Single-Use Systems
A new Age of Drug Making

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PDA
Parenteral Drug Association

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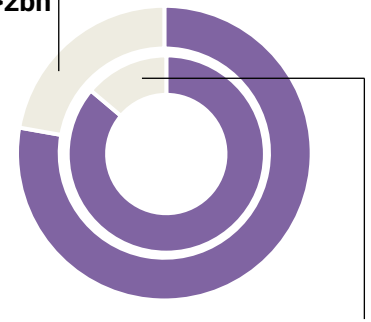
Trends on the Target Markets

Growing and aging population[1]
9 billion people by 2050

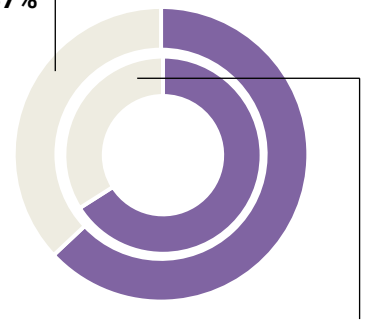
World population over age 60 in 2050
>2bn



World population over 60 in 2021
~1bn

Biologics are gaining importance[2]

Sales share of biologics in 2026
~37%

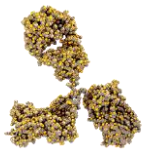


Sales share of biologics in 2021
~34%

~10% CAGR
for the biopharma market
in 2021–2026

1 United Nations: World Population Prospects, 2019 2 Evaluate Pharma: World Preview 2021, Outlook to 2026, July 2021

What are Biopharmaceuticals?

	Active agent	Manufacturing	Administration
Chemical drugs			
	Small molecules	Chemical synthesis	Mainly oral
Biopharmaceuticals			
	Large molecules > 20,000 atoms	Cell culture processes with living cells	Mainly intravenous

“Old” Biopharmaceuticals

- blood & plasma derivatives
- vaccines
- recombinant proteins (*e.g.* insulin)
- mAbs (monoclonal antibodies)
- ADCs (antibody drug conjugates)

