Optimize your biopharmaceutical productivity with mixing and high speed separator solutions

26 August 2021

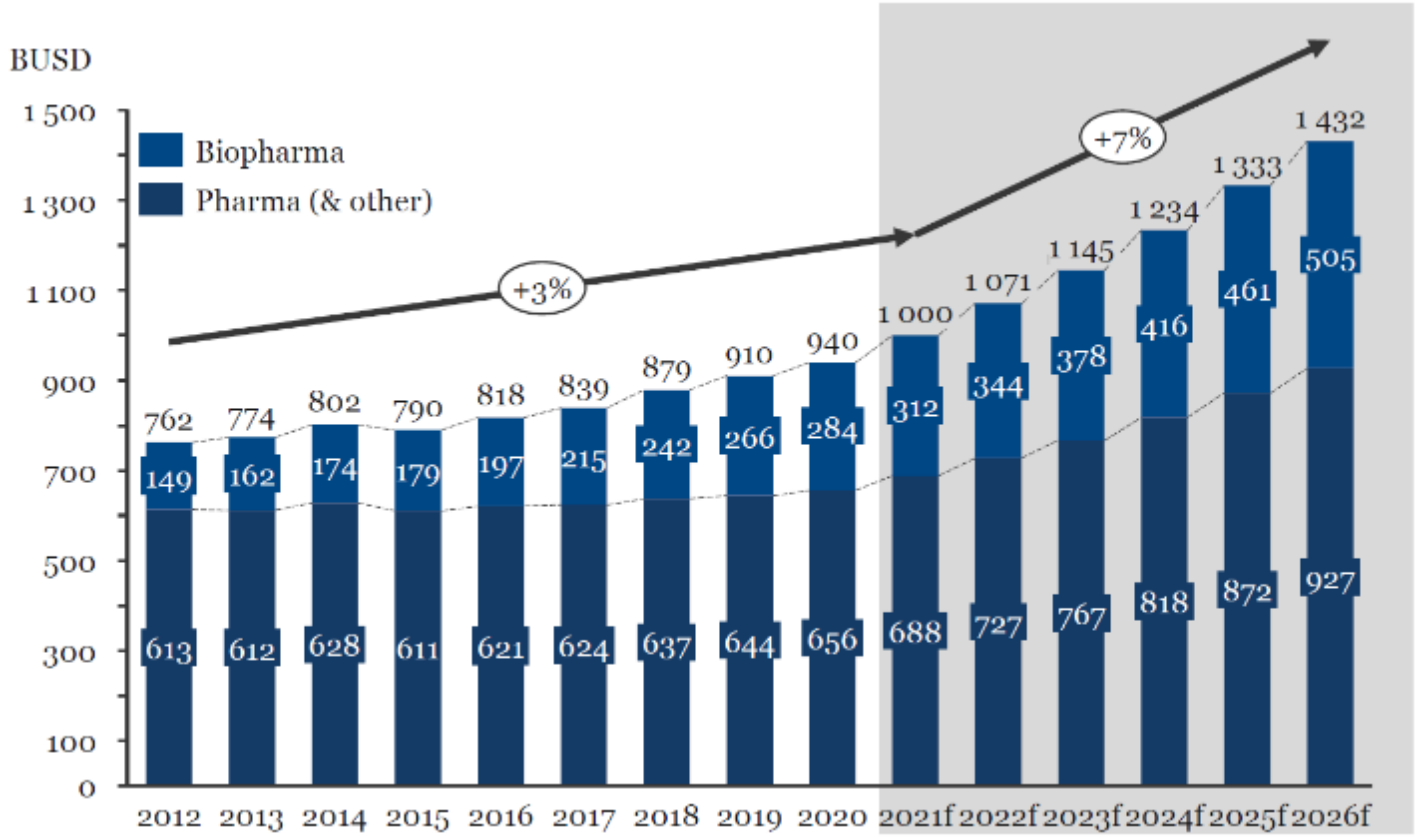
An expert in pharmaceutical industry

- Alfa Laval's presence in the pharmaceutical industry is dated back for more than 100 years ago
- We provide an extensive range of proven components and systems in fluid handling components, separation systems and heat exchangers
- We offer sustainable solutions that meet the highest demands with our equipment and the diversity of our global network of sales and service representatives

Promising growth in the pharmaceutical industry

- Biopharma estimated CAGR (Compound Annual Growth Rate) of 10% (2021-2026)
- 30% of the total pharma market 2020
- Predicted to reach 35% by 2026
- Dominated by proteins (antibodies and insulin)
- New segments such as cell and gene therapy, mRNA and new ways of producing vaccines are growing fast

Pharmaceutical industry revenues



Source: Business Sweden, Statista, Fitch Solutions

- Reactor mixing to secure optimized condition for your culture
- Mixing optimization for quality and cost improvements
- Improve your harvesting processes with high-speed separation
- Optimize your operations with single-use separation

