



# Einwegbioreaktoren in der biopharmazeutischen Industrie

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# Topics



1. Single Use technology in biopharma processing

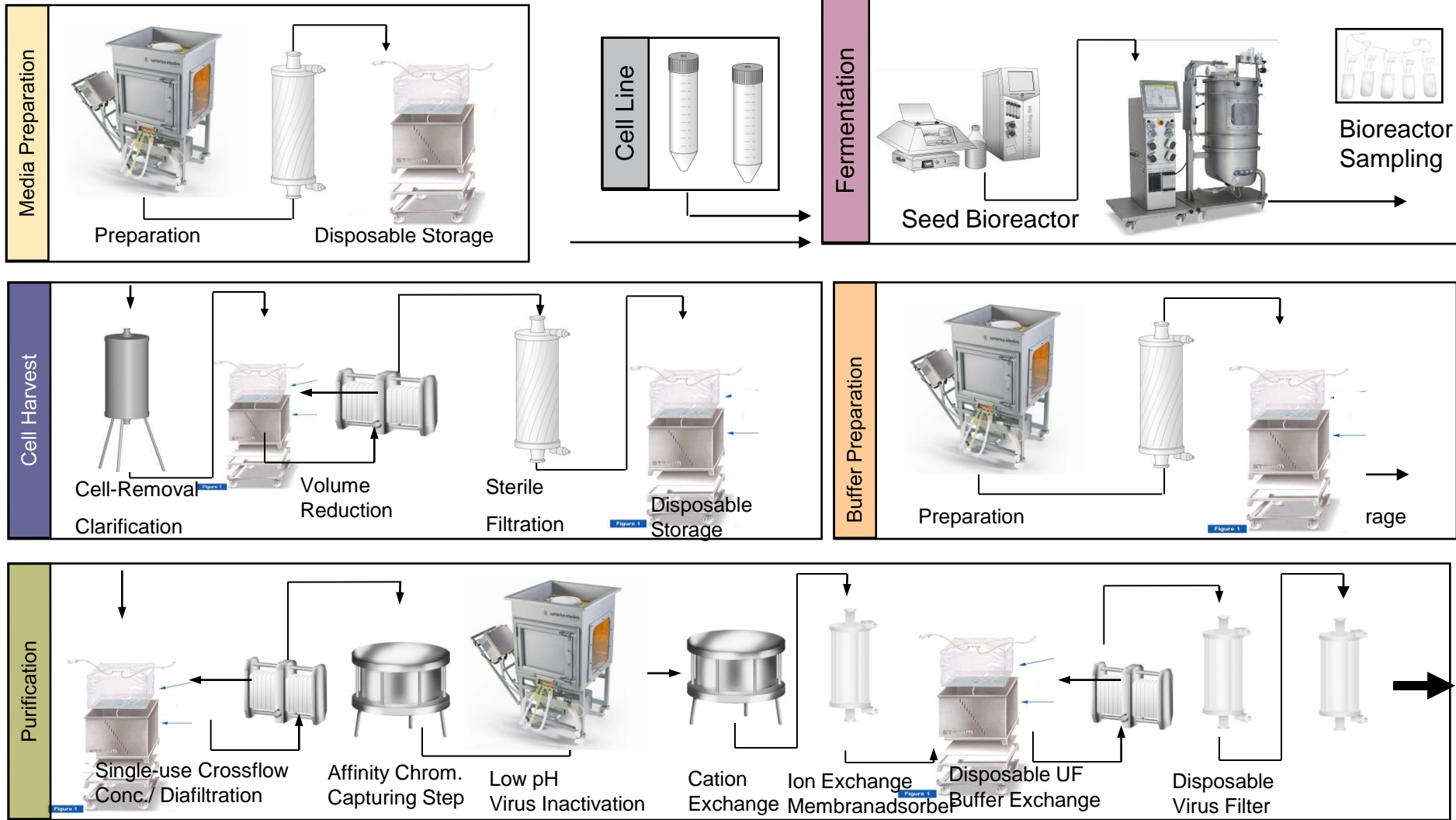
2. Drivers for single use technology

3. Technology Overview

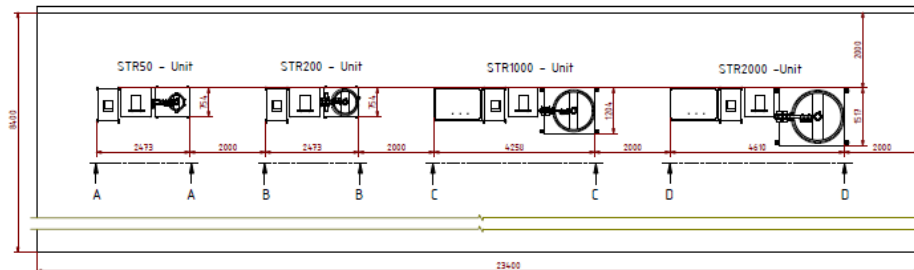
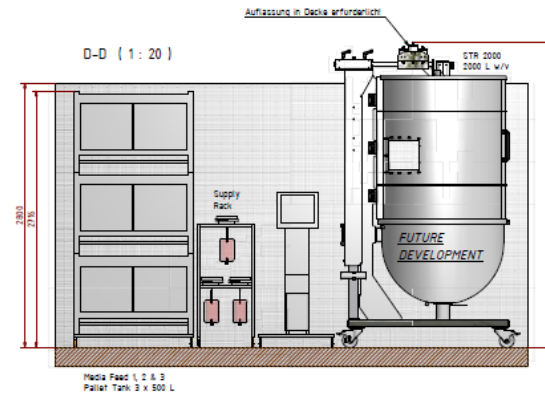
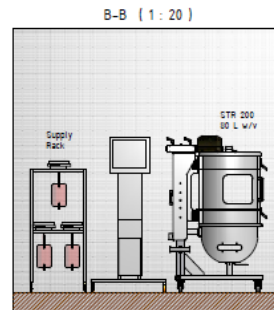
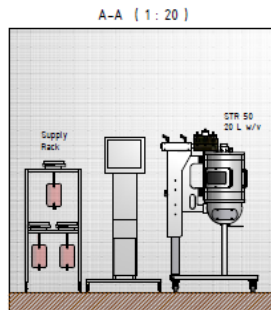
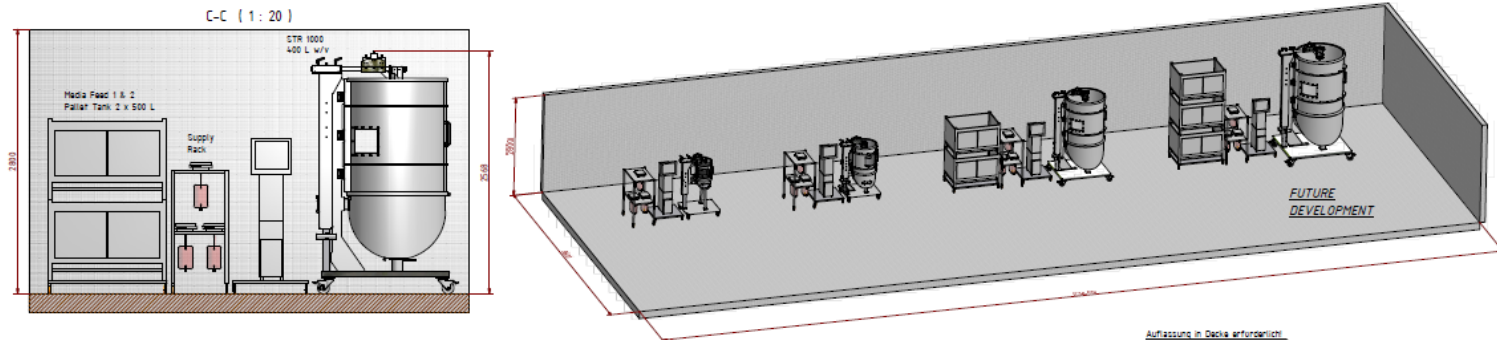
4. Examples

5. Summary

# Single Use in Biopharma Processing



# Single-use Upstream Process



		Aufbauplan für Disp. Reactor Layout Single-Use-Bioreactor Line	
DE-2008-09		1 / 1	

## Closed disposable systems (FlexAct®)



## Drivers of Single Use Technology

### 1. Elimination of CIP & SIP operations

- Reduction of WFI
- Reduction of cleaning agents
- Cost reduction
- Downtime reduction

