores or diffusion membranes are used. When membranes with open pores are used, the culture is in direct contact with the gas from the membrane and the gas-liquid interface is controlled by pressure. In diffusion membranes, the gas first diffuses in the membrane (often silicone) and then migrates into the culture broth. With diffusion, membranes gas transfer rates in the region of those achievable in direct sparging are reached. However, a high gas pressure as well as a large membrane exchange surface is needed. In addition, the membrane aeration is limited to small reactor systems as a large surface of 2 to 3 m of silicone tubing per liter of culture broth is necessary [4]. Besides the membrane aeration, **surface aeration** and the aeration with **spargers** is possible.

Membrane chromatography

is established for polishing applications (removal of DNA and host cell proteins) and the **virus removal** in the production process of **antibodies** (see **biopharmaceuticals**). First applications also arise at the step of virus removal in vaccine production. In the membrane chromatography, thin, synthetic and porous membranes are used that are integrated into a cassette [31]. Examples for single-use membrane chromatography columns are the Sartobind Membrane Adsorber produced by Sartorius Stedim Biotech or the Mustang Q Membrane Adsorber produced by Pall Life Sciences. See **chromatography**.

Membrane filters

are supplied by different manufacturers, made from diverse materials, and are intended for micro-, nano- and ultrafiltration as well as for reverse osmosis. **Perfusion** and **sterile filtration,** but also the **membrane aeration** as well as all classic separation processes such as **micro-**, **ultra-**, **nano-** and **diafiltration**, belong to the typical applications of membrane filters.

Membrane pumps

are **pumps** based on the replacement principle. They are self-priming and the fluid is transported via the membrane. A piston or an eccentric screw behind the membrane is responsible for the movement and can control the size of the piston stroke and adapt the delivery to current process requirements. The single-use quattroflow pumps produced by the company Almatechnik Maschinenbau are based on four-piston membrane technology [45]. These single-use pumps can be easily exchanged as the whole pumping chamber is **disposable**.

Membrane valves

are **valves** that use a membrane to control closing and opening. The product or the medium is only in contact with the membrane surface. All mechanical parts lie outside of the media-moistened area. GEMÜ Gebr. Müller Apparatebau has developed the first single-use membrane valve (GEMÜ SUMONDO). A polypropyl valve body that is welded to the membrane und connected with the impellent forms the single-use component. The valve body is discarded after its separation from the impellent.

Micro-24 bioreactor system

produced by Pall Life Sciences holds a cassette with 24 reactors (with a **working volume** of between 3 mL and 7 mL) the mixing of which is achieved by a shaking plate. The pH value and the dissolved oxygen concentration in each bioreactor can be regulated. See **microbioreactors** and **orbitally shaken bioreactors**.

micro-Matrix

is an automated single-use microbioreactor system for **animal cell cultures** and microorganisms made by Applikon. Its key feature is the bioreactor system consisting of 24 bioreactors with a **working volume** of between 1 mL and 7 mL. See **microbioreactors** and **orbitally shaken bioreactors**.

Microbioreactors

have a **working volume** in the mililiter-scale and are recommended for **screening**. They work with single-use microwell plates and cassettes or rigid plastic vessels into which optical **sensors** (e.g. for the measurement of pH, temperature and dissolved oxygen) can be integrated. Microbioreactors are **mechanically driven** and are run either in **incubators** that control the gas input and the mechanical **energy input** [53, 54] or have their own measuring, control and monitoring unit. Examples for automated microbioreactors are the **ambr15 and ambr250** (Sartorius Stedim Biotech), the BioBLU 0.3-systems made by Eppendorf (see **CElliGen BLU bioreactors**), the **Micro-24 bioreactor system** (Pall Life Sciences), the **micro-Matrix** (Applikon) and the **Biolector** (mp2-labs).

Microcarriers

are carrier materials and are used for the cultivation of **adherent animal cells** and **stem cells.** Their carrier size is between 100-300 µm and their density is slightly higher than those of the cell culture medium.

Microfiltration

is the filtration at a separation cut-off > 0.1µm. See **filtrations** and **membrane filters**.