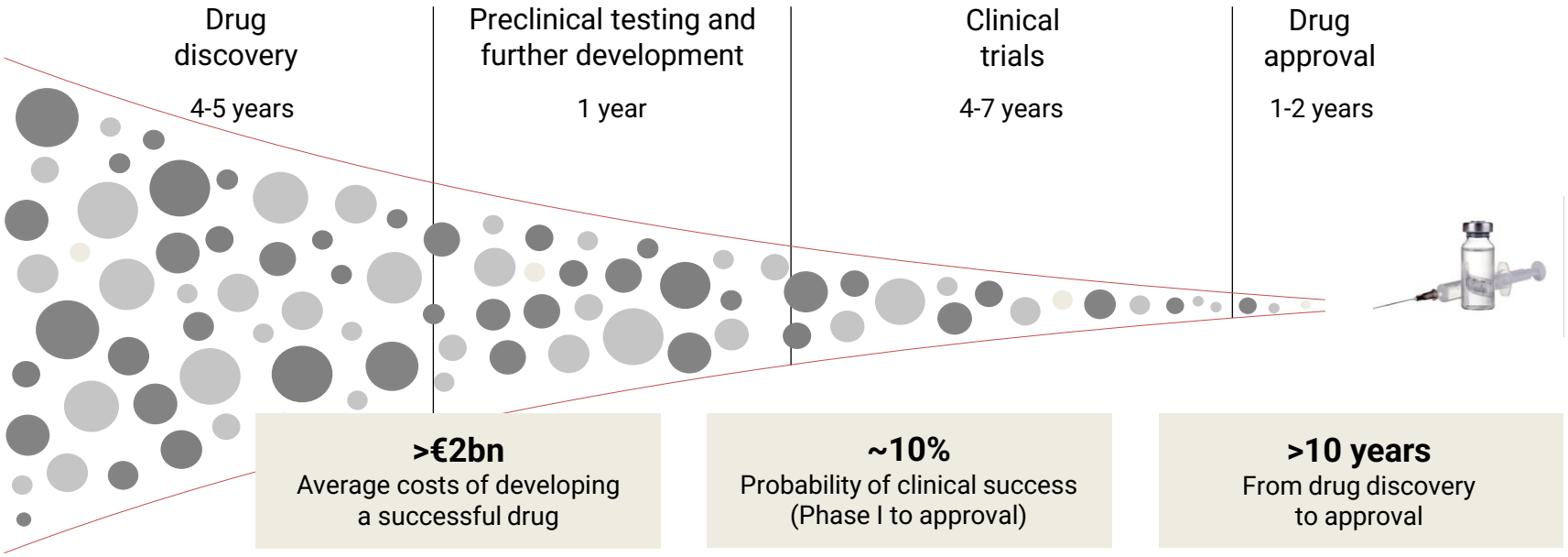
“New” Biopharmaceuticals

- antibody fragments (*e.g.* nanobodies)
- fusion proteins
- cell therapy (*e.g.* stem cells, CAR-T cells)
- viral gene therapy
- tissue engineering

Characteristic of Biopharmaceuticals

- Production inside living cells
- Complex cell cultivation
- High risk of product ‘damages’, e.g. genetic mutations, incorrect post-translational modifications
- oxidation of product, heat or shear force damages
- Very complex downstream processing,
- e.g. difficult final sterilisation (possible only via filtration, not via heating)
- Due to molecular complexity, biopharmaceuticals are usually
- rather fragile (hence injection, not oral take-up)
- Administration via injection / infusion => buffer composition and
- absence of particles are extremely critical topics

Only one out of 10,000 New Drug Candidates reaches the Market



Schematic example of biologic drug discovery with data from the Association of the British Pharmaceutical Industry

Advantages and Challenges

Advantages

- First-time or improved treatment of serious illnesses, such as cancer, multiple sclerosis, rheumatism
- Targeted attack on diseased cells
  - → fewer side effects
  - → High efficiency
- New vaccines