### 2. Minimization of Validation Efforts

- Reduced cleaning validation
- Cost reduction
- Downtime reduction



## Drivers of Single Use Technology

### **3. Enhanced Flexibility**

- Flexible movement from one process to another (Contract Manufacturer)
- Easy transportation of fluids (media, buffers, intermediate products)
- Streamlined production process

### **4. Reduced Risk of Cross Contaminations**

- Pre-sterilized and pre-assembled systems
- Closed system

## Drivers of Single Use Technology

### 5. Reduced Capital Investment

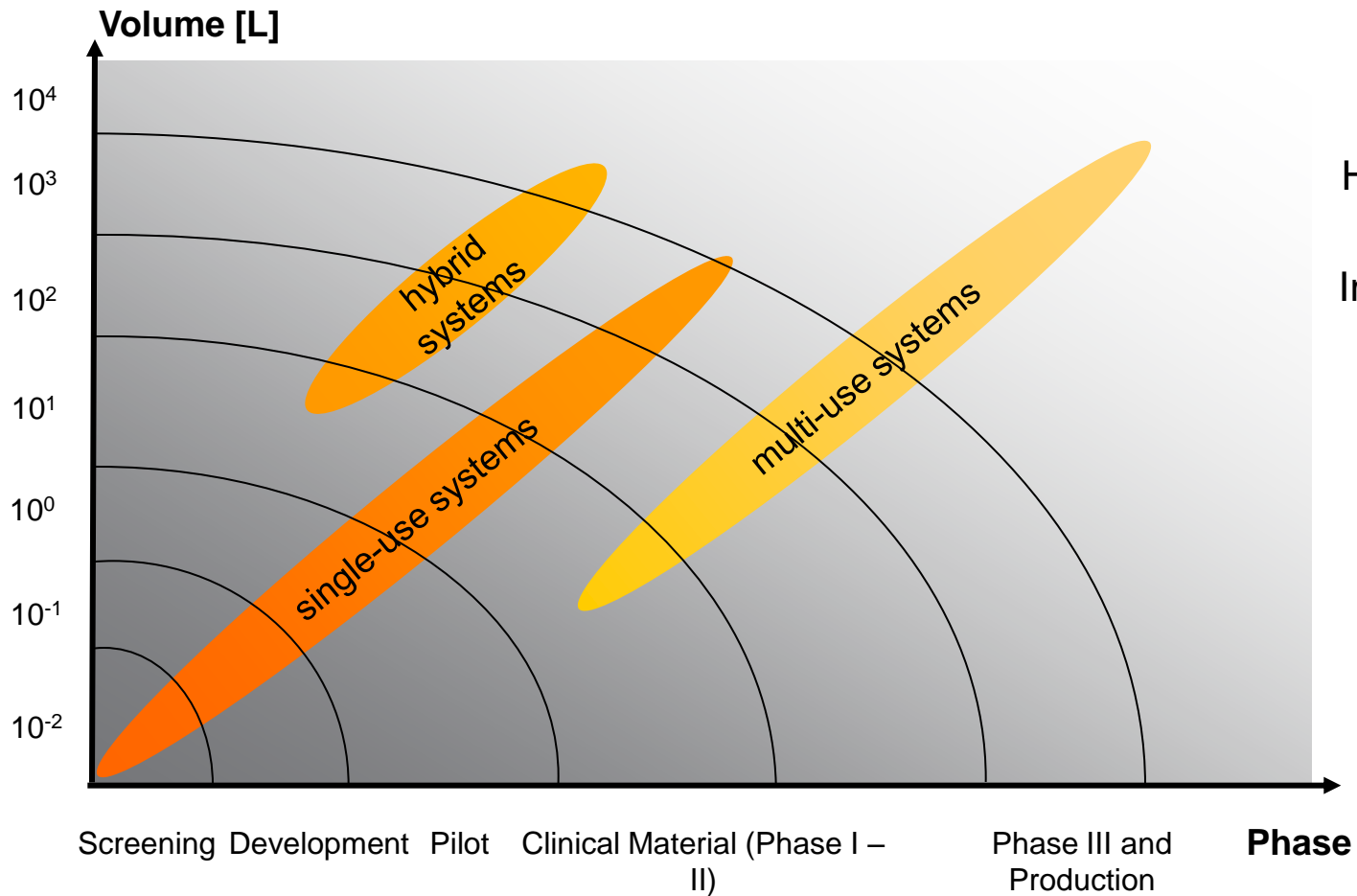
Due to the increase of productivity,  
the quicker facility installation and the  
reduced validation requirements,  
Biopharmaceutical companies can assure  
a faster commercialization of their products.