Mist bioreactors

are **hydraulically-driven** bioreactors for root cell cultures (see **plant cell cultures**). Their key feature is a **disposable bag** (single-use or multi-use) in which the roots are immobilized and aerated on a frame. A two-component jet or an ultrasonic atomizer befogs the culture medium which gets distributed around the supporting frame [15, 55]. The largest disposable mist-bioreactors are currently the 60 liter systems produced by former ROOTec. See **bioreactors**.

Mixing

of the content of mixers and bioreactor systems is an important characteristic [18]. Oxygenation, heat transfer and mass transfer are dependent on the mixing. The degree of intermixing is described with the parameter mixing time [19]. The “Single-use technology” division of **DECHEMA** prepared a recommendation on how to determine the mixing time in single-use bioreactors. See **bioreactors** and **bag mixing systems**.

Mixing systems

see **bag mixing systems**.

Mobius CellReady bioreactors

are stirred **bag bioreactors** for **animal cell cultures** produced by Merck Millipore. Versions exist for 3 L, 50 L, 200 L, 1 m^3 and 2 m^3. See **stirred bioreactors**.

Molding

is the enveloping of plastics and when related to bags, the manufacture of rigid or partly rigid components of a bag [33]. See **bag manufacture** and **tube-to-tube fittings**.

Monoclonal antibodies

are **antibodies** that were produced by a cell clone which is based on a B-lymhocyte and that address a single epitope (surface of an antigen to which the antibody binds specifically). See **biopharmaceuticals**.

Monolayer

is one single layer of cells. See **adherent animal cells**.

Multi-tray systems

are planar plastic shell systems for **adherent animal cells** [79]. See **CellFactory** and **CellSTACKs**.

Multilayer

are **films** made of several layers. A classic, three-layer multilayer for bags contains, for example, a contact layer that guarantees an inert surface, the layer for gas/steam barrier that inhibits the diffusion of gases and aerosols, and the outer layer that increases the stability of the material. A binding layer is included in between the three layers which holds the layers together by physio-chemical interaction. The contact layer must be weldable, flexible, chemically and mechanically resistant and may not emit **extractables** or **leachables**. See **bags** and **bag materials**.

Multipurpose facility

is a **production facility** which is constructed for several products.

MWCO

stands for molecular weight cut-off, and defines the minimal size of molecules that is held back by a membrane with 90 % certainty.

N

Nanofiltration

is the filtration with a separation cut-off of between 1 nm and 10 nm. See **membrane filters** and **virus filtration**.

O

Off-line analytics

is the analysis with a measurement device which is not directly connected to the production process.

On-line analytics

describes a continuous or automated analysis whereby the measuring devices are permanently connected to the production process. Generally, the sample is measured in a bypass where the time in which the product properties change needs to be longer than the time that is necessary for the measurement. See **in-line analysis**.

One step inoculation

is the direct inoculation of a **bag bioreactor** with cells that were frozen and stored over a long period of time in a **vial** with a high cell density (**HCD cell bank**) or in a **bag** with big volume (**LV cell bank**). For the production of **cell banks**, **perfusion** processes have proven their efficacy. Intermediate cultivation steps in a **spinner flask** or a **shake flask** (**Erlenmeyer flask**) are dispensable which leads to savings in both time and cost [22].

Orbitally shaken bioreactors

include non-instrumented systems (well plates, **TubeSpin bioreactors**, **shake flasks**) in milliliter scale, as well as automated **microbioreactors** (e.g. **Biolector**, **Micro-24 bioreactor system**) and **bag bioreactors** (**Current bioreactors**, **OrbShake bioreactors**) up to cubic meter scale. Like **wave-mixed bioreactors**, they are characterized by a more homogenous energy dissipation compared to **stirred bioreactors** for **animal cell cultures**. In addition, the antifoam agent can, in some cases, be omitted due to the negligible foam production which facilitates the **DSP**.

OrbShake bioreactors

are orbitally shaken, single-use bioreactors provided by Adolf Kühner for **animal cell cultures** and **plant cell cultures** with a **working volume** of between 1 L and 2500 L. See **orbitally shaken bioreactors**.

Oxygen input

is a limiting factor in aerobe cultivations (especially when aiming to **high cell densities**) [65]. Therefore, the oxygen input and the following transfer is of great importance when choosing suitable **bioreactors**, when optimizing processes and in the **scale-up** of processes. The bioprocess engineering parameter that is used for characterization is the **volumetric oxygen transfer coefficient**, also named **k_La-value**.