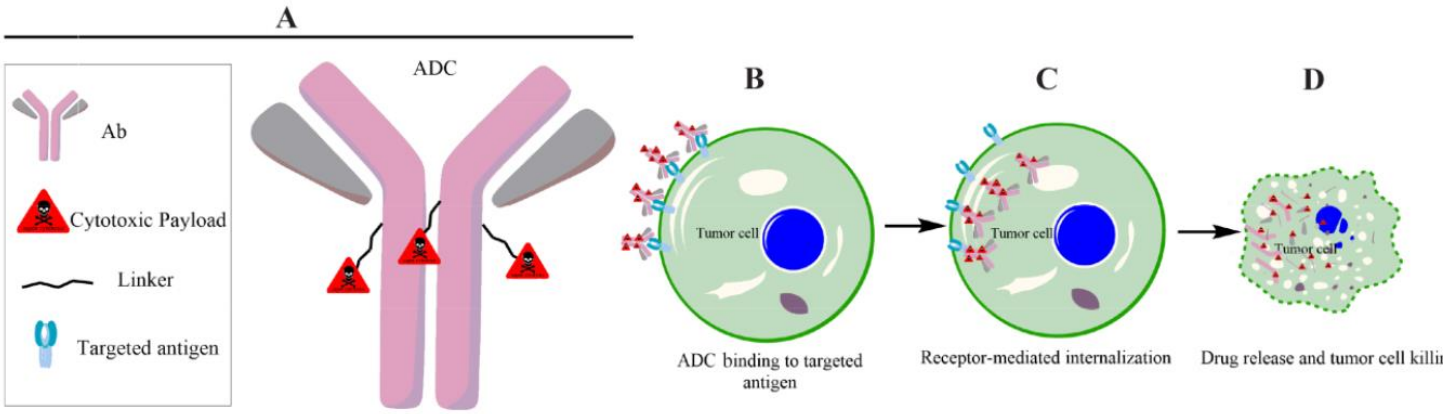
Challenges

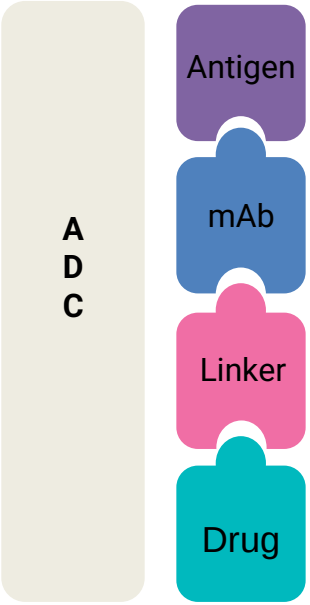
- Difficult and complex analysis
- R&D and production very costly
- High in-production contamination risks
- Can be harmful when released (*e.g.* toxin)
- Treatment costs can be extremely high

The Development and Manufacture of Biopharmaceuticals are complex

Antibody Drug Conjugates (ADCs)

ADCs are new class of highly potent biopharmaceutical drugs composed of a cytotoxic drug conjugated covalently to a monoclonal antibody (mAb) by a linker.





ADC binds to tumor target cell surface antigens leading to trigger a specific receptor mediated internalization (c). The internalized ADCs are decomposed to release cytotoxic payloads inside the tumor cell either through its linkage/linker sensitivity to protease, acidic, reductive agents or by lysosomal process, leading to cell death

ADC Process Development

Considerations

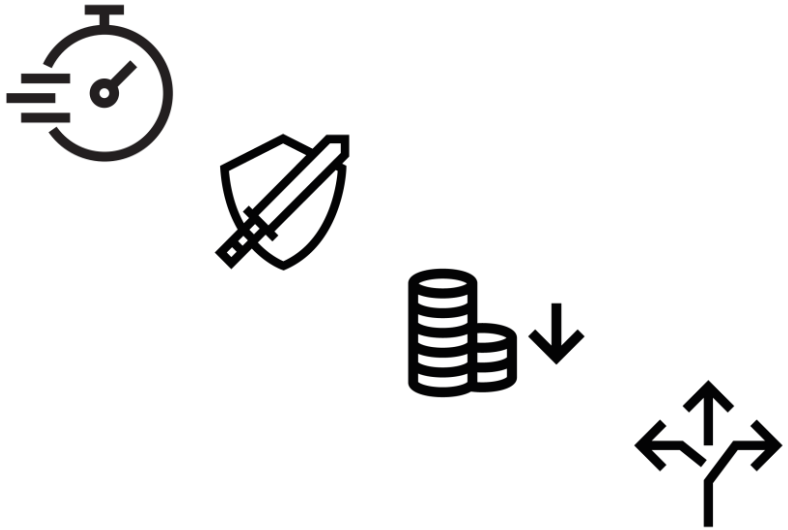
- Safety
- Processing time
- Costs of goods
- Process control
- Batch size
- Volume limitations
- Purification strategies
- Equipment chemical compatibility
- Cleaning validation
- Contaminated waste
- Cross contaminations

Solution = Single-Use (SU) Manufacturing ??

Why Single-Use?

Over the past ~15 years, the market of single-use technologies in biopharmaceutical production processes showed a growth of >15% per year. This growth is forecasted to remain stable through 2025*. Main reasons:

- New ways of treatment: e.g. regenerative medicine instead of chemical drugs
- Personalized medicine instead of blockbusters: large variety of products in small quantities
- Several advantages, e.g.
  - Time Saving
  - Eliminate cleaning validation
  - Cross contamination control
  - Reduced capital investment
  - Increased flexibility
  - Improved productivity
  - Reduced utilities



THE BENEFITS OF SINGLE-USE

SU equipment ranges from simple, single-material items such as a tubing through to complex controlled systems incorporating many components and materials, such as bioreactors. As a rule, many of the more complicated SU systems contain reusable non-product-contact elements.

