Improving Yield and Throughput of Downstream Processing: Biomass Removal & Capture Steps

BioProcess International Conference 2009, Dusseldorf – Post Conference Workshop

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Effect of Reducing Number Operational Units

- Increased yield
- Simpler PD/ process (facility & operations)
- Reduced CapEx & OpEx
- Increased throughput of product / products (facility utilisation)
- Lower burden of QC/QA

Current Manufacturing Trends

- 3 step chromatography to 2 step
- Disposable unit operations eliminate CIP
- Disposable chromatography eliminates repacking
- Process integration - Eliminate UF/DF buffer exchange & concentration step, hold tanks.
- On-line dilution replaces buffer prep.

Current Manufacturing Trends

- 3 step chromatography to 2 step
- Disposable unit operations elimin IP
- Disp repa
- Elim con
- Process integration eliminates ho ks
- On-line dilution replaces ss tanks

FURTHER IMPROVEMENTS

Current Manufacturing Trends

Intravenous immunoglobulin (IVIG) manufacturing

- IVIG sold at $50/g (hyperIVIG, $200-300/g)
- Plant capacities range from 250 kg to 5 tonnes per annum.
- (Yield critical, high demand for product)
- Chromatography increasingly used.

COHN FRACTION II+III PROCESSING

Ethanol Precipitate II+III resolubilised

Depth Filtration

Sterile Filtration

Chromatography

Similarities to high titre mammalian cell culture

- +10g/L IgG
- Large amount of sticky insolubles
- Clarification results in yield losses (5-10%)
- Batch processing time important

COHN FRACTION II+III PROCESSING

Ethanol Precipitate II+III resolubilised

IgG Direct CAPTURE

- Elimination of depth filtration/fine filtration
- 10% increase yield
- 1 extra batch per week possible