*Products get faster to market!!!*

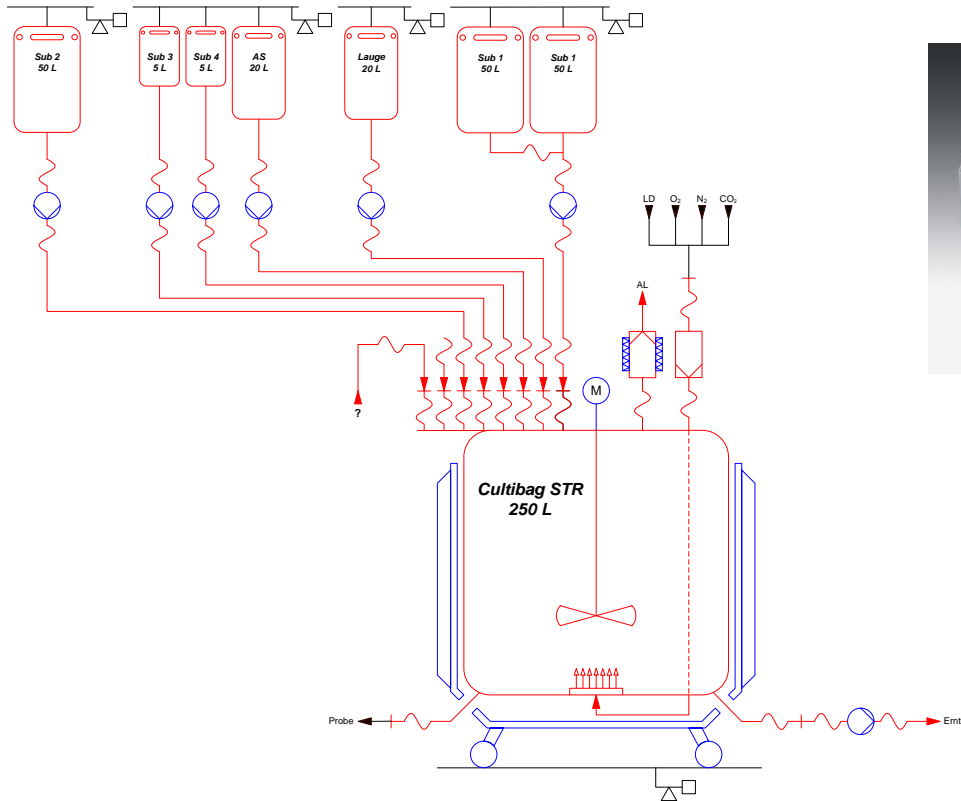


# When to Apply – Single-use, Hybrid or Multi-use Systems

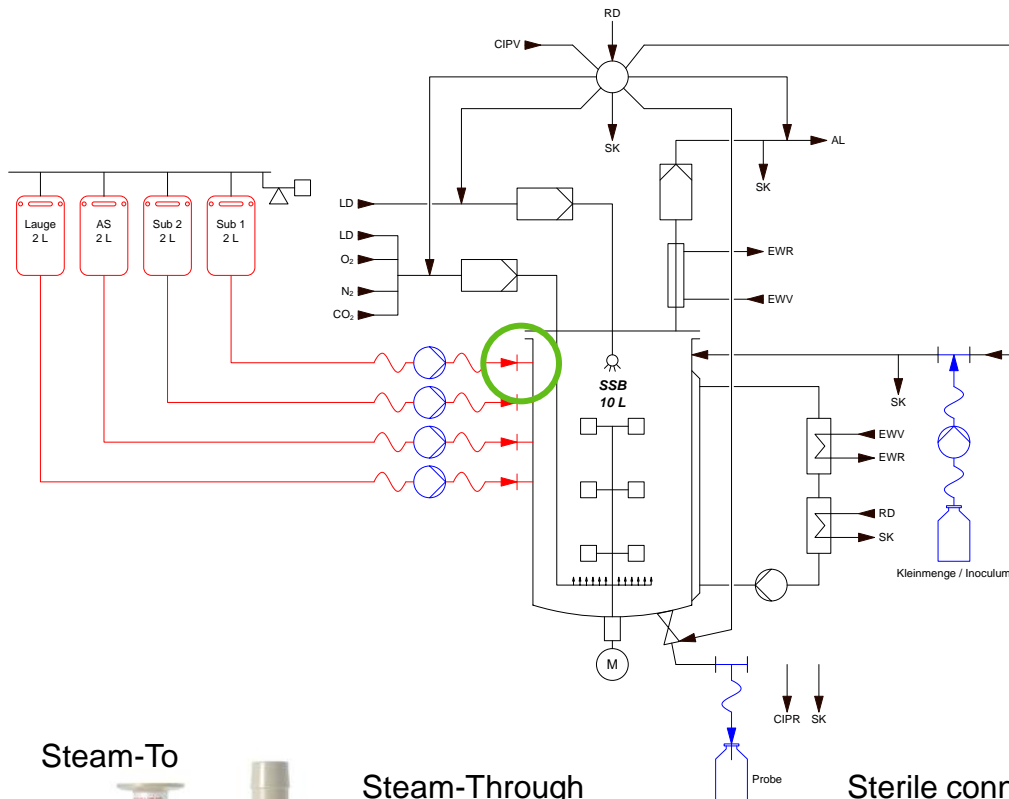


Trends:  
 Higher Expression Rates  
 Increasing Titers & Personalized Medicine  
  
 Reduction in Process Volume

# Example Unit Operation Single-Use



# Example Unit Operation Hybrid



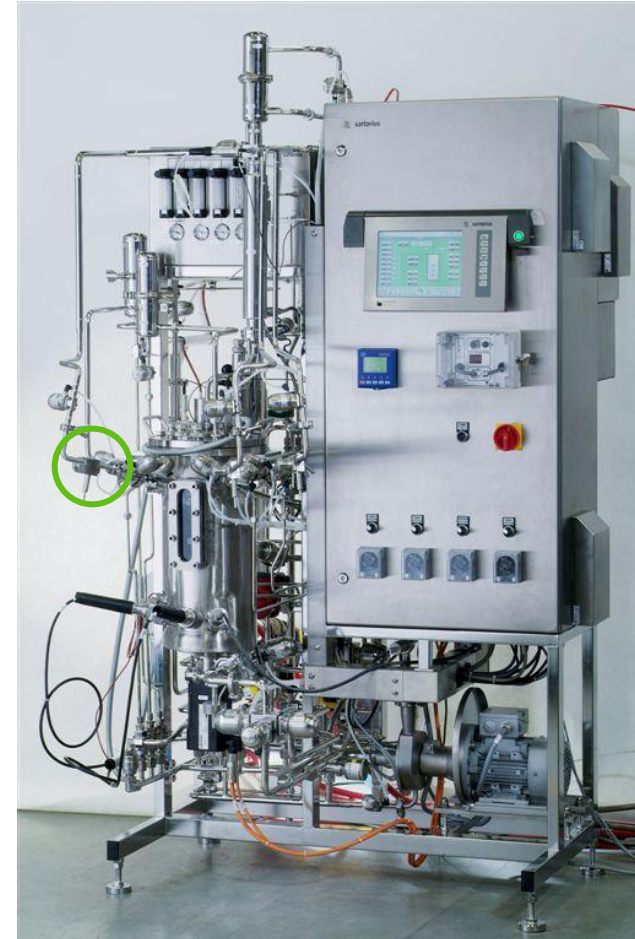
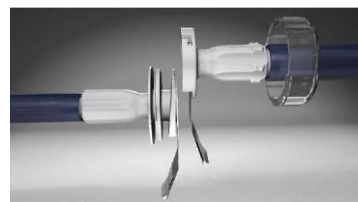
Steam-To