Our speakers

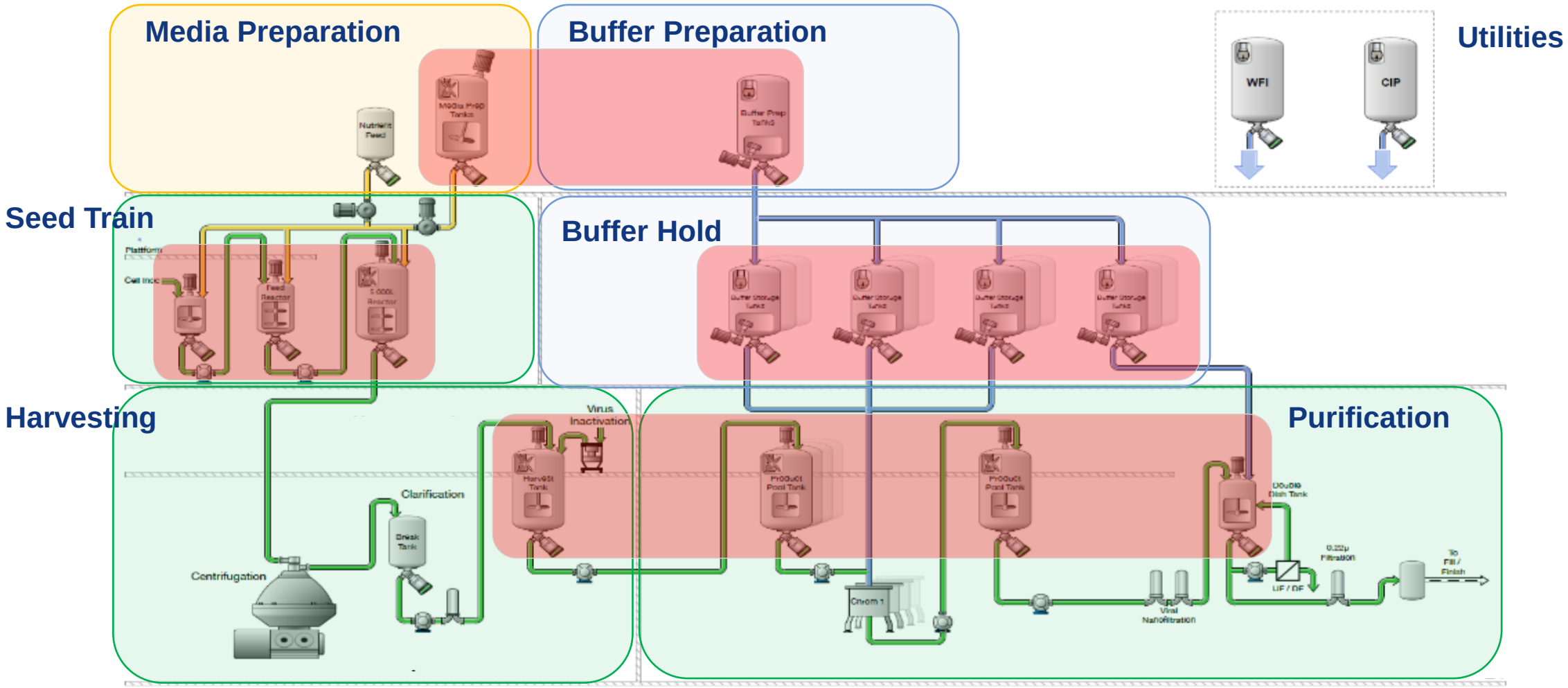
Per-Åke Olsson is the Global Industry Manager for Pharma & Biotech in Alfa Laval. He holds a MSc, Mechanical Engineering from University of Lund, Sweden and eMBA from University of Warwick, United Kingdom. He was also the Member of the Pharmaceutical Technology Europe editorial advisory board between 2006 and 2008, and has been a speaker and chairman at several BioPharma conferences and seminars in Asia, America and Europe. He has been with Alfa Laval for close to 20 years with massive experience and knowledge in pharmaceutical and biotechnology industries under his belt.

Xiaoguang Li holds a Electrical Automation MSc from China Jiangsu University. He is the Global Sales Manager for Biopharma specializing in high speed separators and has been with Alfa Laval for 23 years. With more than 15 years of experience in biopharma industry, he is actively developing solutions. He is based in Tumba, Sweden.

Securing optimized mixing conditions for your cell culture to boost yield and productivity

Per-Åke Olsson
Global Industry Manager - Pharma & Biotech

Mixing in biopharmaceutical processing



Reactor - Bacteria vs. Mammalian cells

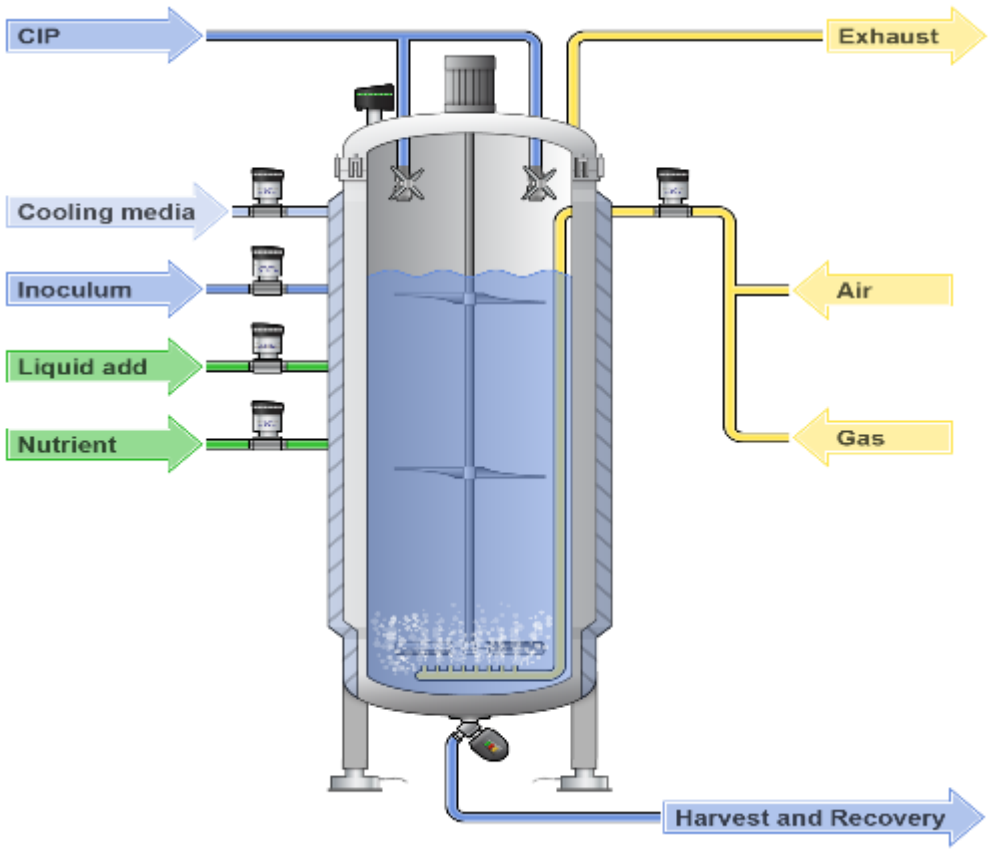
Parameter	Fermentor	Bioreactor
Platform	Bacteria cells* e.g. E-coli	Mammalian cells e.g. CHO (Chines Hamster Ovary)
Manufacturing cost	Medium	High
Drug substances	Intra-cellular	Typically, Extra-cellular
Concentration in tank	High concentration	Low concentration
Media & nutrient	Few ingredients, mainly glucose and salts	Many ingredients, mainly proteins and vitamins
Media sterilization	Typically heat sterilized	Typically filter sterilized (the media is heat senistive)
Tank sterilization	Heat sanitized with filled media	Heat sanitized, without media
Process cycles	“days”	“weeks”
Oxygen uptake	High 5-100 (-400) mmol/liter-hour	Low 0.5 – 5.0 mmol/liter-hour
Gas rate	High 0.5 to 1.5 VVM[1)]	Low < 0.3 VVM[1)]
Heat load	High, requires heat removal (tank internals common)	Low, requires heat addition (jacket adequate)
Shear sensitivity	Robust	Shear sensitive
Agitator power	High 5+ kW/m^3	Low < $1kW/m^3$
Agitator type	Radial flow, or combination of radial/axial impellers	Axial flow, or combination of radial/axial impellers
Reactor size	< 300 m^3	< 30 m^3
Tank height	H/D ratio 2.5-3.0	H/D ratio ~1,5