Direct Capture For Monoclonals

Centrifugation or Microfiltration

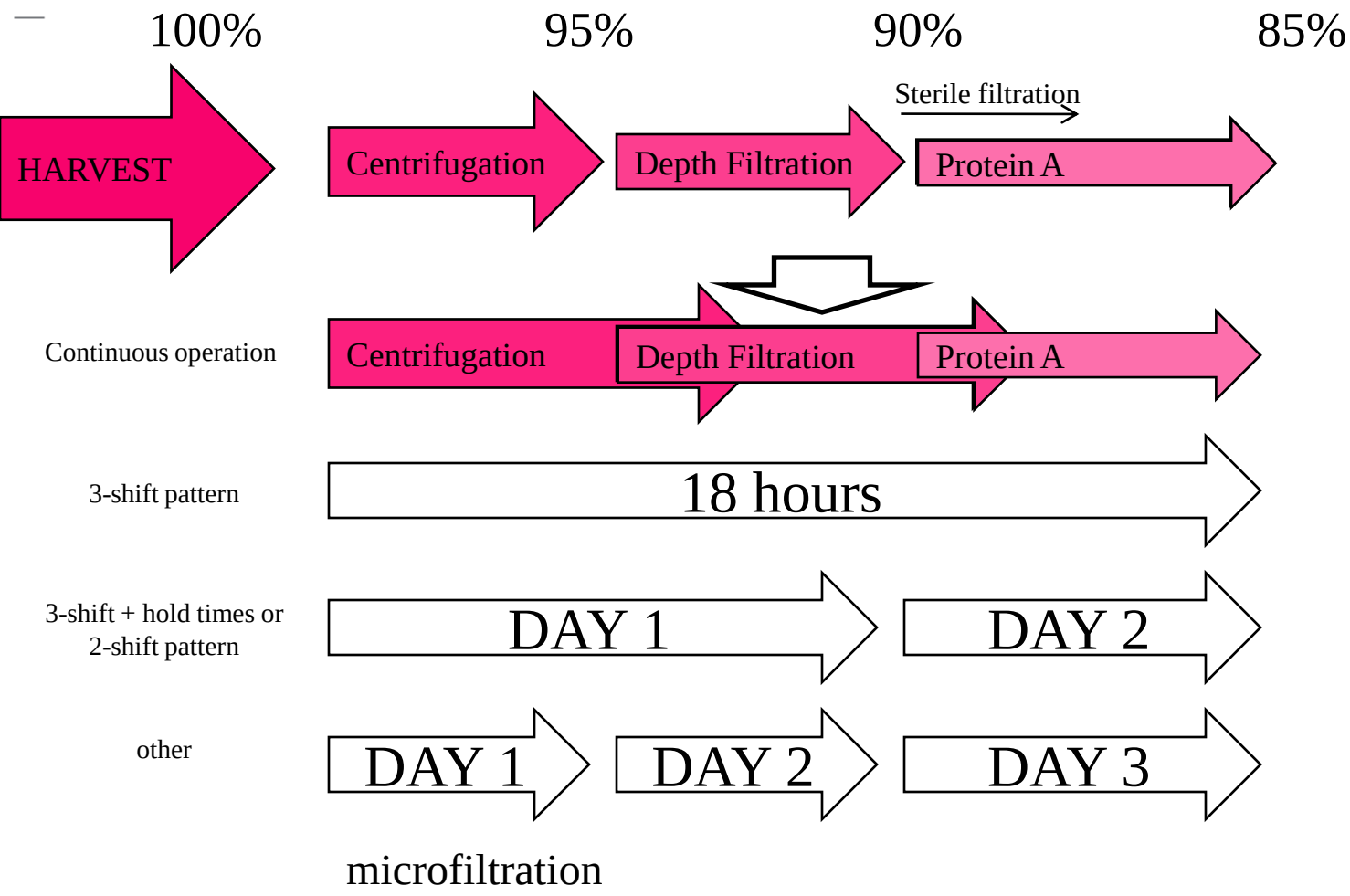
Depth filtration

Fine/Sterile filtration