Steam-Through

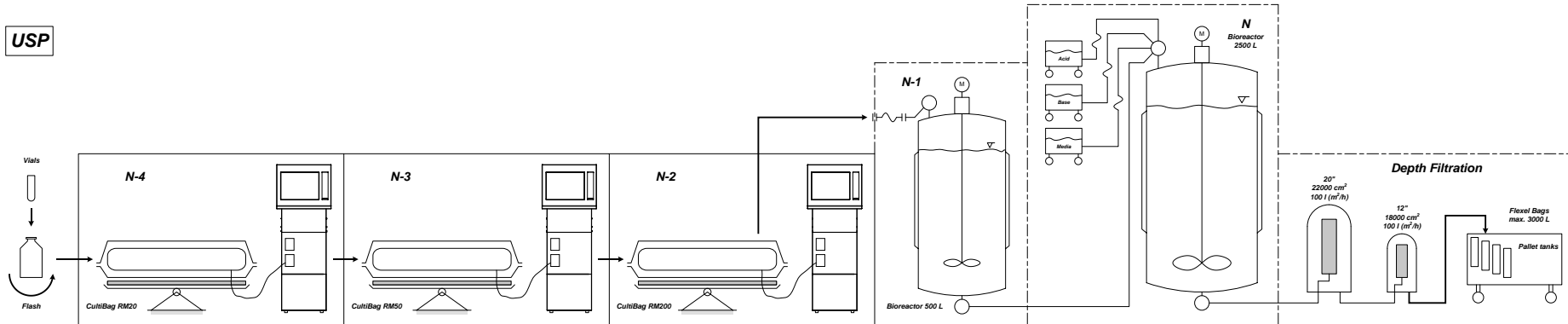


Sterile connector

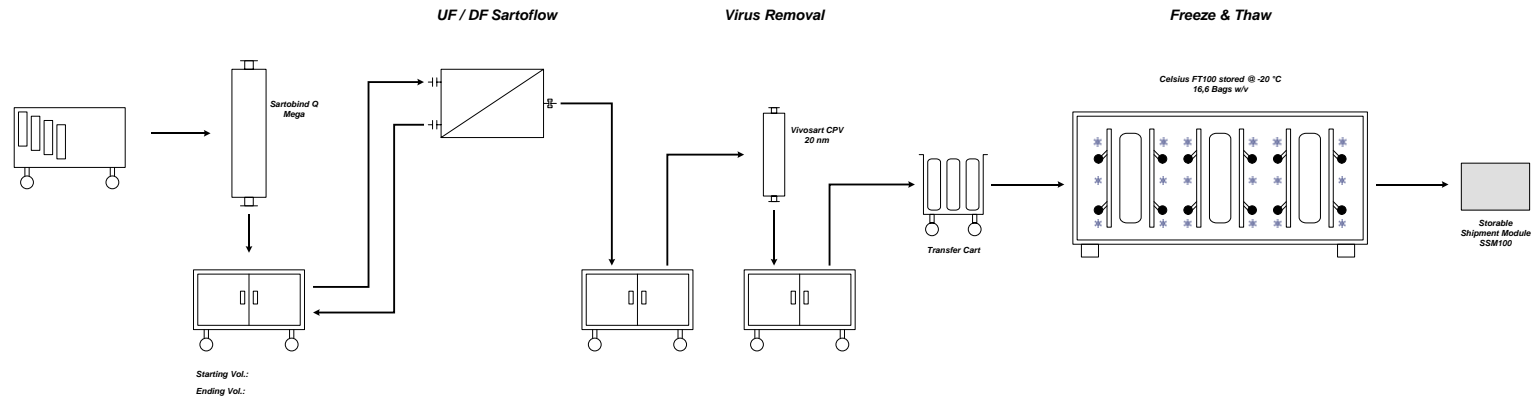


# Unit Operations based generic mAb -Process

USP



DSP



**MAb classical:**

**Harvest / Capturing**

- Separator
- Depth Filtration
- Protein A Column
- Low pH Virus Inactivation

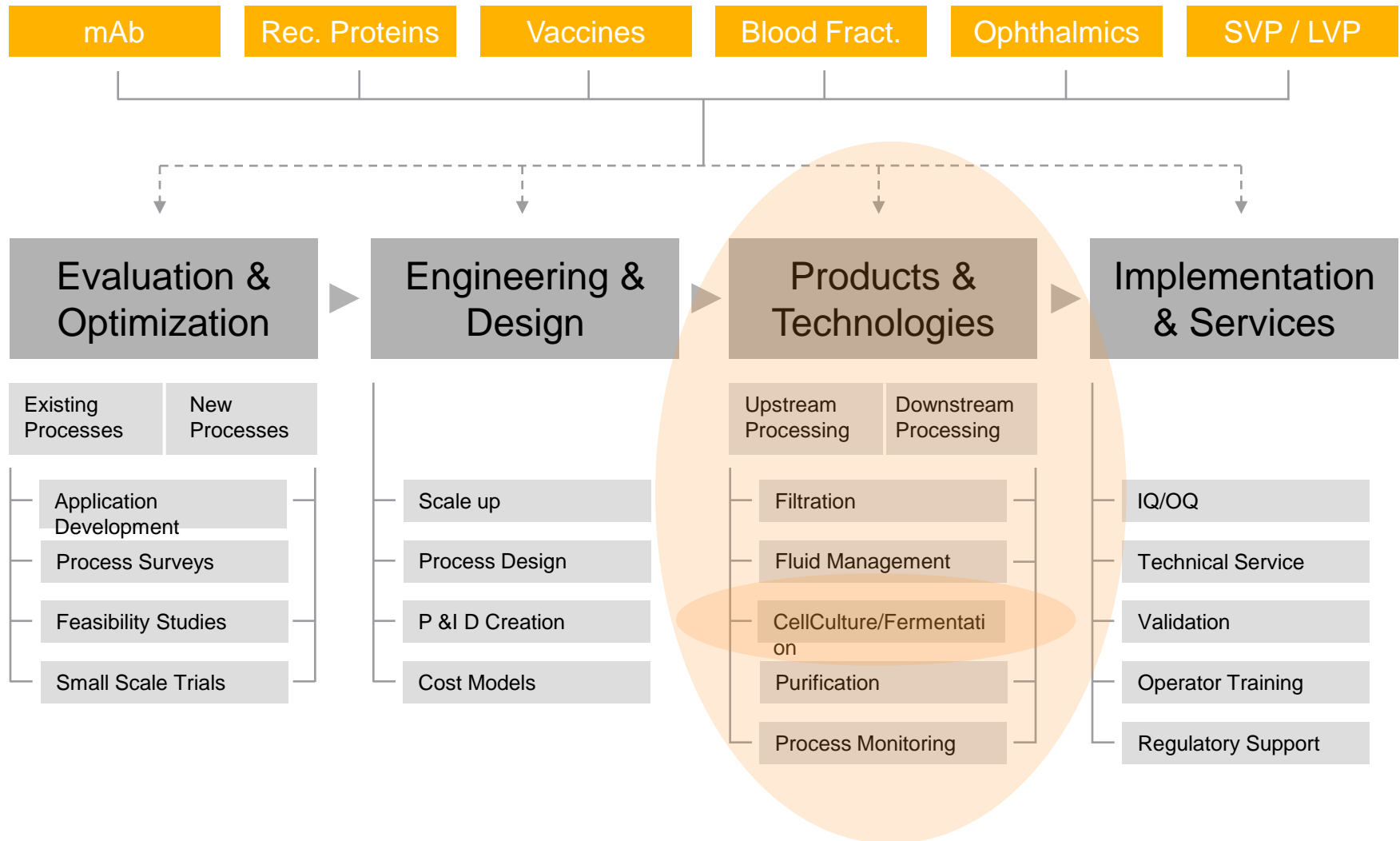
**Purification 1**

- Q-Sepharose Column
- HIC Column
- Virus Filtration

**Purification 2**

- UF / DF
- Bulk Fell
- API Storage

# Total Solution Provider Along Our Customer's Process Chain



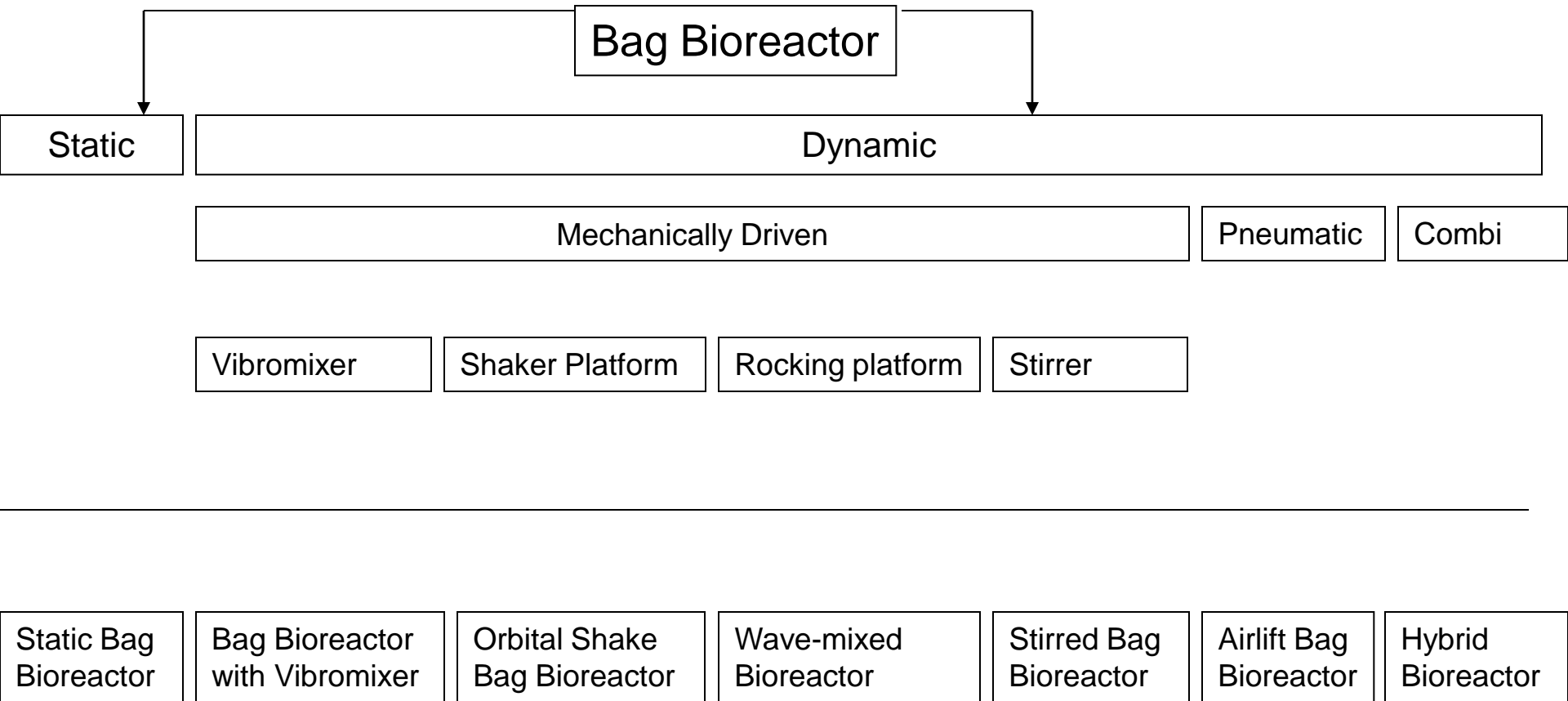
## Technology

Stainless steel bioreactor: One dominant design, the cylindrical stirred tank

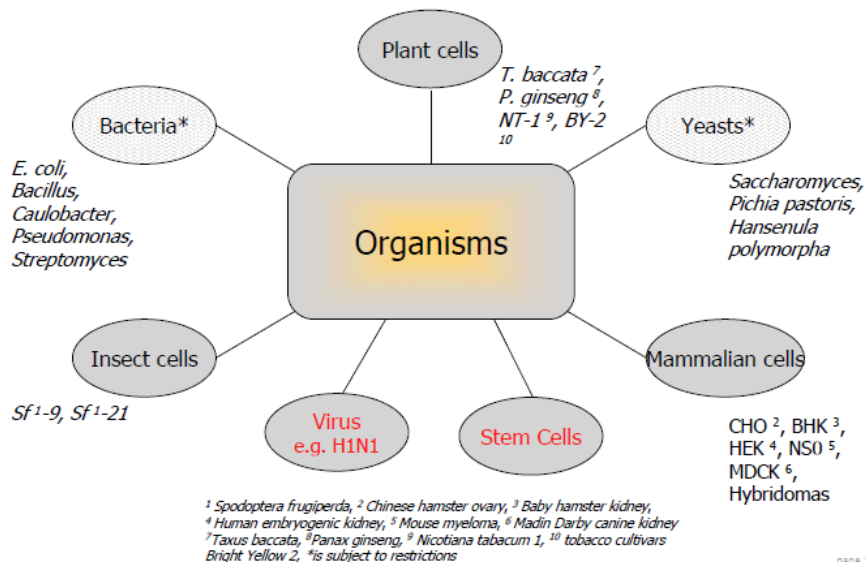


Disposable bioreactor: different designs and technologies on the market





# Single use bioreactor: Which technology to choose? Need for application-based approach



## Application based influences:

- Process needs:
  - Shear stress
  - Oxygen demand
  - Mixing behavior
- Type of culture
  - Virus, Stem cells, Insect, Mammalian, MO,...
  - Suspension
  - Microcarrier
- Process step
  - Screening
  - Seed
  - Production reactor
  - Scale up
- Facilities
  - Footprint
  - Utilities
  - Handling & mobility