Oxygen sensors

in single-use **bioreactors** are generally based on the optical principle of oxygen quenching. The sensor is thereby illuminated with a filtered light source [20]. The dye (often an oxygen sensitive fluorophore) emits light that differs in wavelength, phase and intensity from the source and contains less energy. If oxygen is near the fluorophore, the oxygen molecule takes up the spare energy which results in a reduction of the fluorescence signal (quenching). A photo diode catches the emitting fluorescence and separates it from the radiated light with the help of dichroic mirrors [40]. The extent of the quenching is dependent on the concentration of oxygen. Ambient light and background noise can disturb the measuring signal of the optical oxygen sensors [66]. However, they can be used for small concentrations and allow measurements in very small volumes (less than 1 mL). See **sensors**.

P

PadMixer

is a series of single-use **mixing systems** (max. 1000 L) produced by the company Pall Life Sciences with integrated **tumble stirrers**.

PadReactor

is a series of single-use **bioreactors** (max. 1200 L) produced by the company Pall Life Sciences with integrated **tumble stirrers**.

Parenteral Drug Association (PDA)

is an organization with over 9500 members worldwide that was founded more than 70 years ago and supports the producers of **biopharmaceuticals**. In Autumn 2014, they published guidelines for support when using single-use systems called “technical report number 66 for the application of **single-use systems** in the pharmaceutical production”.

Perfusion

means cell or biomass retention, generally performed in continuous cultivation mode (see **continuous processes**). It is possible to work with dilution rates higher than the maximal specific growth rate. Thereby, up to 10-fold higher cell concentrations with higher product concentrations can be reached in a reduced working volume compared to **feeding** processes [42, 43]. Perfusion processes, however, are more complex in both implementation and admission.

Perfusion can be implemented externally with **single-use systems** (centrifuges, hollow-fiber modules, **TFF** cassettes, **ATF-modules**) in combination with single-use **stirred bioreactors** and **wave-mixed bioreactors**. In addition, an internal perfusion with **hollow-fiber bioreactors**, wave-mixed bioreactors with special perfusion bags (with integrated membranes), **fixed-bed bioreactors** with **macrocarriers** as well as single-use bioreactors with **microcarriers** can be run. See **crossflow filtration**.

Peristaltic pumps

are among the basic equipment of many laboratories and production facilities due to their comparably easy handling. They are classical, displacement pumps. The transport through the tube is achieved by outer mechanical deformation of the tube. As it is only the tube which is in contact with the product, batch or product chances can be carried out easily and with a reduced danger of **cross-contamination** [45, 59]. With peristaltic pumps, substances with a higher amount of solid particles or a high viscosity can be transported. Also, the dosage of small quantities is possible. However, the tube pinching causes shear forces as a consequence of the pulsatile transport. See **pumps**, **tubes**.

pH sensors

are designed as single-use versions and are based on the optical and potentiometric measuring principle [20]. The optical determination of pH can be based on fluorescence or absorption, whereby fluorescence-based dyes such as fluorescence derivates or absorbing substances like phenol red are applied. The dyes are pH sensitive and show a pH value-dependent fluorescence or absorption in the solution. The advantage of optical pH sensors lies in their miniaturizability. However, the dyes can lose their sensitivity and are applicable only in a limited pH range of around 3 units. Potentiometric pH sensors measure the potentiometric deviation between the working and the reference electrode [41]. They are also miniaturizable. Today, it is not yet possible to achieve comparably exact measurements as with conventional pH probes [62]. See **sensors**, **instrumentation**.

Plant cell culture

are used for the commercial production of therapeutic proteins (ELELYSO) and secondary metabolite-based bioactive compounds for the pharmaceutical and cosmetic industry [15]. Especially plant **suspension cells** are used whose growth corresponds with an increase of culture broth viscosity. In research and semi-commercial productions, root cultures are utilized additionally. See **illumination**.

Pneumatically driven

describes the **energy input** by direct gassing with the help of an **aeration system** (**sparger**) [20, 61, 62]. See **airlift bioreactors**, **bubble column bioreactors**.

POD facility platform

is a single-use production concept for **biopharmaceuticals** produced by G-CON Manufacturing. The concept is based on preassembled **cGMP**-compliant autonomous clean rooms (clean room container) which can be coupled according the production flow, the functionality and the space requirement. See **flexible single-use biomanufacturing**, **production facilities** and **process platforms**.