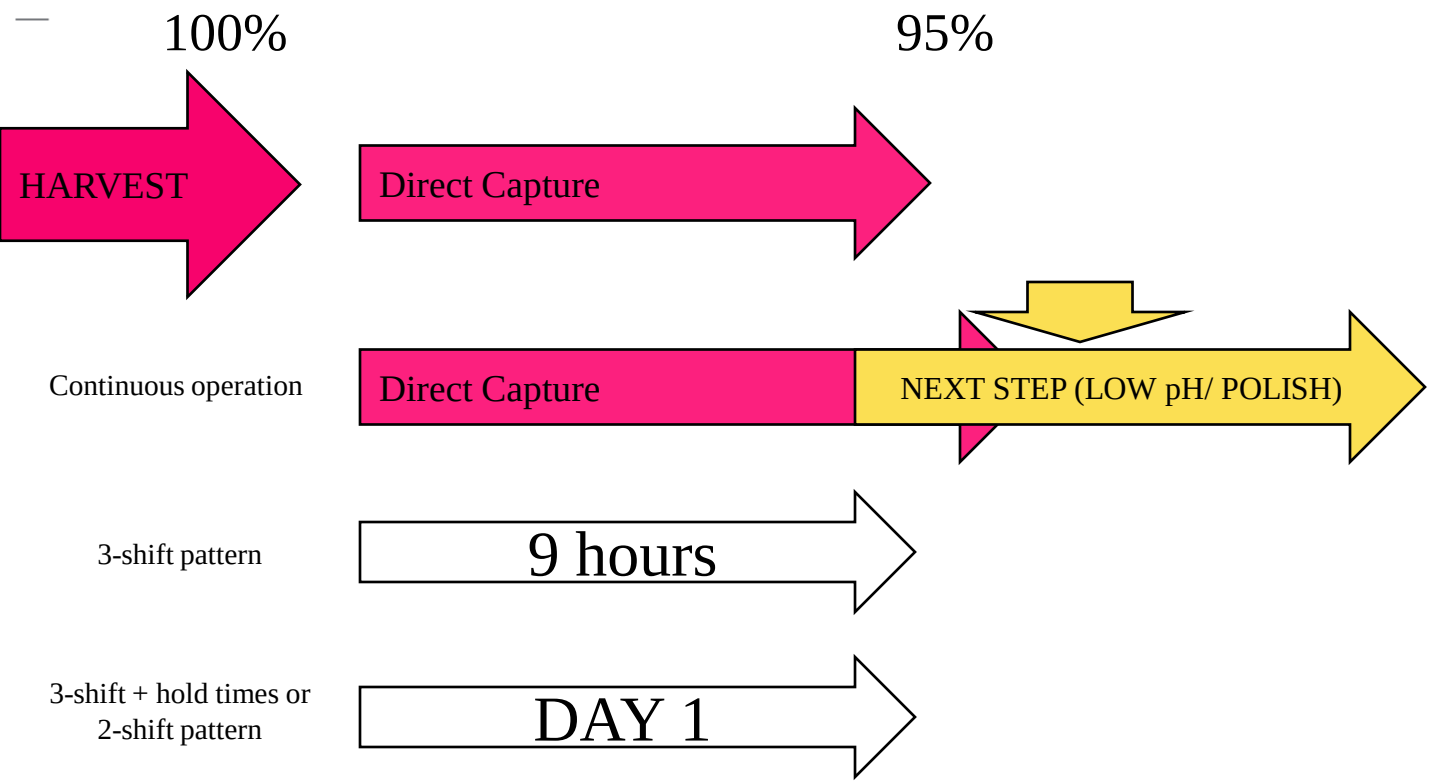
Packed bed Protein A

Direct Capture For Monoclonals

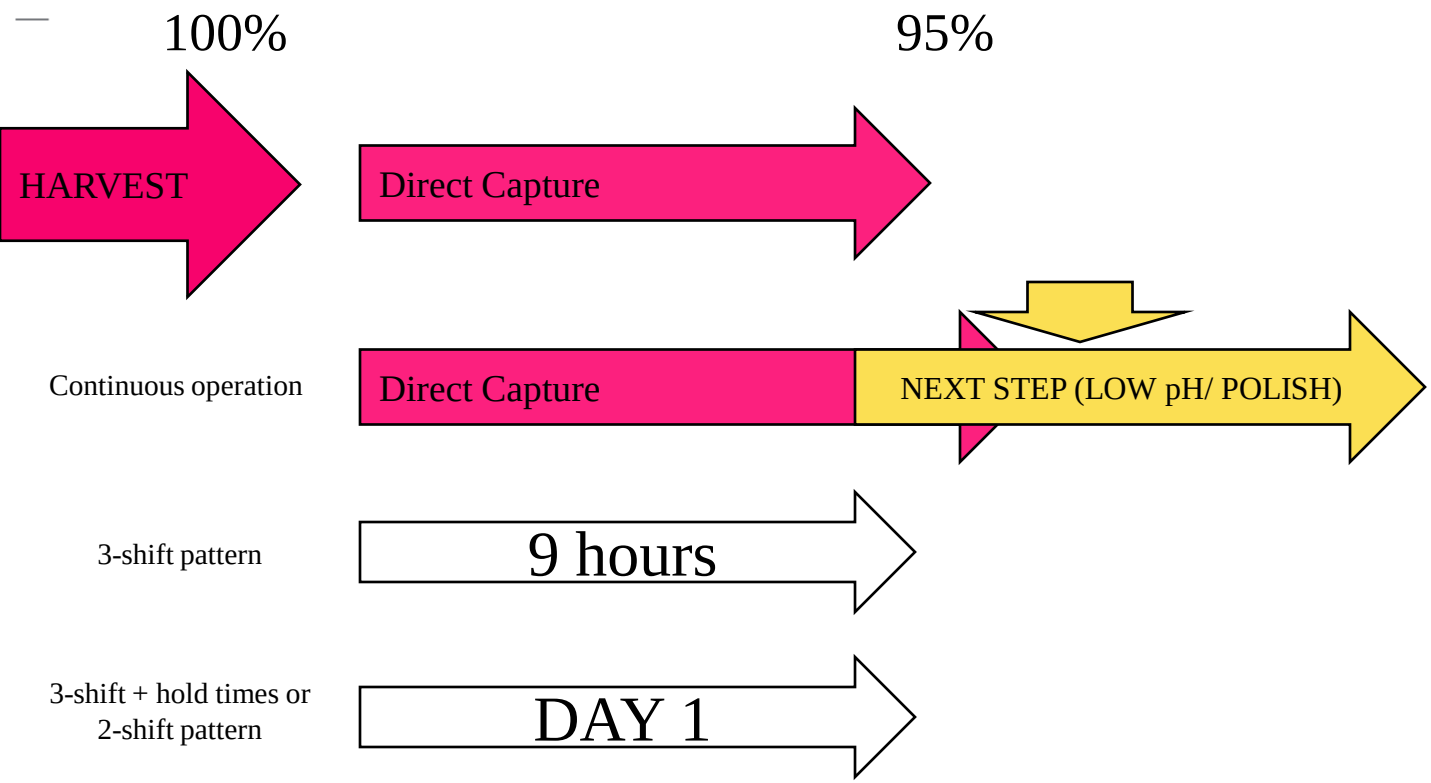
Value of Throughput in Different Facilities