* Can also be Filamentous Fungi, Yeast, Insect cells, Plant cells (all of these has a cell wall)

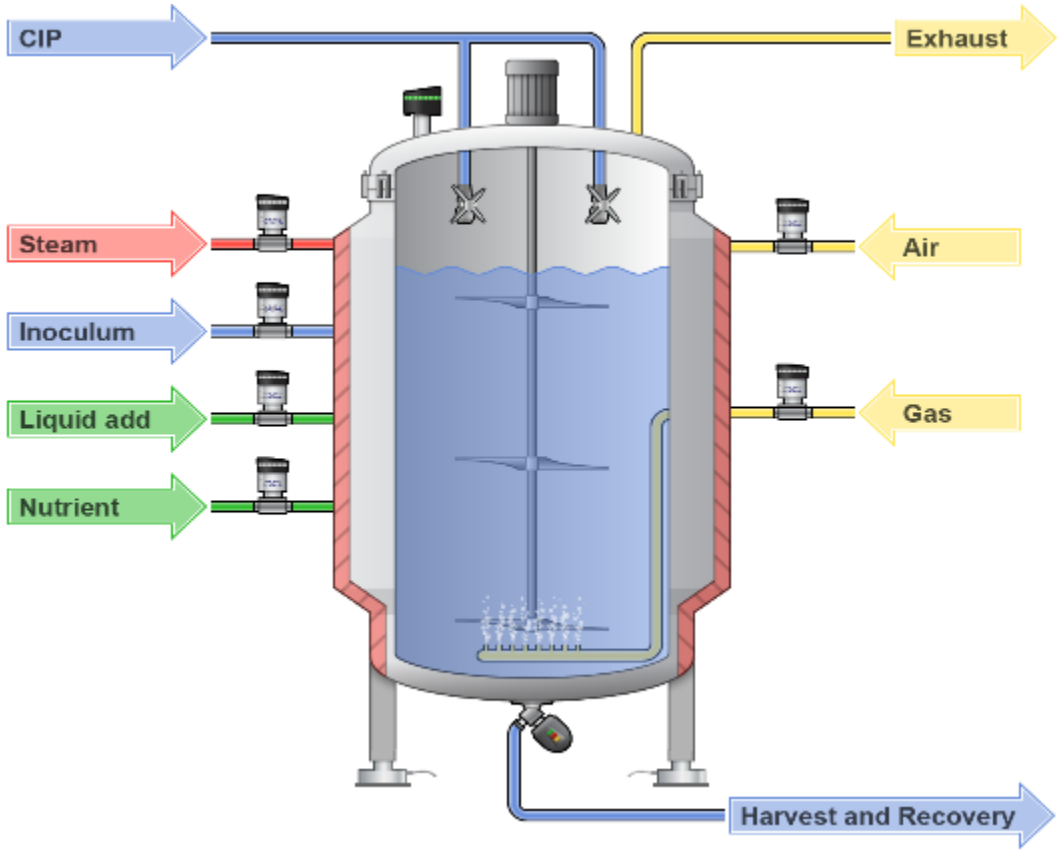
1) VVM (Volume of air per volume of medium and minute)

Fermentor & Bioreactor

Fermentor

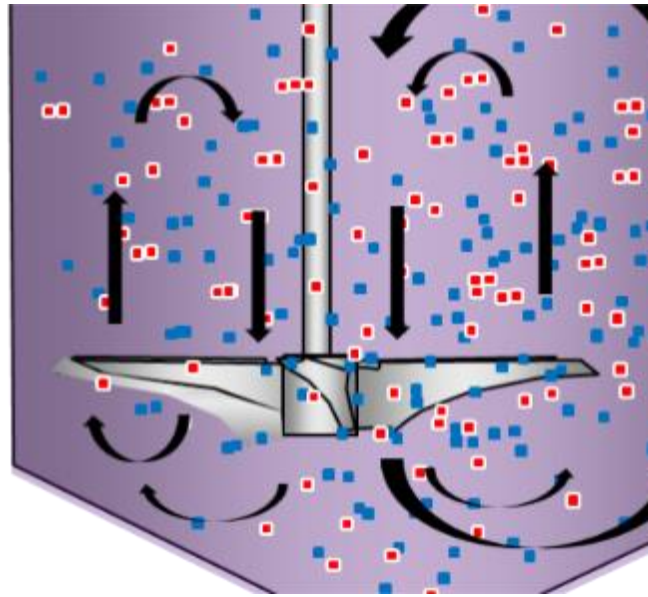


Bioreactor



Critical factors for cell growth

Critical factors	Fermentor	Bioreactor
Homogeneity (nutrition, pH, temperature)	Less sensitive	Sensitive
Gas dispersion (O_2 & CO_2)	Important	Less importance
Shear	Less sensitive	Sensitive
Heat transfer	Less sensitive	Sensitive
Sterility	Less sensitive	Sensitive



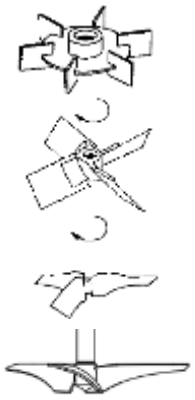
How to select the right mixer?