The benefits of deploying SU technologies in biomanufacturing include reduced contamination risks; quicker time to market; simplicity of use; lower preliminary investment in facility; reduced operator requirement; more rapid processing speed, efficiency and flexibility. Increased competition from biosimilars and other follow-on biologics is forcing established manufacturers to find or develop and integrate new manufacturing technologies to stay competitive and conserve their market share. Single-use technologies and continuous upstream processes have proven to be cost-efficient options to increase biomass production.

EudraLex, Vol. 4, Part I, Chapter 5.9: GMP Production (2014)

"Operations on different products should not be carried out (...) in the same room unless there is no risk of mix-up or cross-contamination."

EudraLex, Vol. 4, Part I, Chapter 5.21: GMP Production (2014)

"Technical (...) measures (...) to control risks for cross-contamination (...) could include (....) use of single-use disposable technologies"

The Future of BioManufacturing: Disposable Single-Use Technologies – Evolution Search Partners (evolutionexec.com)

Challenges in SU Processes

- Concerns regarding
  - Quality of single-use components and assemblies: product loss and/or risk to operator due to leakages
  - Extractables / Leachables: which substances can / will get into the product?
  - Greatest possible safety regarding delivery and changes in the raw materials (change control, supply chain)
  - Integrity tests – performed at the manufacturer / at the user site
  - Automation
  - Project lead time
  - Standardization vs customization

CHALLENGES & CONCERNS

The reasons for employing SU technologies in biomanufacturing are persuasive, however there are several challenges and concerns related to their use. Firstly, SUs can significantly increase the ongoing operating costs related to the buying and disposal of consumables. Secondly, there are concerns with leachable and extractable substances arising from product contact surfaces, which may increase the risk of contamination.

An additional challenge is the fact that there are product sourcing limitations associated with purchases of single-use equipment. In Biopharmaceutical manufacturing, it is desirable to have several vendors that offer comparable offerings/services in order to mitigate the risks of supply issues with a single vendor impacting on end product manufacture. Given that there are as yet no consistent and uniform standards of quality, installation and use, there is a risk that such challenges could impact production.

The Future of BioManufacturing: Disposable Single-Use Technologies – Evolution Search Partners (evolutionexec.com)

Single-Use Processes

- Success of SU products through:
  - Optimal product quality – robustness and ease of use
  - Documentation, validation and training of the operators
  - Standardization: connectors, materials, configurations
  - Clear and independent guidelines

- Business drivers for the adoption of SU systems:
  - **Capital design** – investment costs, floor space requirements, validation costs, etc.
  - **Operating costs** – Labor costs, energy costs, run costs, loss costs, maintenance, etc.
  - **Drug development and process assessment** – time to market, no. of batches & products
  - **Time** – construction time, processing time, change-over time, assembling time, etc.
  - **Green manufacturing** – waste generation & treatment, resources, etc.
  - **Value-added activities** – cost of quality, cost of failure, outsourcing activities, etc.

Singe-use products in the manufacturing of biopharmaceuticals, PDA Technical Report No. 66 (2014)

Increased implementation of single-use products

CONCLUSION

Despite these risks, biopharmaceutical manufacturers ranging from small start-up companies to large product sponsors and CMOs are increasingly implementing disposables. Ultimately it is still unclear whether there will ever be a completely 100% standalone SU-only biomanufacturing facility, or if future biomanufacturing facilities will be of a hybrid nature. Certainly, there is a strong case for 100% SU adoption in situations where the production capabilities are associated with multi-product, small-volume facilities which could also be a satellite of a larger plant location. An exception to this may be Vaccines where rapid market scale quantities have been demonstrated.

As companies strive to remain competitive in a global market, strategic implementation of single-use technologies has the potential to increase flexibility and overall output, decrease manufacturing costs, reduce facility footprint and inventory and supply chain issues faced by the pharmaceutical industry today. The proliferation, diversification and uptake of disposable technologies by biomanufacturing factories will play a vital role in enabling the manufacturing of affordable biologics as the industry adapts to the rise of biologic drug development.