Facility Utilisation with Direct Capture

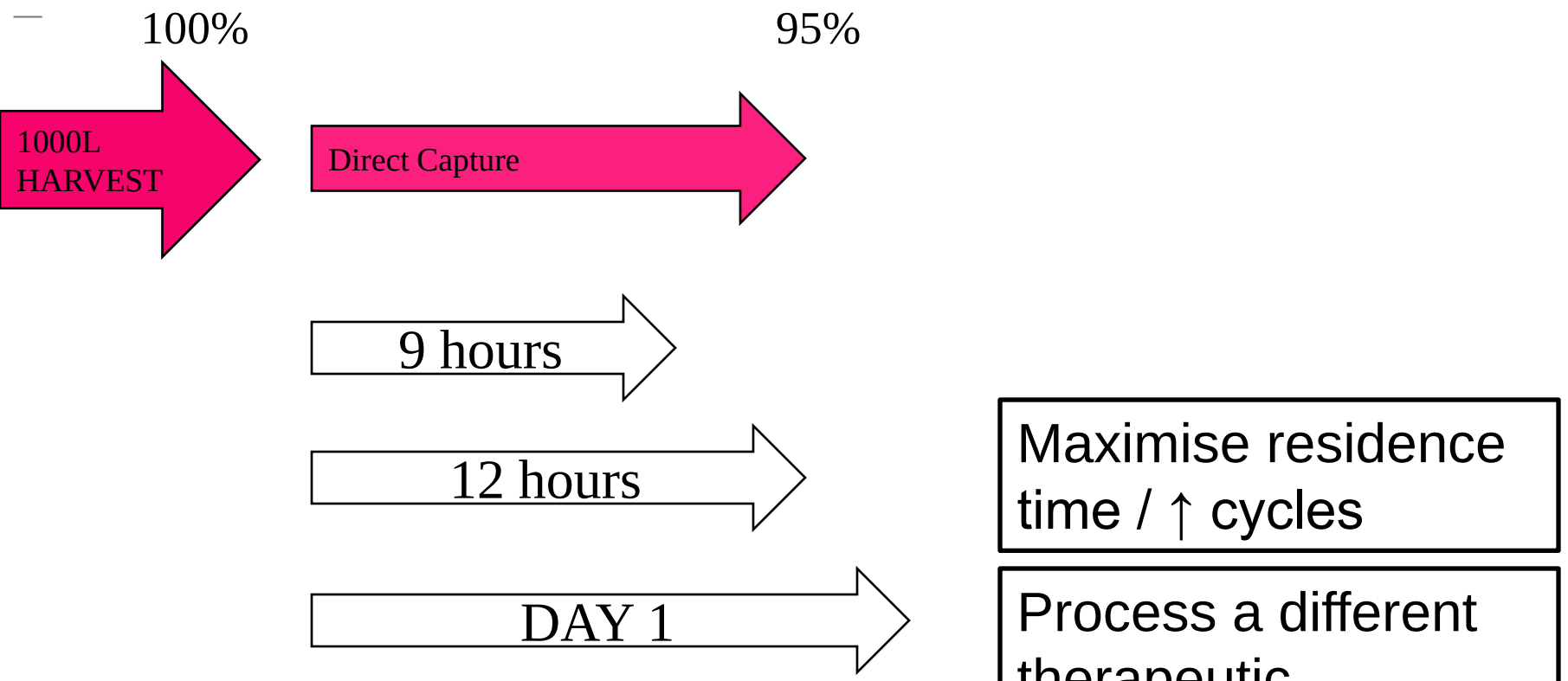


Facility Utilisation with Direct Capture

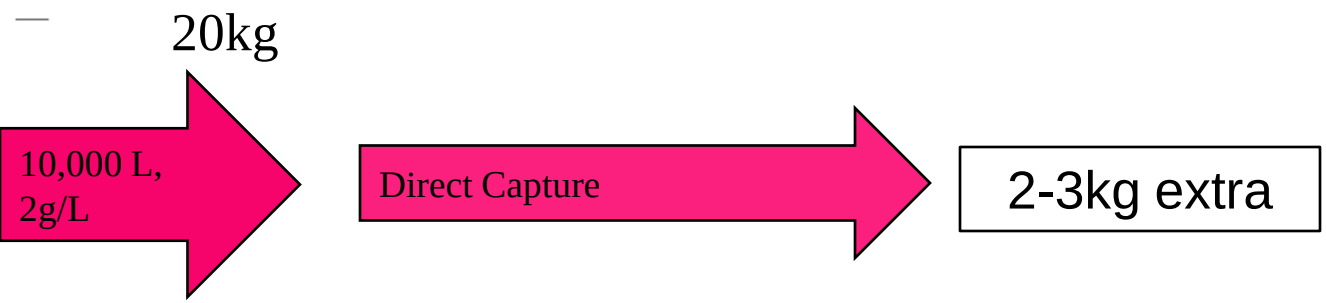


- Improve facility scheduling / extra bioreactor runs

Effect of Single-Use Direct Capture on Facility Utilisation



Yield Increase 10±5%



- Sales value ($2000/g) = **$2-3 million per bioreactor run**
- Manufacturing value ($150/g) = **$300,000-$450,000 /bioreactor**
- Increase facility production capacity
- Number of products / projects ?
- Lower burden of QC samples ?
- etc

Direct Capture Processing Advantages

- Throughput (Productivity)
- Yield
- Footprint
- Cost of Goods

Considerations Of Future Processes

High Titre Feedstocks
Smaller reactors
Multi-product facilities

Clarification issues