Powder transfer bag system

is a gamma-sterilized bag for solid substances such as powder. The bag is equipped with an aseptic transfer system and is available with a maximum volume of 100 L [46]. See **bags**, **gamma-sterilization**.

Power input

see **energy input**.

Pressure resistance

describes the maximum pressure load, which lies between 50 and 60 mbar for **bags**.

Process platforms

are a sequence of systems forming a process line [7]. Single-use process platforms for media production, fermentation, biomass separation, virus separation (**virus removal**) and **virus inactivation** and the **formulation and filling** are available from the market leaders of **single-use systems** (GE Healthcare, Pall Life Sciences, Merck Millipore, Sartorius Stedim Biotech, ThermoScientific).

Product purification

see **DSP**.

Production facilities

for **biopharmaceuticals** are made completely out of stainless steel or exist as **hybrid** and as single-use types. Hybrid production facilities contain single-use systems combined with reusable systems from glass or stainless steel. They are the state-of-the-art.

Single-use production facilities in general are production facilities in which the substance conversion, transport and storage of feedstock material, intermediate and final products take place mainly or completely in **single-use systems**. Such single-use production facilities can be divided into single-use production facilities of the closed type or single-use production facilities operating in stations.

In single-use production facilities of the closed type, the individual single-use systems are pre-fabricated and coupled in the order of processing steps. The raw material, intermediate and final products are transported from one single-use system to the next by free flow or pressure. Such production facilities are currently limited to simple technologies and small volumes.

In single-use production facilities operating in stations, the raw material, intermediate and final products are transported from one processing step to the next in single-use systems. This requires single-use **process platforms**, transportable, single-use containers (**container systems**), the logistics to identify and operate the systems, the sterile coupling of the systems with each other and with other single-use systems, as well as the technology to maintain the mixing state and the reaction conditions in the containers.

There is a current trend for production facilities where the **USP** is completely performed in single-use systems (e.g. the 2000-L system from Shire in Lexington, Massachusetts). These production facilities allow a station operation where raw material, intermediate and final products are transported from one processing step to the next via mobile containers. Single-use production facilities, like the one produced by Wuxi PharmaTech in Shanghai that exclusively work with single-use systems, are still rare (10 %). See **ballroom concept**.

Pumps

that are counted among the single-use versions include **peristaltic pumps**, **membrane pumps**, syringe pumps for dosages and **centrifugal pumps**.

Purification

see **DSP**.

Q

Quality by Design (QbD)

describes a quality principle of the international conference on harmonization through which the quality of a biopharmaceutical process is ensured. Thereby, the design of the production process serves as basis for a consistent, high-quality and secure product and a meaningful construction of the production process is aspired to [63].

Quantum Cell Expansion Bioreactor

is a hollow-fiber bioreactor distributed by Terumo BCD with a maximal growth surface of 2.1 m^2 for **adherent animal cells** and human cells such as **T-cells** and **stem cells**. See **hollow-fiber bioreactors** and **hydraulically driven**.

R

ReadyToProcess WAVE

is a wave-mixed bioreactor for **animal cell cultures** and **plant cell cultures** from GE Healthcare. Its **working volume** ranges between 200 mL and 25 L.

Repeated fed-batch processes

are a special type of the **fed-batch processes**. Here, the culture medium is exchanged uniquely or periodically (semi-continuous process), whereby a part of the culture medium is retained to serve as inoculum for a new process.

RFID technology

is the contact-free radio-frequency identification. It allows the automatic tracing of **single-use systems** in a **GMP** process via RFID-chips (also called RFID-tags) [64].

Roller bottles

belong to the oldest **single-use systems** and are used for productions with **adherent animal cells** (maximum growth surface of 4250 cm^2). As a consequence of their slow rotation in a tray, the whole surface of the bottle is moisturized [1].

S

Sandbox

describes an isolated area in which every realized procedure has no influence on the surrounding area.

Scale-up

describes the increase of the **working volume** in a biotechnological production. The scale-up is often conducted empirically according to the “trial and error” principle, which is both very time and labor-intensive. Quantitative models and similarity laws can improve the scale-up. This includes, for example, identical height and diameter proportions, an identical specific **energy input** or the same **volumetric oxygen transfer coefficient**, or an identical stirrer **tip speed** in **bioreactors** of different sizes.