Mixing theory

Q = Pumping capacity (m^3/min)
P = Power consumption (W)
N_Q= Pumping number (unit-free)
N_P= Power number (unit-free)
D = Impeller diameter (m)
ρ = Density (Kg/m^3)
n = Speed (rpm)

$Q=N_Q x n x D^3$
$P=N_P x \rho x n^3 x D^5$

$P \propto Q^3 / D^4$
$\propto$ Proportional relation



Impeller type	N_P	N_Q	N_Q/N_P
Rushton	5.20	0.72	0.14
Pitch Blade Turbine (45°)	1.27	0.79	0.62
Hydrofoil	0.30	0.56	1.87
EnSaFoil	0.19	0.40	2.11

- When increasing the impeller diameter the rpm and consequently the energy consumption is reduced at constant pumping capacity
- Halving the impeller diameter at constant pumping capacity increases the energy consumption by factor 16!

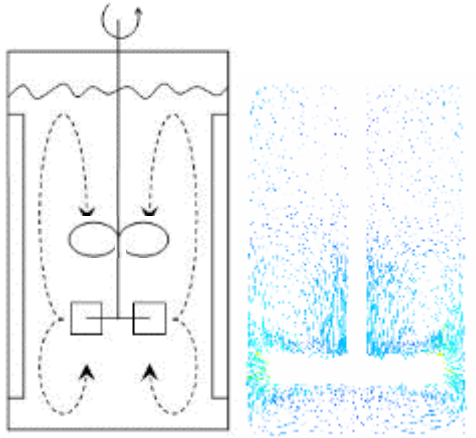
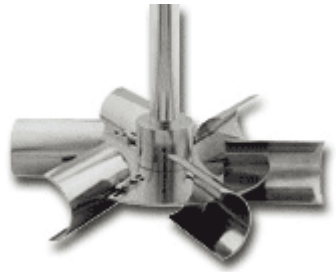
Mixing in fermentor’s & bioreactor’s

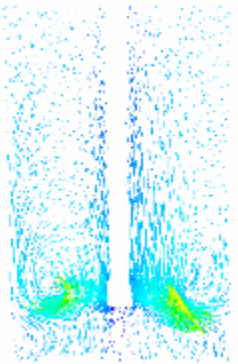
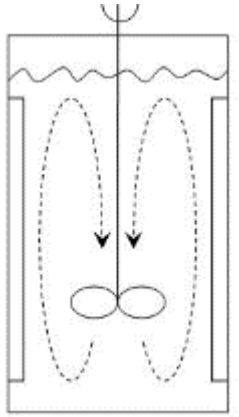
Fermentor mixing

- High power input (>5 kW/m^3)
- Radial impellers (Rushton or Smith turbines) are common – high speed and shear
  - or Radial impeller combined with hydrofoil impellers
- Primary scaling criteria is oxygen transfer rate

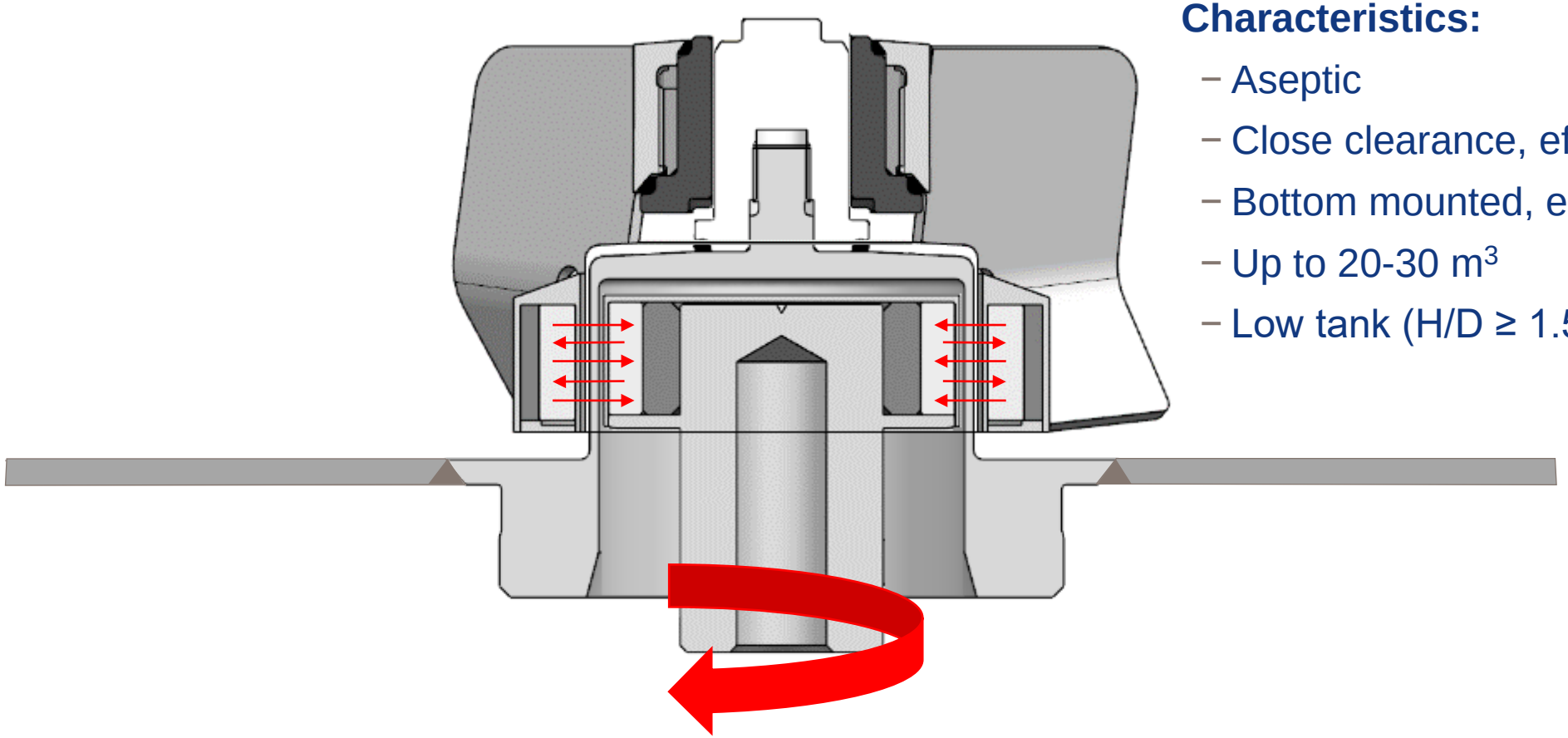
Bioreactor mixing

- Low power input (<1kW/m^3) (shear sensitive)
- Axial/radial flow hydrofoil impellers with high mixing capacity (but low shear)
  - or Magnetic mixers
- Primary scaling criteria is blending/uniformity
  (Prevent variations in dissolved nutrition, pH, oxygen, temperature)