## Technology

- single use bioreactors are very well suited for seed and production for mammalian cell cultures with excellent results
- they have been used since 10 years for cell cultivation
- they are used at some stage (mainly seed) in the production of many biopharmaceutical compounds

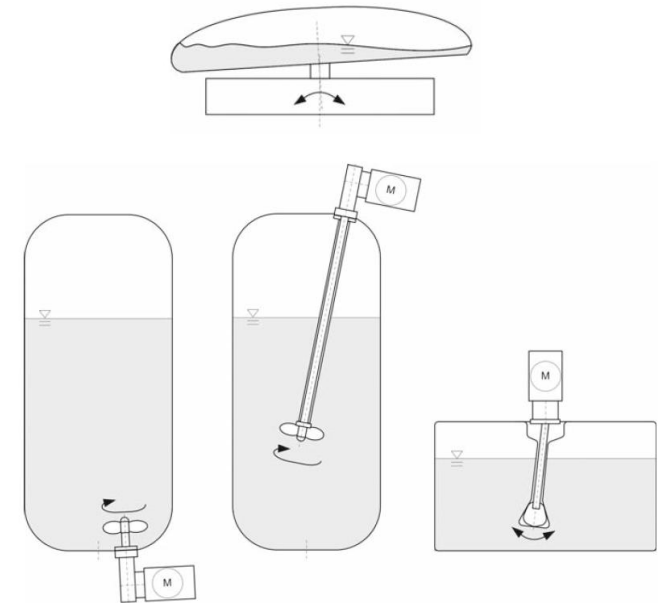
### **newest trends and technological advancements**

- S.U. bioreactors with comparability to conventional stirred tank reactors
- making S.U. bioreactors suitable for microbial cultivations

# Single-Use Bioreactors: Making them comparable to their stainless steel brothers

## Challenges in transfer from reusable to disposable bioreactors due to:

- Change of Mixing Technology & behaviour
  - Wave induced mixing
  - Non-classical stirrer position
  - Non-classical impellers
- Gassing strategies
  - Only surface aeration
  - Non-classical sparger



From R. Eibl and D. Eibl; Adv Biochem Engin/Biotechnol (2009) 112: 183–207

## And

- Single-use not existing for all volumes
- Variations between reusable and currently existing single-use systems

# Single-Use Bioreactors: Challenges during scale-up

## Challenges during scaling:

- some parameters which proved their usefulness are:
    - same geometry/ratios
    - impeller design
    - tip speed
    - Power input per volume (P/V)
    - Gassing strategy
    - kla
  - Knowledge and experience are nearly as important as the scale up parameters
- ⇒ Need for improvements in comparability reusable and disposable processes
- ⇒ **BIOSTAT® CultiBag STR design is based on classical bioreactors!**



## Bag Design - Flexibility in plastic

### **CultiBag STR Design:**

- Multilayer film structure, Stedim 40
- Pre-installed stirrer
- Ports for harvesting, sampling, probes, addition, aeration
- Disposable sensors pre-installed



## Bag Design - Stedim 40

### 1 Polyethylene terephthalate (PET)

acts as a light, strong and clear protective outer layer

### 2 Polyamide (PA)

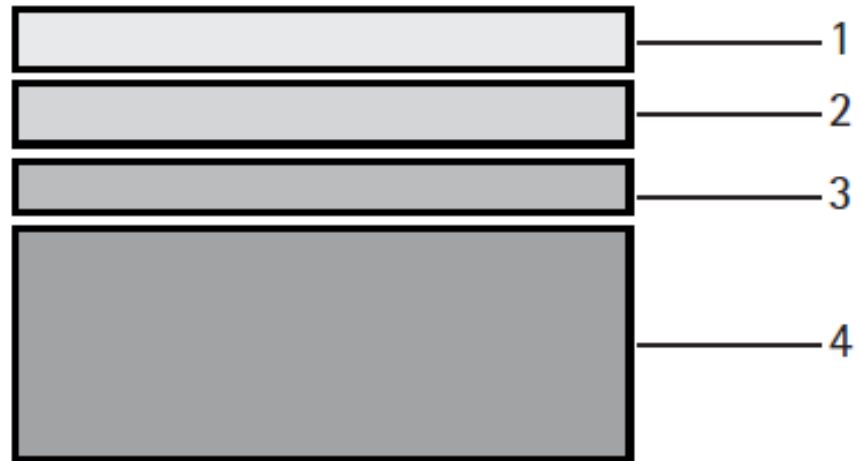
increases durability and strengthens the bag

### 3 Ethyl Vinyl Alcohol (EVOH)

acts as the main gas barrier

### 4 Ultra-Low Density Polyethylene (ULDPE)

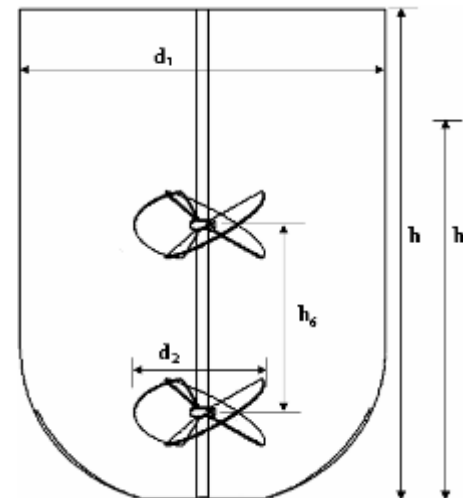
acts as the fluid contact layer. The S40 Polyethylene material is in compliance with usual pharmacopoeias and provides a clean, inert and highly chemical resistant contact layer



# Bag Design:

Scale up: same geometry/ratios.

BIOSTAT CultiBag STR	50	200	500	1000
Total volume [L]	70	280	700	1300
Max. working volume [L]	50	200	500	1000
Min. working volume [L]	12.5	50	125	250
Bag diameter $d_1$ [mm]	370	585	815	997
Bag height $h$ [mm]	666	1055	1467	1800
Ratio $h/d_1$	1.8	1.8	1.8	1.8
Liquid height $h_1$ [mm]	480	783	1005	1360
Ratio $h_1/d_1$	1.29	1.34	1.23	1.36
Impeller diameter $d_2$ [mm]	143	225	310	379
Ratio $d_2/d_1$	0.39	0.38	0.38	0.38
Distance between impellers $h_6$ [mm]	186	300	403	493