Screening

describes a selection process which serves the evaluation of high performance production cell lines, drug candidates, optimal bioprocess parameters or the optimal media composition. With the development of the single-use technology, instrumented cultivation systems in the milliliter-scale were brought to the market with the idea of saving time. Beside automated **microbioreactors**, multiwell plates equipped with optical pH and oxygen sensors, **shake flasks**, **T-flasks** and **TubeSpin bioreactors** entered the market. The **sensors** (e.g. those produced by PreSens) are, in the latter case, spots glued to the inner surface of the transparent cultivation container and connected to a transmitter (which takes up the measuring signal and transfers it to the issuing point).

Sensors

monitor processes. It is possible to couple reusable sensors via **aseptic connectors** or to use already integrated single-use sensors [68]. The latter can be used, for example, for measuring the dissolved oxygen concentration (see **oxygen sensors**), the carbon dioxide concentration (see **carbon dioxide sensors**), the pH-value (see **pH sensors**), the pressure, the flow rate, the conductivity (See **conductivity sensors**), as well as the concentration of substrates, metabolites or biomass [20].

Shake flasks

are **orbitally shaken bioreactors**. Single-use versions often consist of polycarbonate and polyethylene terephthalate and are preferably not instrumented for maintenance cultures, the **inoculum production** and **screening** of microorganisms, **plant cell cultures** and **animal cell cultures** with a total volume of up to 3 L. See **Erlenmeyer flasks**.

Single-use systems

is equipment the parts of which are in contact with cell, media or product are typically made of plastic material and are determined for one single usage. Three categories of single-use systems can be differentiated: (1) systems for daily labor use (e.g. syringes and pipettes), (2) simple peripheral elements (**bags**, **connectors**) and (3) equipment for bioprocess unit operations and process platforms (e.g. **bioreactors**, **pumps**, **mixing systems**).

Slug bubble bioreactors

are disposable **airlift bioreactors** that Nestlé-scientists developed for the cultivation of plant cell cultures with **working volumes** up to 100 L. By varying the air inlet pressure, and the valve opening time the formation of bubbles, so-called slug bubbles, can be controlled [1, 20]. The slug bubbles are formed on the reactor bottom and rise to the head space.

Smart sensor

is a complex sensor in miniature format where the registration of the measure, signal preparation and processing is combined in one case.

Spargers

are **aeration systems** and an important element in bioreactors for aerobe processes. Most frequently, ring

spargers are applied [4, 56] that display macrospargers. They generate large bubbles and once these burst this causes high shear forces, bringing with it the danger of cell damage.

Alternatively, microsparger can be used, the smaller bubbles of which cause less shear stress, but whose formation is accompanied by a generation of a stable, hardly opposable foam layer.

Spinner flasks

were the golden standard for the propagation of suspension cells of animal origin (see **inoculum production**) [1, 69, 70]. The user can rely on versions of different manufacturers with integrated magnetic stirrer. Single-use versions exist up to a volume of 3 L.

Spray bioreactors

are **hydraulically-driven** bioreactors for root cultures (see **plant cell cultures**). In contrast to the **mist bioreactors**, the medium is distributed in liquid form (instead of mist).

Static cultivation systems

are cultivation systems in which the substance and energy transfer takes place solely through diffusion, which leads to lower cell densities and product titers compared to the dynamic opponents (see **dynamic bioreactors and mixing systems**). Single-use versions are the **CELLine**, the **CellFactory**, **CellSTACKs** and **T-flasks** [20].

Steam in place (SIP) connectors

are connectors that are used for the connection of single-use systems with reusable systems. They can be sterilized with steam and allow the formation of a sterile connection (see **aseptic connections**) up to the sterile barrier.

Stem cells

are cells that renew themselves and that can develop into one or several types of differentiated cells. They replicate on their own, divide themselves asymmetrically and have a high proliferation and differentiation potential [71]. Besides embryonal stem cells, induced pluripotent stem cells and mesenchymal stem cells (mainly from adipose tissue, bone marrow and umbilical cord) are worked with [18]. They are, among others, used for the development and production of **cell therapeutics**.

Sterile filtration

is applied for liquids or gases. A filter with a pore size of 0.1 µm or 0.2 µm is used, which holds back contaminants such as bacteria or yeast (excluding viruses) and which is determined for one single usage [6, 72].