Magnetic mixer in bioreactor’s



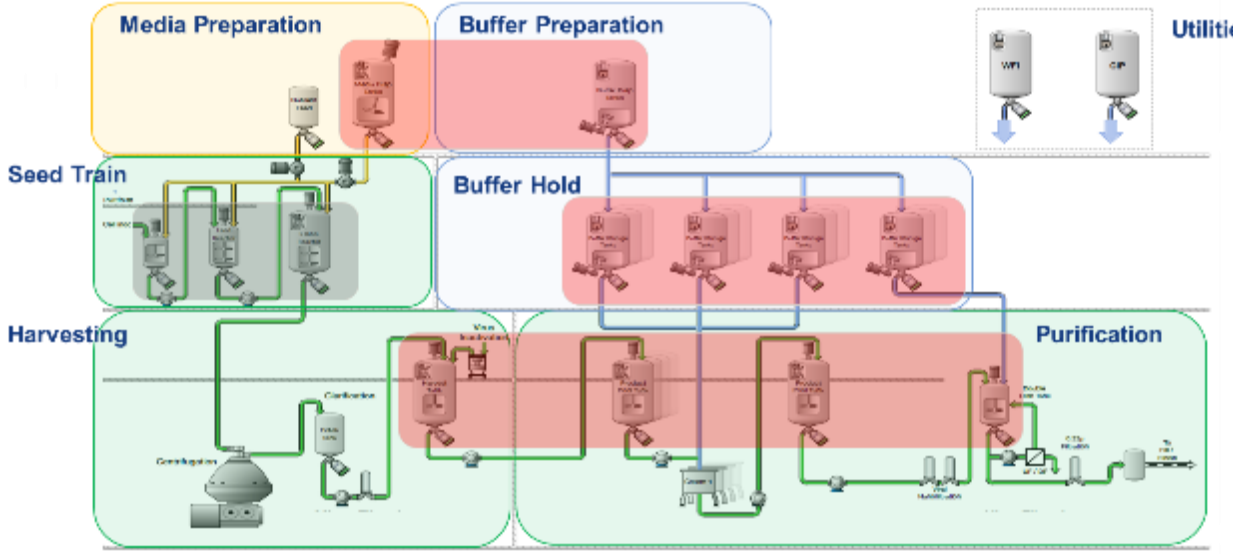
Characteristics:

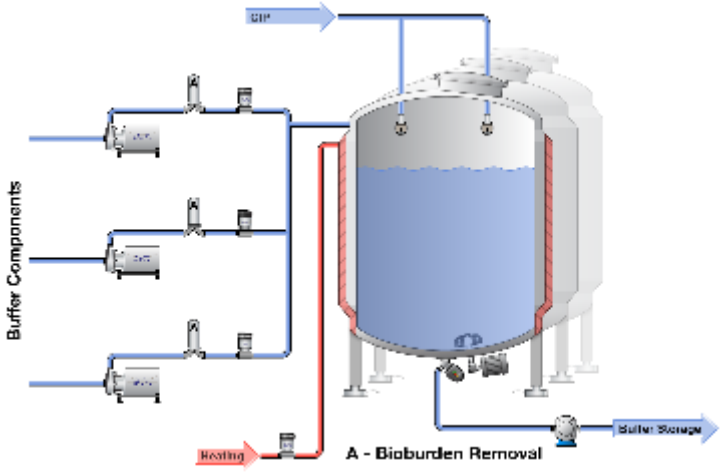
- Aseptic
- Close clearance, effective mixing
- Bottom mounted, easily accessible
- Up to 20-30 m^3
- Low tank (H/D ≥ 1.5)

Buffer, Media & Nutrient mixing – Quality & Cost

Challenges:
- Large volumes to mix
- Labor intensive
- Large floor space occupied

Requires:
- Fast & efficient mixing
- Complete and homogenous mixing
- Low energy consumption
- Mixing to last drop
- Bioburden control





Alfa Laval Agitators & Mixers

Agitators

- ALT
- ALB
- ALS
- ALTB

Magnetic Mixers

- LeviMag UltraPure

Powder Mixers

- Hybrid Powder Mixer M15
- Hybrid Powder Mixer S15

Don’t hesitate to contact us for:

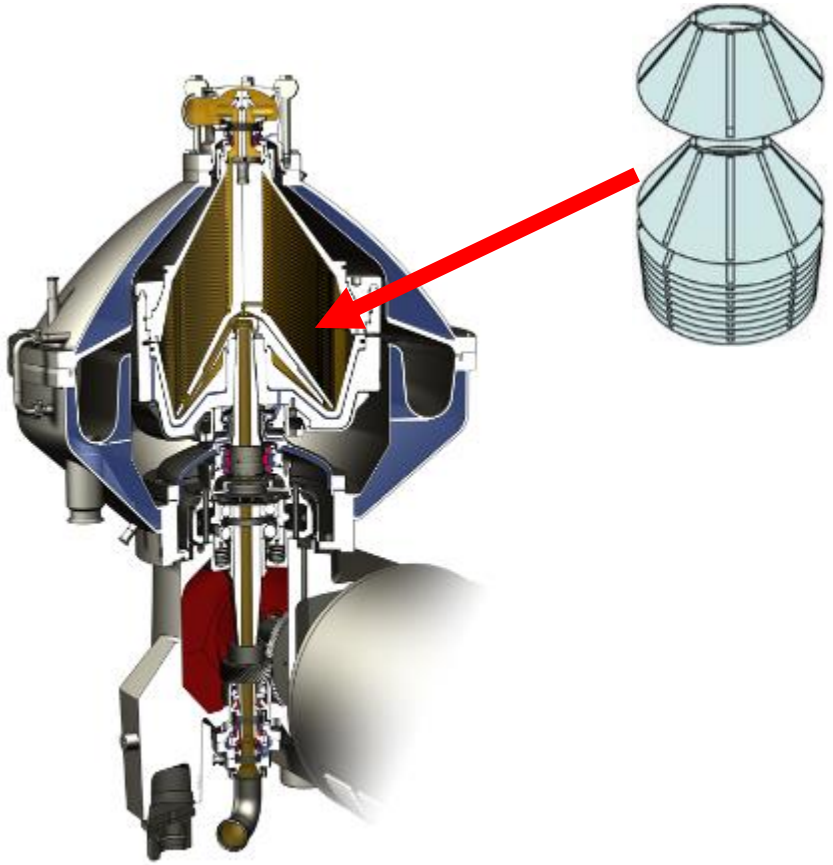
- Reactor mixing to secure optimized condition for your culture
- Mixing optimization for quality and cost improvements