- Process development required
- Increased solids entrapment (dead-end) vs processing time (TFF)
- Increased single use consumable cost (disposable centrifuge/depth filtration)

Cost of Goods

	Contribution	Comments
No requirement for clarification	C of G ↓	Major effect = yield increase
	Cap Ex ↓	Eliminate centrifugation/depth filtration/fine filtration units (disposable clarification)
No CIP (adsorbent or operating system)	C of G ↓	WFI, acid, alkali, steam, time
	Cap Ex ↓	Validation, CIP equipment, tanks
Flexibility / Facility Utilisation		Optimal use of clean rooms

Economic Considerations

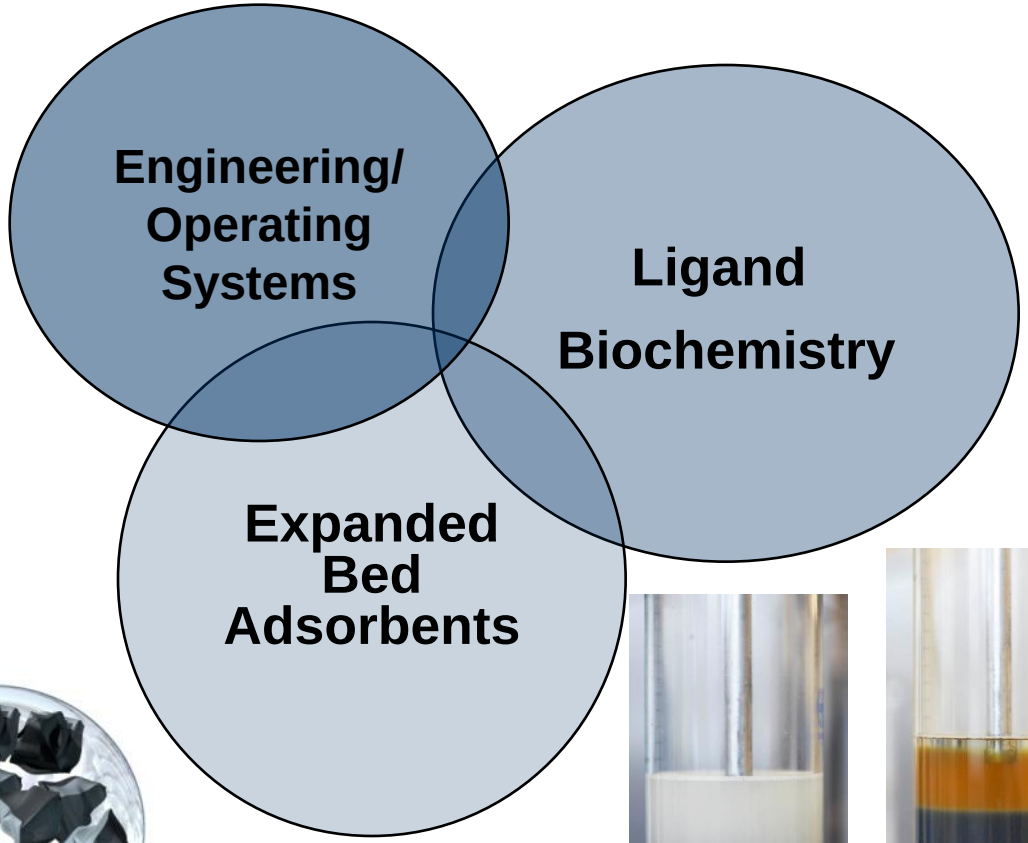
	Contribution	Comments
Consumable cost (low number of cycles)	C of G ↑	Adsorbent cost usually mitigated by cycling
Waste management	C of G ↑	Incineration costs