Sterilization In Place (SIP)

is the sterilization of a production facility in place without the need to disassemble of the construction or parts of it.

Stirred bioreactors

are **mechanically-driven** bioreactors that are most frequently used in biotechnological production processes and regarded to be the most reviewed bioreactor. Single-use versions are available to a **working volume** of 2 m^3.

Storage and transport systems

serve the storage and transport of substances (raw materials, culture media, buffer solutions, intermediate and end products) in fluid or frozen state (rarely powders). The storage as liquid has the disadvantage that proteins can aggregate or oxidation can cause spontaneous reactions during containment (e.g. bag). When stored in a frozen state, aggregation and oxidation is decelerated and the risk of product loss is reduced. The single-use system and its instrumentation which are used for storage and transport systems depend on the type and the amount of the substance and its necessary requirements [46, 49]. See **bags**, **bag handling systems** and **container-systems**.

Surface aeration

is a type of aeration without active sparging whereby the gas input is realized only through the surface of the liquid (interface between head space and liquid). Gas transfer as well as the **scale-up** are hereby limited [4, 56].

Suspension cells

are free cells which are cultivated swimming in suspension [73]. They rarely grow as single cells, in fact, they rather form multi-cellular aggregates. Suspension cells of plant, animal or human origin are also referred to as suspension cell cultures. See **plant cell cultures** and **animal cell cultures**.

T

T-cells

or T-lymphocytes belong to the white blood cells. They support the immune defence and are used either in a non-genetically modified form or in a genetically-modified (CAR-T-cells) for novel cell therapies. T-cells can be expanded using **hollow-fiber bioreactors**, **stirred bioreactors** and **wave-mixed bioreactors**. See **cell therapeutics**.

T-flasks

are static, stackable plastic bottles for **animal cell cultures**. Their planar growth surface lies between 25 and 300 cm^2. The **oxygen input** is achieved via diffusion and a sterile filter in the lid or through the not completely closed bottle with lids without filters (**surface aeration**) [12]. T-flasks serve the maintenance cultivation of cells in the laboratory and are generally not used with **instrumentation**.

Tangential flow filtration (TFF)

see **ATF-modules** and **Crossflow filtration**.

Tank Liner

is an open bag for cylindrical plastic containers. In most cases, it is not sterilized and only serves to physically separate bag content and container. Typical applications for tank liners are the open mixing as, for example, when preparing media or buffer and when formulating remedies if a large amount of solid substances needs to be added or dissolved. See **bags**.

Temperature shift

is a decrease in temperature to values of between 28 °C and 35 °C which is executed in the production of many **antibodies** after reaching the desired cell density. This protracts the apoptosis (programmed cell death) and allows an increase in the antibody production of 50 % to 200 %. While the shift between temperatures of 30 °C to 35 °C is realised in the middle of the logarithmic growth phase, shifts to lower

temperatures are generally conducted in the initial stationary growth phase. See **fed-batch processes**.

Thaw

see **freeze and thaw**.

Tip speed

is the stirrer velocity. It is measured in m s^{-1} and is calculated from the product of Pi, the stirrer diameter and the stirrer rotation speed. See **scale-up**.

Tri clamp connections

are (single-use or reusable) clamp-connections that are often used in the pharmaceutical field. They consist of two identical clamp-stubs, the clamp-sealing and the clamp-bracket with the wing nut. See **aseptic connections**.

Tube material

in biopharmaceutical productions needs to meet specific requirements. It must be resistant to heat and chemicals and possess suitable characteristics concerning elasticity, abrasiveness, gas permeability, color, density, mechanical stability, light sensitivity and rigidity. At the present time, five different tube materials are available: 1) thermoplastic elastomers (low cleavability, high weldability, low gas permeability) 2) platin-hardened silicon (flexible, temperature resistant, no leachables, low-priced) 3) peroxide-hardened silicon (good biocompatibility, no leachables) 4) modified polyolefin (high purity, chemical resistance, high pressure resistance) and 5) modified polyvinyl chloride (broad chemical resistance and enduring flexibility). The thermoplastic elastomers are preferred for biopharmaceutical productions [67].

Tube sealing machines

are so-called Bio- or Tube Sealers and serve the aseptic sealing of thermoplastic tubes. After the **tubes** are sealed by heat and pressure, the aseptic disconnection can take place (e.g. of a bag unit, see **aseptic disconnections**). An aseptic surrounding is not necessary [1].