Separation solutions for biopharma application

Xiaoguang Li
Global Sales Manager - Biopharma

Separation technologies in biopharma applications

- Disc stack separator is **efficient, big in capacity, and low in operation cost**
- High speed disc stack separator is a centrifuge for liquid-solid, liquid-liquid, liquid-liquid-solid **mechanical separation**
- It's a unique separation equipment based on settlement theory. It's often to see other technologies in Biopharma factories -
  - Filtration. Like hollow fiber filter, membrane filter
  - Tubular centrifuge
  - Chromatography



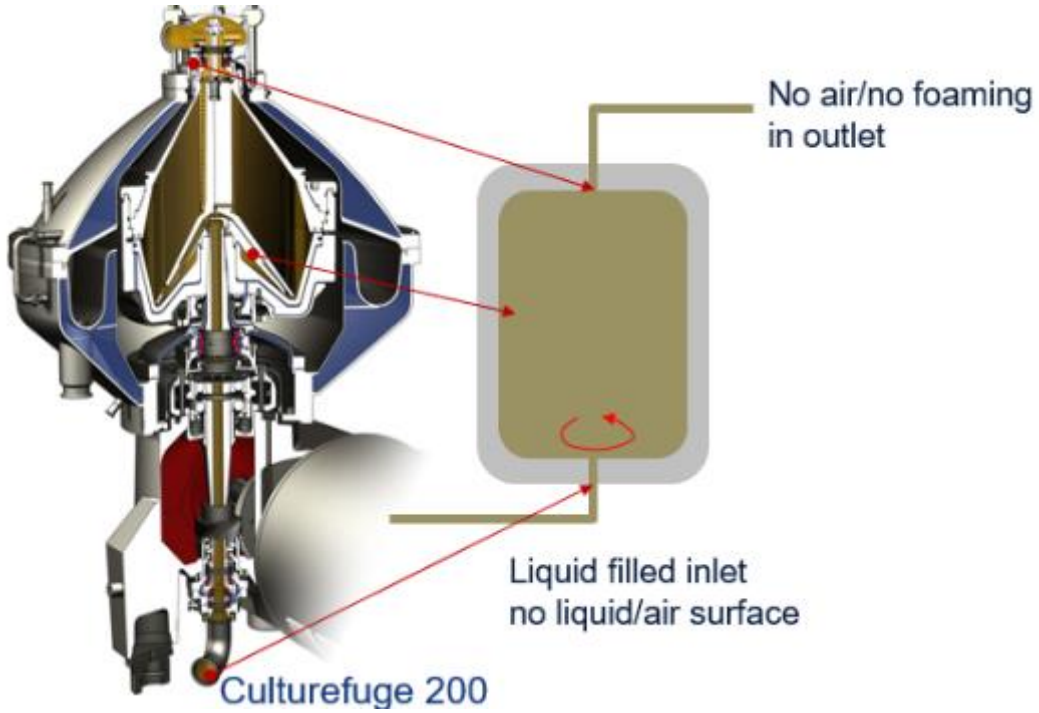
Current challenges to the disk stack separator in biopharma applications

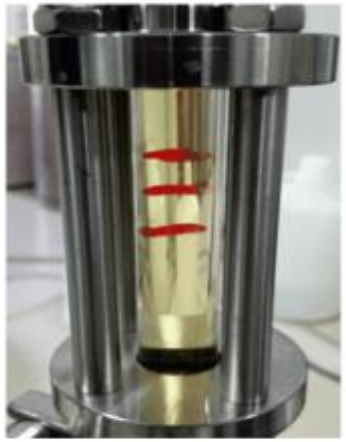
1. Temperature pick up during separation
2. High feed solid content and high viscosity of solid
3. Mammalian cell culture separation
4. Clean validation to separation system

1. Temperature pick up during separation

- **Typical feed**: probiotics, virus for vaccines
- **Challenge**: denaturing the target protein and decline the bio-active of protein, then generate less product value or product losses
- **Reason**: separator bowl and outlet device fricate with air to generate heat to conduct to process medium

Solution: Full hermetic separator, less temperature pickup because of no air contact with product

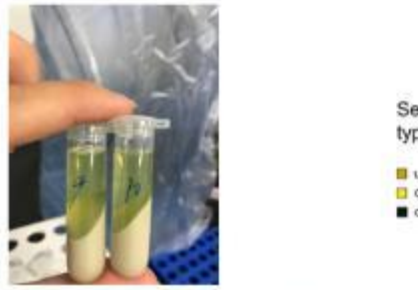




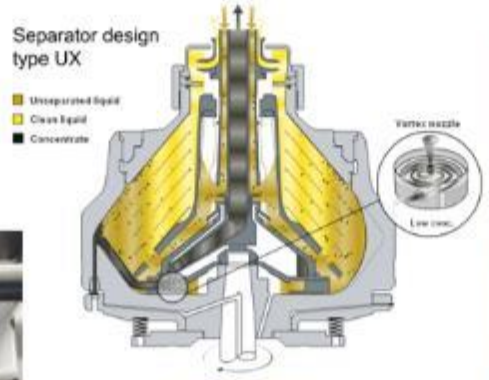
2. High feed solid content and high viscosity of solid

- **Typical feed**: Pichia yeast
- **Challenges**:
  - High fermentation density, solids content ~50%PCV, reach discharge interval limitation
  - High viscosity in solid phase due to high concentration.
  - Product yield >95%