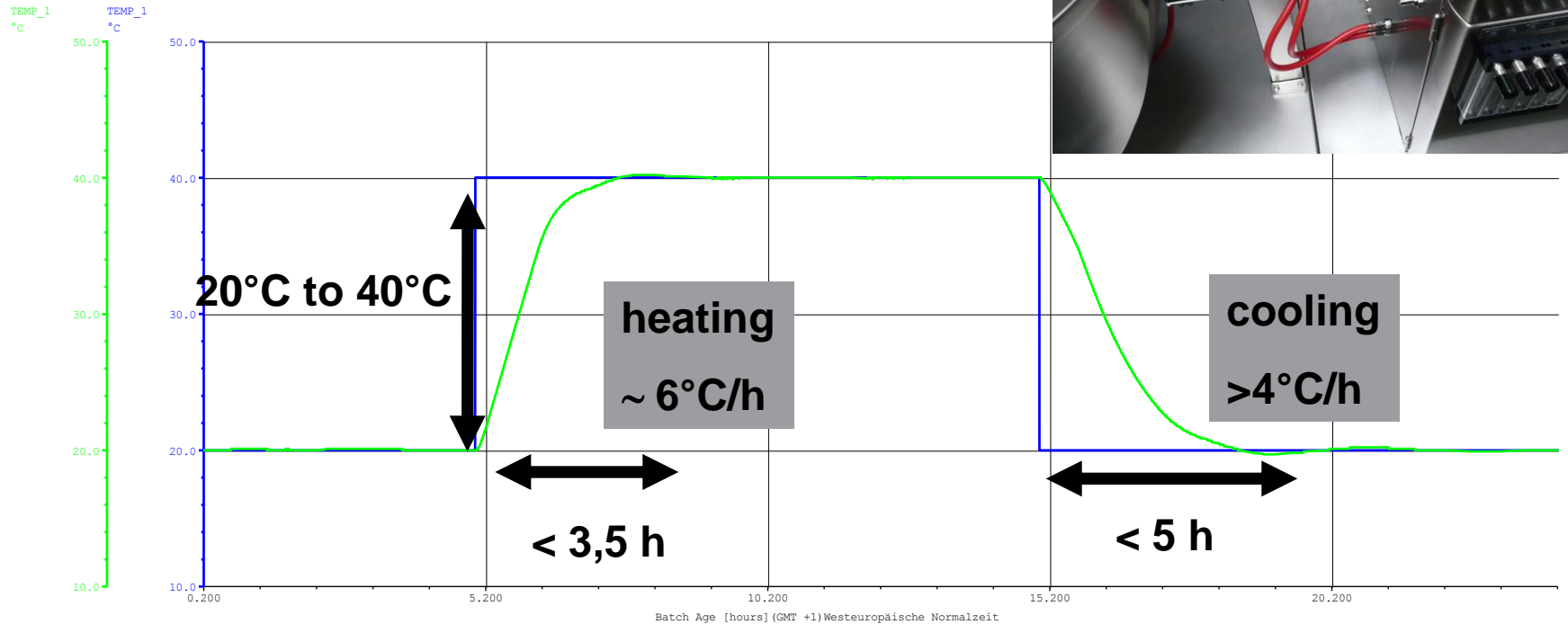


# Double wall (heating and cooling) – STR 200

## History Plot

Tempstest\_STR\_DW\_1/1(Finished) Selection :30.04.2009 14:16:27 - 01.05.2009 14:16:27

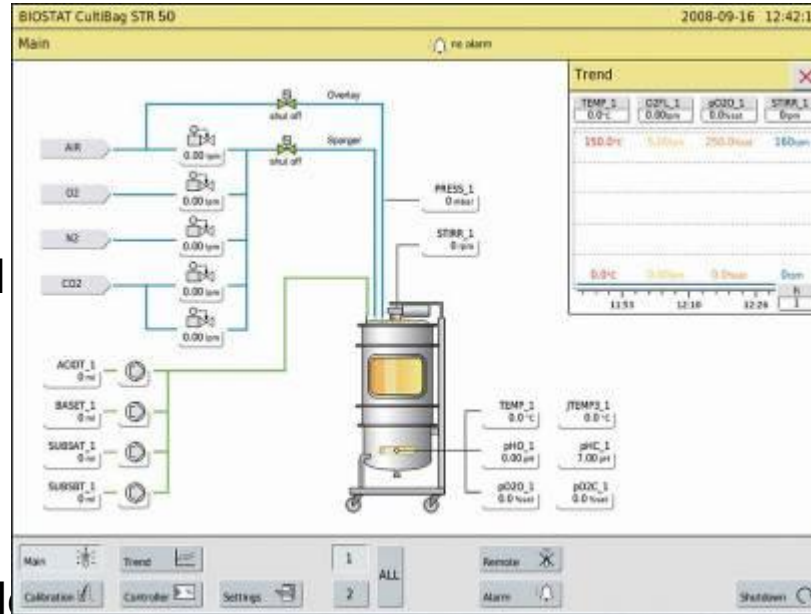
— TEMP\_1.Setpoint;Db 0.10 °C  
— TEMP\_1.Value;Db 0.10 °C



# Single use bioreactors with full automation process control

## Control Tower Design:

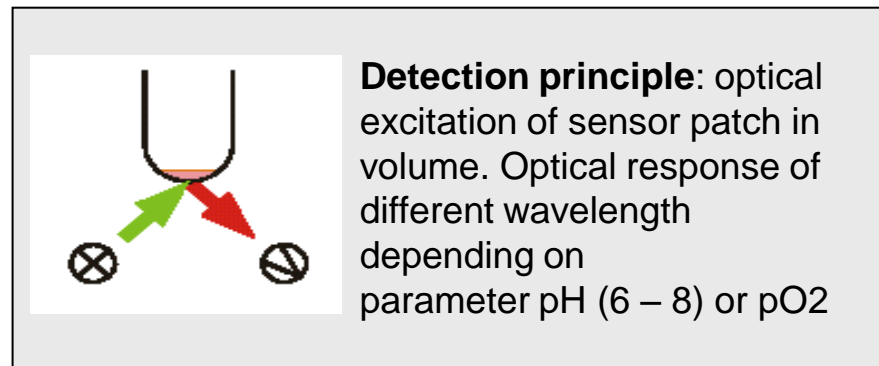
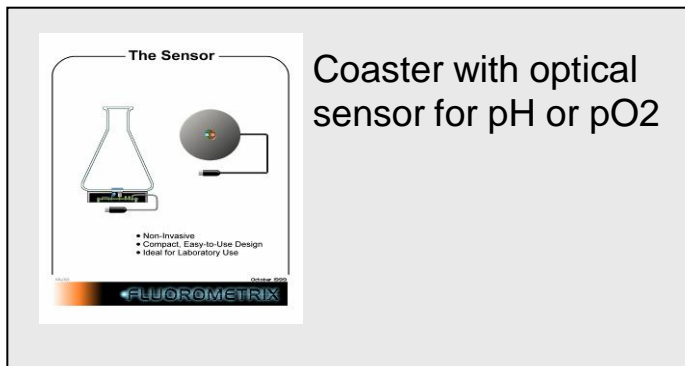
- Control:
  - pH, T, DO, Stirrer speed
  - multistage controller
  - Feedback control
- Automated liquid dosing
- Advanced gassing possible
- **Single-use sensor technology**
- Connected to advanced SCADA software or process automation systems such as Siemens or DeltaV