Tube to tube fittings

allow inseparable connections to be established between individual components of a transfer line. They are available in a variety of geometries and diameters.

Tube welding machines

are used to connect two thermoplastic **tubes** of the same diameter without the use of **aseptic connectors** (see **aseptic connections** and **aseptic welding**). First, the tubes are placed parallel, in opposite directions in the provided holder, fixed, and pressed together while a preheated and defined blade, depending on the tube quality, cuts the tubes. After the cutting, the cut tubes are sealed at the blade. After a cooling phase, the two tube endings are aseptically connected. The whole welding process takes between 1 and 4 minutes depending on the **tube material** and tube diameter [67].

Tubes

are used to transport substances instead of permanently installed pipe systems. As the tubes are in direct contact with the biopharmaceutical product, high demands on their biocompatibility are made [67]. See **tube material**.

TubeSpin bioreactors

are orbitally shaken centrifugation tubes with a gas permeable polytetrafluorethylene filter in the lid. They

were developed for the **screening** of **suspension cells**. Three sizes are available (e.g. from TPP): the TubeSpin 15, 50 and 600 bioreactor. The maximum **working volume** is 400 mL. See **orbitally shaken bioreactors** and **surface aeration**.

Tumble stirrers

are stirrers with tumbling (overlay of two circular movements) instead of the common rotating stirrer movement in stirred bioreactors. Pall Life Sciences has included single-use **mixing systems** and **bioreactors** in their portfolio, with the **PadMixer**s and the **PadReactor**s consisting of a cubical bag with integrated tumbling stirrers. The design of the stirrer in the form of a paddle allows them to be equipped with additional **spargers** (see **aeration system**) [74].

Two-compartment systems

are non-instrumented, single-use **bioreactors** such as the **CELLine** that consist of a medium storage (compartment 1) and the production area as well as the production compartment (compartment 2). The cultivation chamber is separated from the medium storage by a semi-permeable membrane. The membrane (dialysis membrane) allows molecules and substrates to diffuse from the medium to the cells in the production compartment.

U

Ultrafiltration

is the filtration with a separation boarder of > 0.01 µm. See **filtrations** and **membrane filters**.

UniVessel SU

is a stirred, single-use benchtop bioreactor with a rigid plastic container (0.6 L to 2 L **working volume**). It was successfully applied for the cultivation of **animal cell cultures** but also of **plant cell cultures** and human cells (e.g. **stem cells**). See **stirred bioreactors**.

USP

is the upstream processing within a biotechnological production process. The media production, the **inoculum production** and the bioproduction in the bioreactor itself belong to the USP.

V

Vaccines

are produced more and more often in **single-use systems** [18]. Roller flasks (see **Roller bottles**) and **CellFactories** (see **CellSTACKs**, **multi-tray systems**) have been replaced by wave-mixed and stirred bag bioreactors in recent years [36, 37]. See **biopharmaceuticals**, **wave-mixed bioreactors**, **stirred bioreactors**.

Valves

distribute and dose liquids, steam and aerosols. See **membrane valves**.

Vertical wheel bioreactors

are single-use **bioreactors** produced by PBS Biotech. Central piece of these systems is a vertically integrated wheel in a U-shaped cultivation chamber, which is either driven magnetically or pneumatically (see **pneumatically driven**). The magnetically driven series was developed for applications with shear-sensitive cells and **microcarriers** (e.g. **stem cells**) in a **working volume** of between 20 mL and 15 L. The pneumatically-driven version is scalable between working volumes of 600 mL and 500 L and is recommended for **animal cell cultures**.

Vials

are plastic tubes (**working volume** of 1 mL to 10 mL) that are used for the **cryoconservation** of **animal cell cultures**. They are seen as a standard system for the establishment of **cell banks**.

Vibromixer

are mixers (**mechanically-driven**) where the mixing is accomplished by perforated disks that are fixed to a vertically oscillating shaft. A single-use version is the Saltus marketed by Meissner.

Virus adsorption

is a method of **virus removal** that uses chromatographic methods. See **membrane chromatography**.

Virus filtration

is a method used in **virus removal** to effectively remove small and non-enveloped virus (size exclusion). 20-nm filters have proven to be efficient [78]. See **nano filtration**.