Solution: Improve the product yield in the washing step



Feed

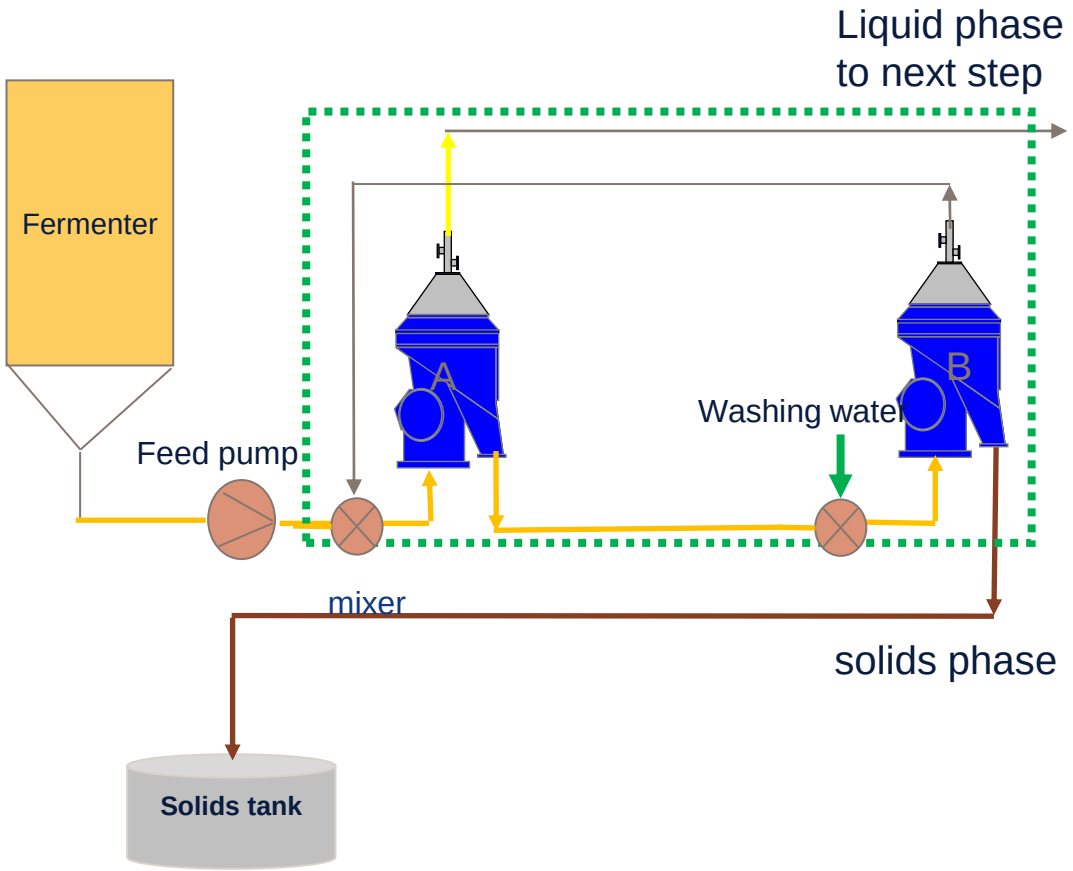


MBUX 510

Liquid phase

Solid phase

2. High feed solid content and high viscosity of solid (cont.)



3 stages count-current Pichia yeast washing line

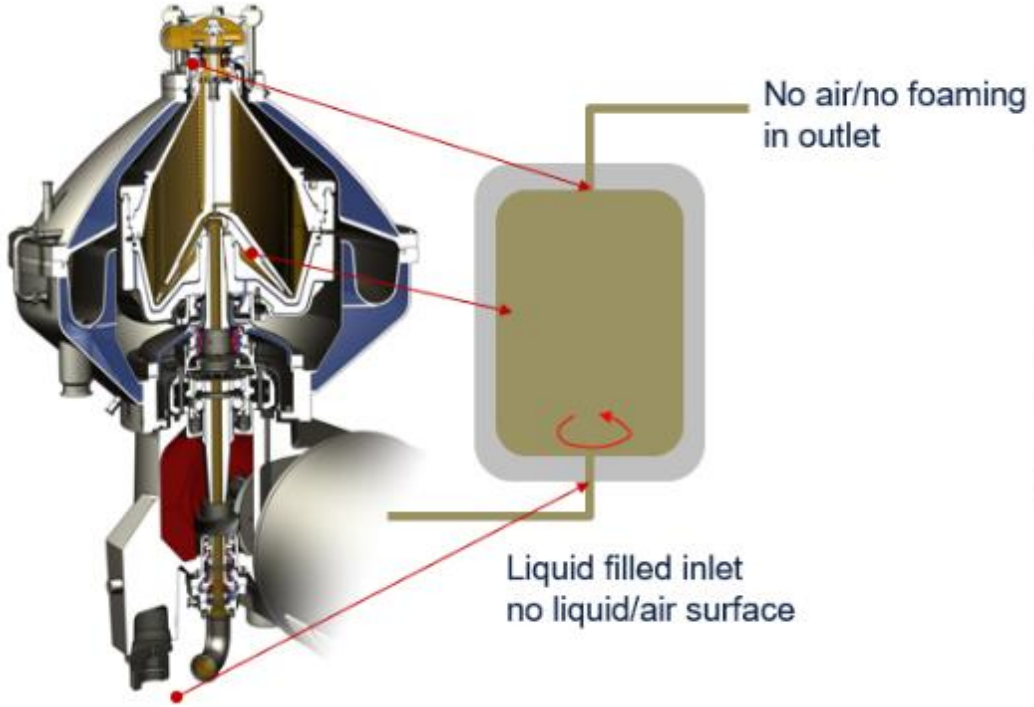
3. Mammalian cell culture separation

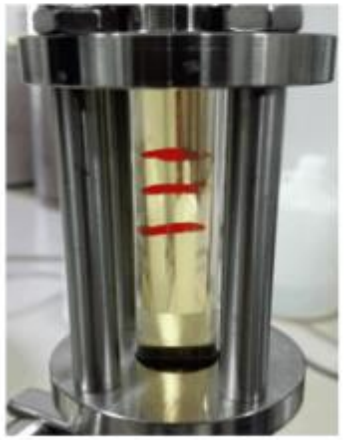
- **General aspects**: Extra cellular proteins, high-value drug

- **Separation aspects**:
  - Large compared to bacteria (10-20 micron)
  - Extremely shear sensitive because without cellwall protection
  - Long fermentation time

- **Important notes**:
  - Shear force in feed zone of separation will damage the cell to release intracellular protein to generate extra cost in chromatography section
  - Generating additional cell debris to let separation become difficult.