The Future of BioManufacturing: Disposable Single-Use Technologies – Evolution Search Partners (evolutionexec.com)

Correct handling as factor to success

- Education of the operator
- Data integrity
- Etc.

PDA technical report 66 (2014), Chapter 7.6
Application of Single-use Systems in Pharmaceutical Manufacturing

"Training is a GMP requirement and an integral part of SUS technical implementation"

"Factors that may contribute to the leakage of bags are:

- Poor handling during deployment
- Mechanical stress on films and welds
- Accidental puncture or stressing of the SUS during handling and setup

SUS – A new Age of Drug Making Course Content

SUS + GMP = SOS ??

Single-Use Systems
- Manufacturing of consumables
- Smart wetware design
- General applications (mixing, filtration, storage, dis/connections)
- Integrity tests
- Handling of consumables
- Working under GMP regulation

Good Manufacturing Practice
- Regulative situation: rules & recommendations
- External Requirements
- Data monitoring and evalutation
- Data integrity
- Data analysis
- Fault handling

Agenda* – Day 1 (June 14th, 2022)

Time	Duration	Trainer	Topic
08:30 – 09:00 am	30 min	ALL	Introduction
09:00 – 09:45 am	45 min	Ulrike Stollberg	Introduction to SU Bioprocessing
09:45 – 10:30 am	45 min	Dominic Perry	GMP Update on SUS (part I)
10:30 – 10:45 am	15 min	ALL	BREAK
10:45 – 11:15 am	45 min	Dominic Perry	GMP Update on SUS (part II)
11:15 – 12:15 pm	60 min	Dominic Perry	Hands-on Exercise I (Gowning)
12:15 – 01:15 pm	60 min	ALL	LUNCH
01:15 – 02:00 pm	45 min	Tanja Sedlacek	Basics in single-use bioprocessing focus on bags
02:00 – 02:15 pm	15 min	ALL	BREAK
02:15 – 04:15 pm	15 min	Tanja Sedlacek Ulrike Stollberg	Hand-on exercise 2 (bag types and workshop connection/disconnection)
04:15 – 04:30 pm	15 min	ALL	BREAK
04:30 – 05:00 pm	30 min	ALL	Wrap-UP
06:30 pm		ALL	Dinner ☺

*subject to change

Agenda* – Day 2 (June 15th, 2022)

Time	Duration	Trainer	Topic
08:30 – 09:15 am	30 min	Andreas Prediger	Sensors and Automation in single-use systems: Overview and demonstration
09:15 – 10:15 am	60 min	Tanja Sedlacek Ulrike Stollberg	Hands-On Exercise III Outcome/presentation workshop connection / disconnection
10:15 – 10:30 am	15 min	ALL	BREAK
10:30 – 11:30 am	60 min	Dominic Perry	Data integrity, Data Analysis and Monitoring
11:30 – 12:15 pm	45 min	ALL	LUNCH
12:15 – 13:00 pm	45 min	Mathias Siebner	Filtration & CCT
13:00 – 02:00 pm	60 min	Mathias Siebner	Hands-on Exercise IV (Filter Integrity Testing)
02:00 – 02:15 pm	15 min	ALL	BREAK
02:15 – 02:45 pm	30 min	Dominic Perry	Filter Integrity Testing fault handling – GMP view
02:45 – 03:30 pm	45 min	Dominic Perry Mathias Siebner	Hands-on Exercise V (GMP practical session, failed filter IT)
03:30 – 03:45 pm	15 min	ALL	BREAK
03:45 – 04:15 pm	30 min	Khaled Khalili	Data Recording & Evaluation
04:15 – 04:30 pm	15 min	ALL	Wrap-Up + End of Course

*subject to change

Enjoy this course and have fun ☺