Virus inactivation

is a method of **virus removal** where a virus is inactivated with solvents, detergents, a low pH or UVC radiation. A disadvantage of this method lies in the partly incomplete inactivation of small, non-enveloped viruses. In addition, the procedures are generally dependent on the time or the temperature. The UVC-inactivation works with radiation of a low dose of 254 nm, which penetrates the virus and in smaller viruses irreversibly damages DNA and RNA [76]. Commercially available, **single-use systems** are based on the pH inactivation [78].

Virus removal

is a part of the **DSP** as the risk of virus contamination is present in all biotechnological products from animal cells. A contamination with viruses is possible via the production cells or the medium (that can get into the cells and the product). Three methods of virus removal are possible with applicable single-use technologies: (1) the **virus inactivation**, (2) the **virus adsorption** and (3) the **virus filtration** [75, 76, 77].

Volumetric oxygen transfer coefficient

is a measure for the efficiency of the oxygen input or the oxygen transport from the gas to the liquid phase, and is also referred to as k_La-value. The parameter is generally influenced by the bioreactor geometry, its impellent and the aeration system, as well as the characteristics of the culture broth. See **k_La-value** and **oxygen input**.

W

Wave and undertow bioreactors

are **disposable bag bioreactors** from Nestlé that are exclusively designed for **plant cell cultures** with a **working volume** of up to 100 L. They are dedicated to the **wave-mixed bioreactors**. The bag filled with the cells and the medium is fixed onto a horizontal platform, one or two ends of which are flexible. Through a periodical up and down-movement of one or two ends of the platform, a wave is induced in the bag, which is responsible for the mixing in the bubble-free surface aeration (see **surface aeration**) [5].

Wave bioreactor-system

from GE Healthcare is a representative of the **wave-mixed bioreactors**. With a **working volume** of between 0.2 L and 500 L, it is suitable for preferably the cultivation of **animal cell cultures** and **plant cell cultures**.

Wave-mixed bioreactors

are **mechanically-driven** bioreactors. As a consequence of the rocker movement with the **bag(s)** that contains the medium and the cells, a wave is induced. The **energy input** is highest with the minimal **working volume**, maximum angle and maximum rocking rate. Through the permanent renewal of the medium surface in the bubble-free surface aeration (see **surface aeration**), the foam formation is negligible. The largest wave-mixed bioreactors (see **wave bioreactor system**) have a bag volume of 1000 L which corresponds with a working volume of 500 L.

Working volume (bioreactor)

characterizes the usable volume of a bioreactor. It generally calculates at 50 % of the total reactor volume for **wave-mixed bioreactors** and at approx. 75 % for stirred single-use bioreactors (see **stirred bioreactors**) [10].

X

Xcellerex XDR bioreactors

is a single-use series of stirred **bag bioreactors** produced by the company GE Healthcare with **working volumes** of between 4.5 L and 2000 L. These reactors are suitable for the cultivation of **animal cell cultures**. See **stirred bioreactors**.

Xcellerex XDR MO fermentors

is a single-use series of stirred **bag bioreactors** produced by the company GE Healthcare (**working volumes** of between 10 L and 500 L) for microorganisms. See **stirred bioreactors**.

XD-technology

is a **concentrated fed-batch process** that was patented by DSM Biologics and allows **antibody** concentrations in mammalian cells of 27 g L^{-1} at most to be reached. See **ATF modules**.

Xpansion multiplate bioreactor

is the single-use version of a **hydraulically-driven** parallel plate bioreactor (maximum growth surface of 12.2 m^2) for **adherent animal cells** and human cells from Pall Life Sciences.

Xuri Cellbag bioreactors

are **wave-mixed bioreactors** produced by GE Healthcare developed for the cultivation of human cells (**T-cells** and **stem cells**). The **working volume** ranges between 200 mL and 25 L.

Z

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DECHEMA Gesellschaft für Chemische Technik und Biotechnologie e.V.

Executive Director: Dr. Andreas Förster
Chairman: Dr. Klaus Schäfer

Theodor-Heuss-Allee 25
60486 Frankfurt am Main
Germany

Tel: +49 69 7564 -0
info@dechema.de

Association Register no.: VR 5293 (local court of Frankfurt am Main)
VAT Reg No.: DE 114234833