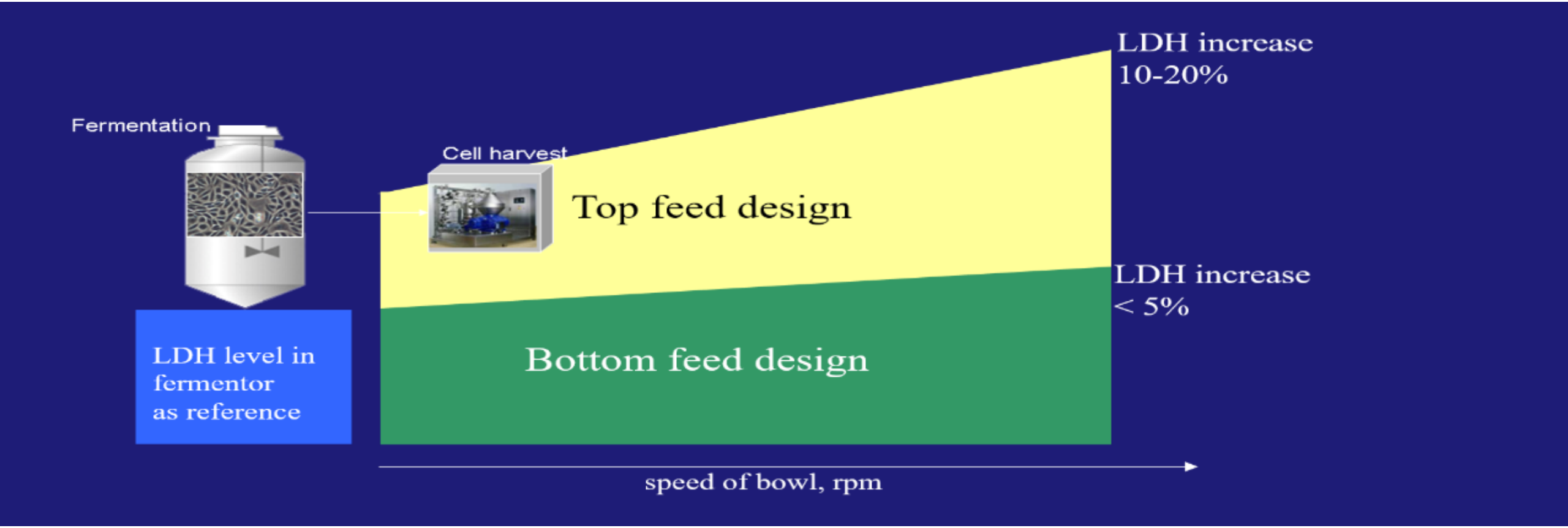
- **Solution:** Full hermetic separator, gentler treatment and lower shear force





3. Mammalian cell culture separation (cont.)

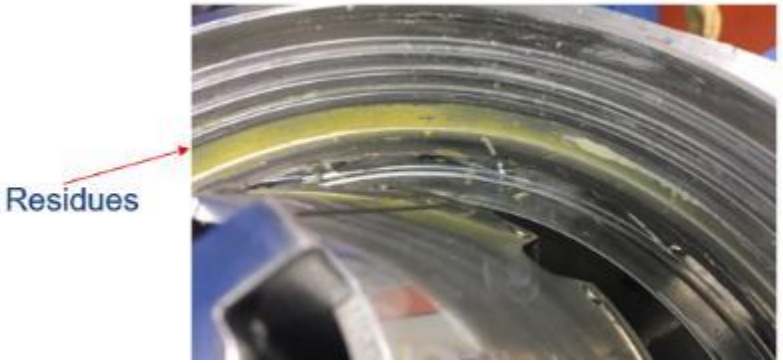
– Additional lysis shall be minimized



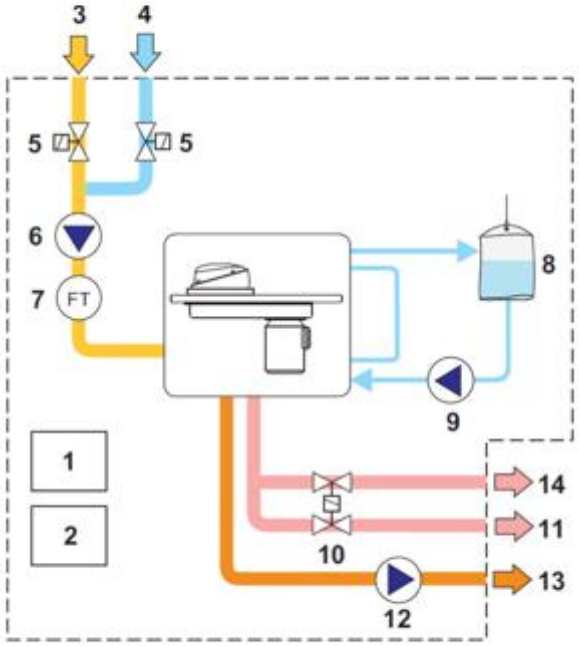
LDH = Lactate dehydrogenase, an enzyme indicate the cell lysis level

4. Clean validation to separation system

- **General aspects**:
  - Concerning about aseptic operation, the structure of disc stack separator is complicate, it's difficult to be completely cleaned by means CIP and pass through the CIP validation.
  - Separator clean validation sometimes by means of riboflavin test, but it's very hard to pass.



- **Solution:** Single-use separator



4. Clean validation to separation system (cont.)

– Single-use separator

- Small scale production meets upscale performance with single-use separator; CultureOne
- It is a disc stack full hermetic separator
- CHO cell separation capacity: up to 250l/h.
- Solid phase continuously discharge.
- Doesn’t need CIP/SIP facilities
- Easy for clean validation
- Fast connection and no maintenance requirement

Our references from around the world

Customer uses Alfa Laval separation module to treat living cell in Lonza (UK)

Customer uses Alfa Laval module with SIP for flu vaccine manufacturer in **Indonesia**

Janssen uses Alfa Laval CultureOne single use separator for CHO cell separation in Germany

Alfa Laval handed over two separation modules to customer for Covid-19 vaccine manufacturing in China

Summary of the key benefits of Alfa Laval's separators in biopharma applications

- Higher separation efficiency by means of more gentler treatment and lowest shearing force
- Higher product yield by less temperature pickup during separation low extra lysis and washing
- Higher biosafe (hygienical) level, easy for CIP and passing clean validation

- Reactor mixing to secure optimized condition for your culture
- Mixing optimization for quality and cost improvements
- Improve your harvesting processes with high-speed separation
- Optimize your operations with single-use separation