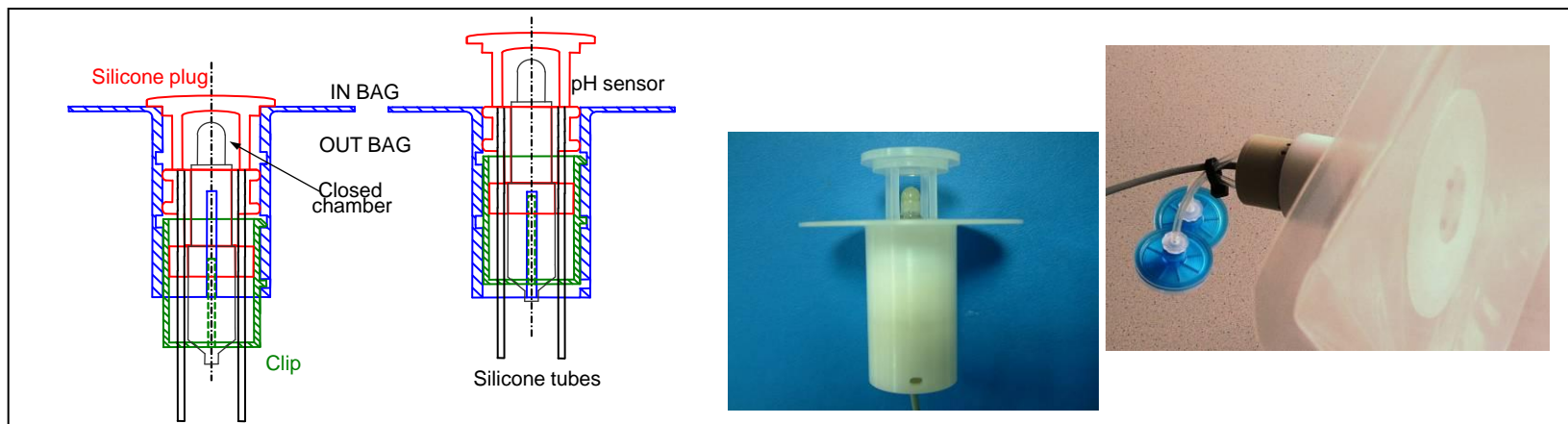


# Enabling Technologies: Single Use Sensors

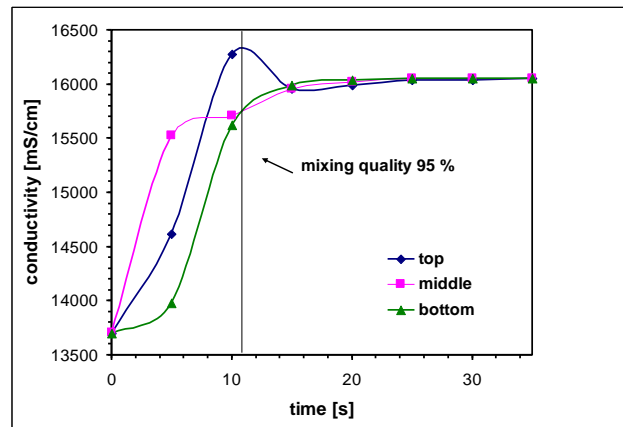
## 1. Single-use optical sensors



## 2. Classical electrodes in single-use (full pH range)

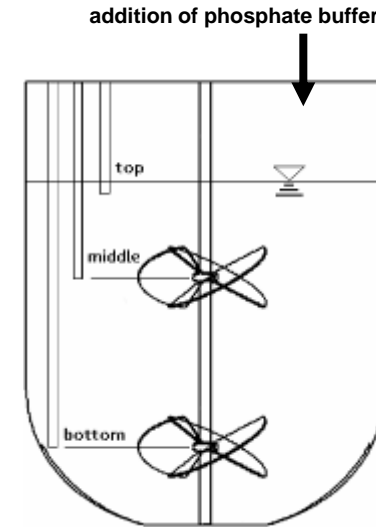
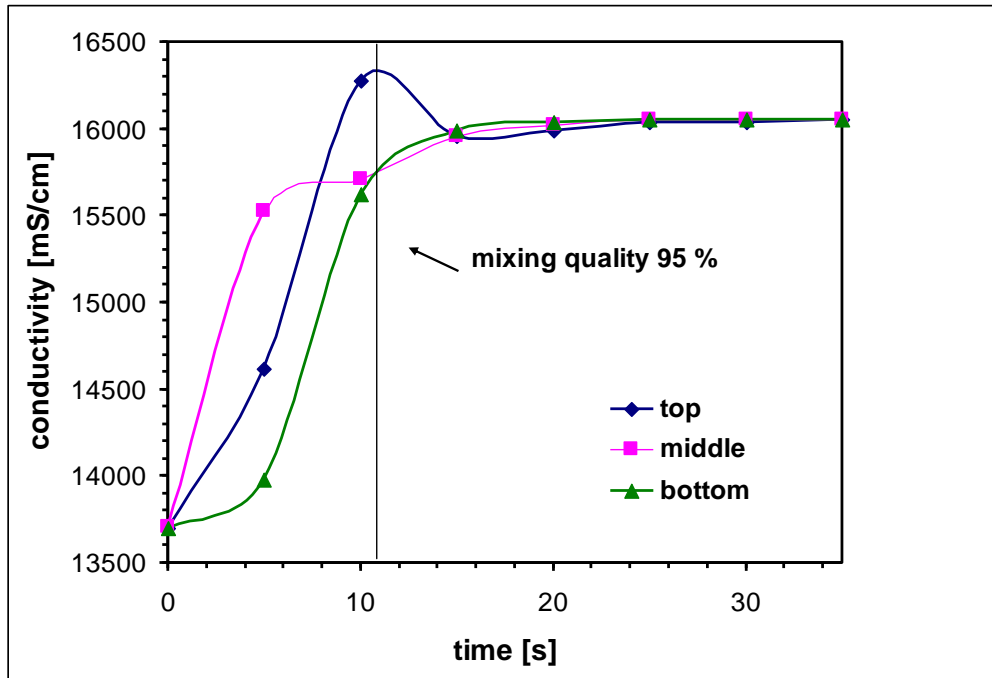


# Process engineering parameters – Scale up

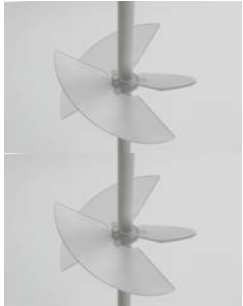


# Mixing Studies STR 200 L

200 L, 2 x 3-blade segment impeller, 150 rpm

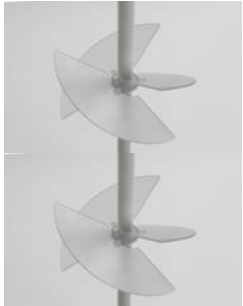


# Scale Up : mixing time



tip speed [m/s]	mixing time [s]	mixing time [s]	mixing time [s]
0,6	22	24	71
1,2	16	16	19
1,8	6	11	16

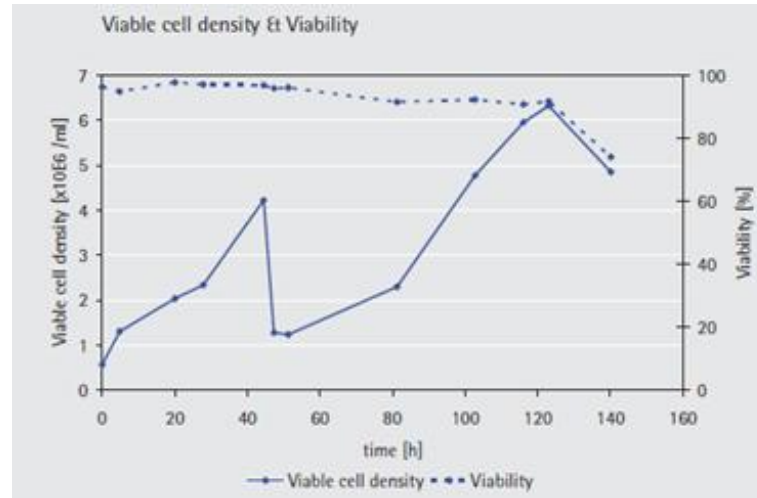
# Scale Up : $k_L a$ -values



tip speed [m/s]	$k_L a$ [1/h]	$k_L a$ [1/h]	$k_L a$ [1/h]
0,6	7	3	9
1,2	9	6	16
1,8	15	10	16

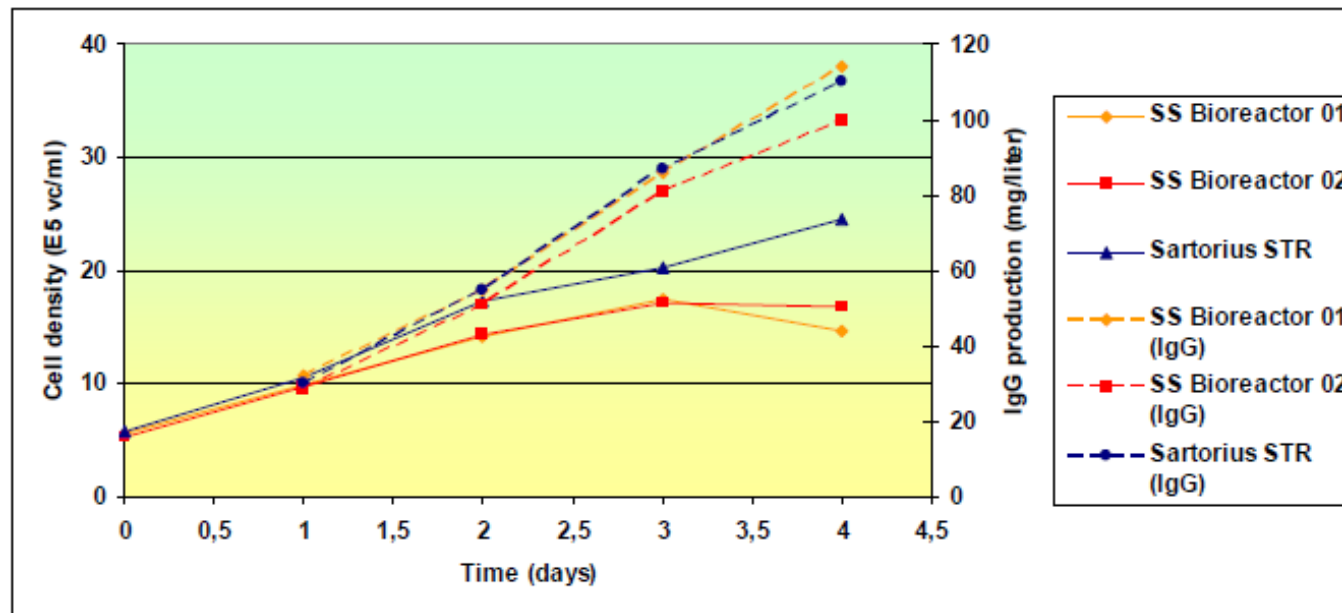
Process Conditions: Max. filling, 0,1vvm air, ring sparger, 1 x PBS, 37°C, gassing-out method

## Case study (mammalian cell culture)



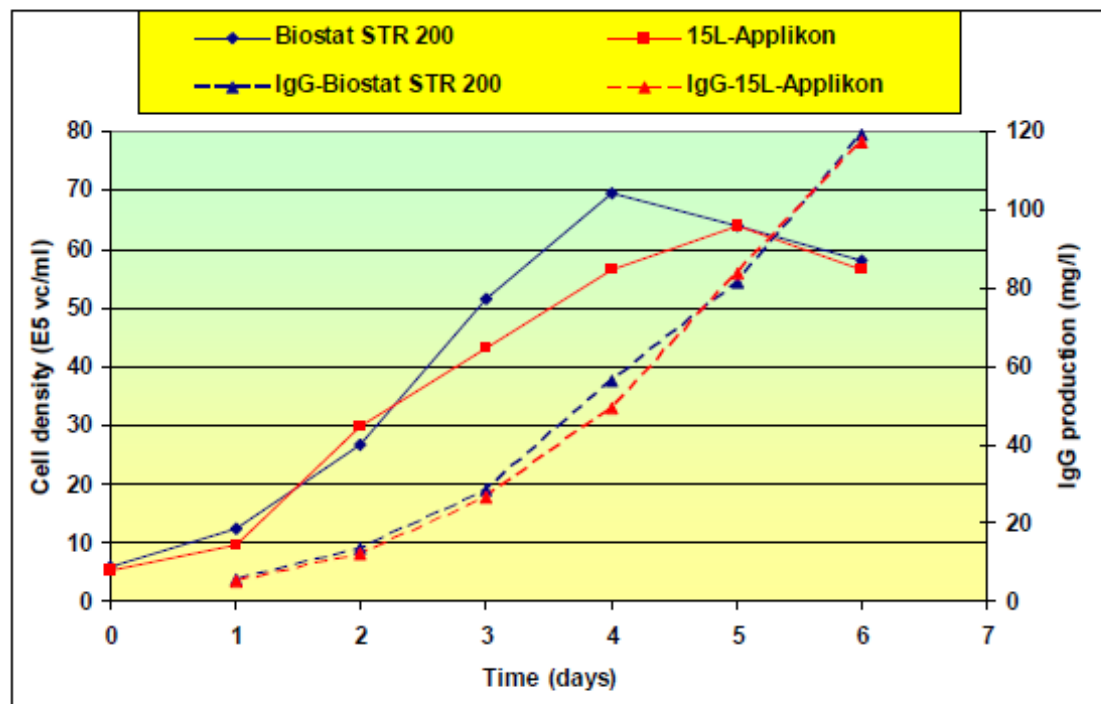
# Case study 1 – batch-mode Mab process

Comparison of cell growth and IgG production in a 250 liter Biolaffite stainless steel bioreactor and in a **BIOSTAT® CultiBag STR 200** single-use bioreactor



## Case study 2 – comparison of cell growth and IgG production

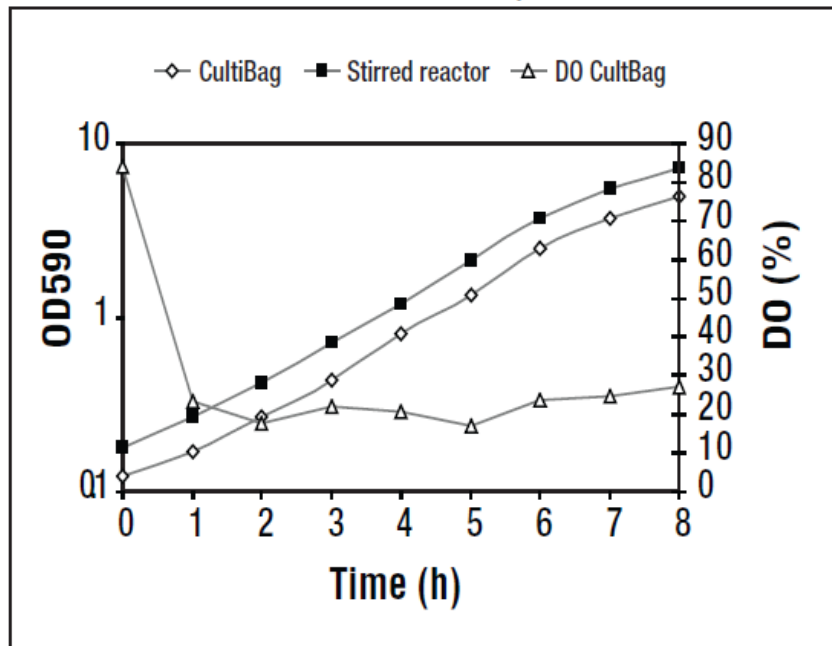
Comparison of cell growth and IgG production in a 15 liter Applikon autoclavable bioreactor and in a **BIOSTAT® CultiBag STR 200** single-use bioreactor





single use bioreactors are suitable for MO applications

**Figure 1.** Growth of the *C. diphtheria*.

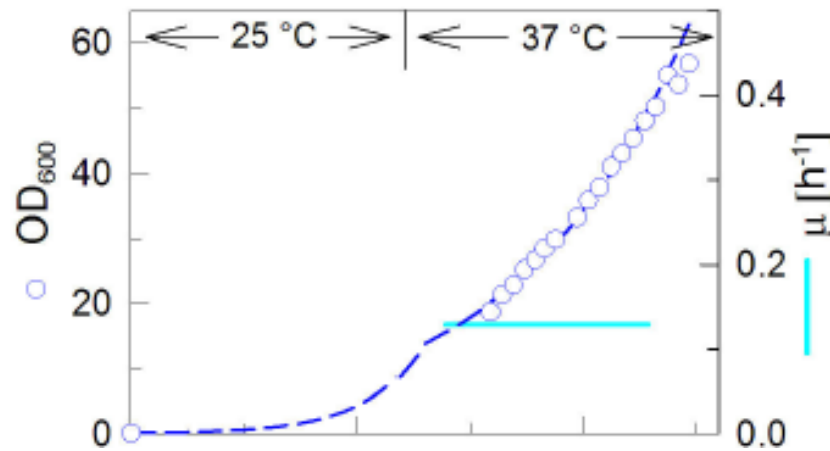


Evaluation of CultiBag RM as seed reactor  
in diphtheria vaccine production  
at Wyeth Vaccines, USA

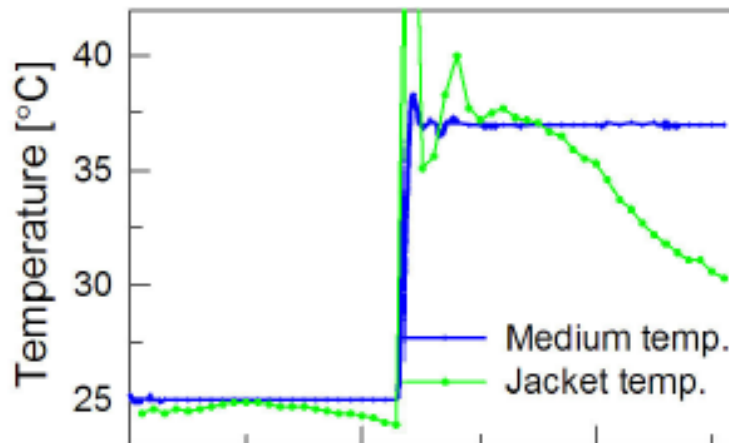
\*Millie Ullah, Terry Burns, Bhallah Amardeep, Hanz-Wilhelm Beltz, Gerhard Greller, Thorsten Adams *Disposable Bioreactors*

for Cells and Microbes. Biopharm International Nov 2008

single use bioreactors are suitable for MO applications



*E. coli* BL21 in DO stat fed batch culture



\*J.Glazyrina, E. Materne, T. Dreher, S. Junne, T. Adams, G. Greller, P. Neubauer *Glucose-limited high cell density cultivation and recombinant protein production with Escherichia coli in a rocking-motion-type bioreactor*. Microbial Cell Factories, submitted

## Summary

- Single use technologies are widely used in the industry
- Single use bioreactors are one of the hottest topics in biopharmaceutical production and research
- Their main benefits for single use technologies come from reduced validation, cleaning, costs, and faster time-to-market
- Single use bioreactor technology is becoming more mature
  - » tailored solutions for many applications and cost models available
  - » new reactors with complete comparability to stainless steel have been launched (BIOSTAT® CultiBag STR)
  - » improvements in process control and technical performance make systems suitable also for microbial application

**Thank you for your attention**