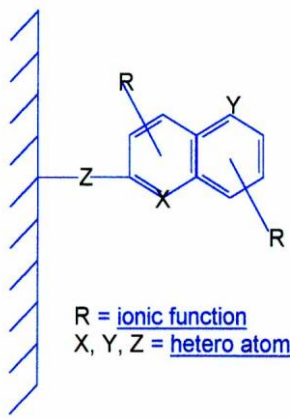
Economic Considerations

	Contribution	Comments
Consumable cost (low number of cycles)	C of G ↑	Adsorbent cost usually mitigated by cycling. However, Direct Capture eliminates consumable costs of clarification steps.
Waste management	C of G ↑	Incineration costs. Direct Capture eliminates extra waste from clarification steps.

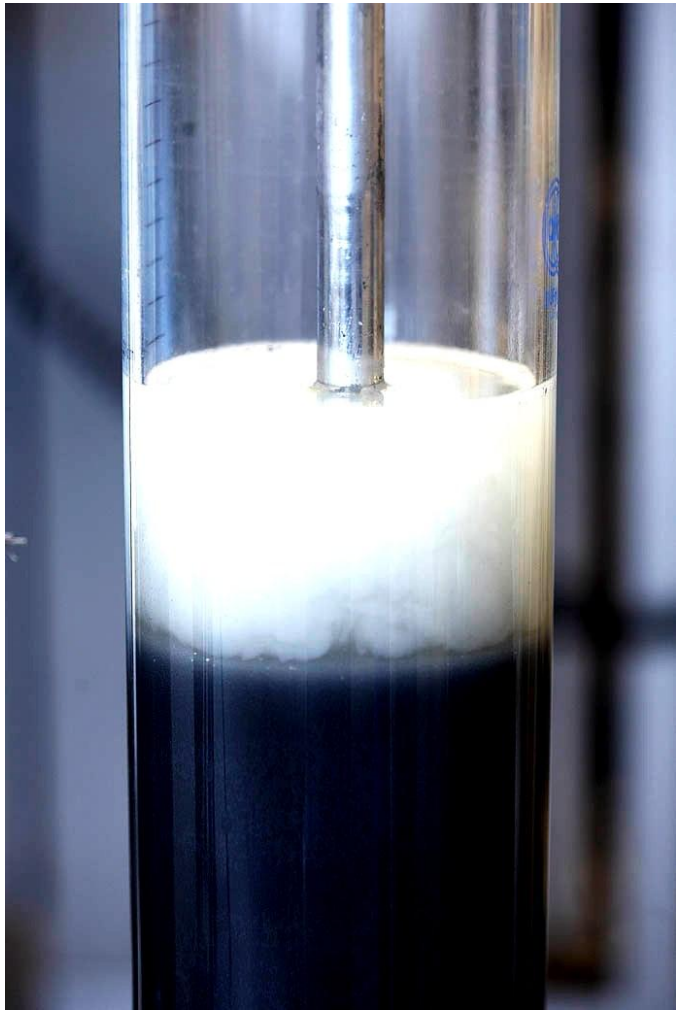
Direct Capture Technology

CRITICAL INNOVATION AREAS





Second Generation – EBA v 2.0



Reduced buffer consumption

- Tall column (50cm sbh)
- Reduce expansion during washing and elution

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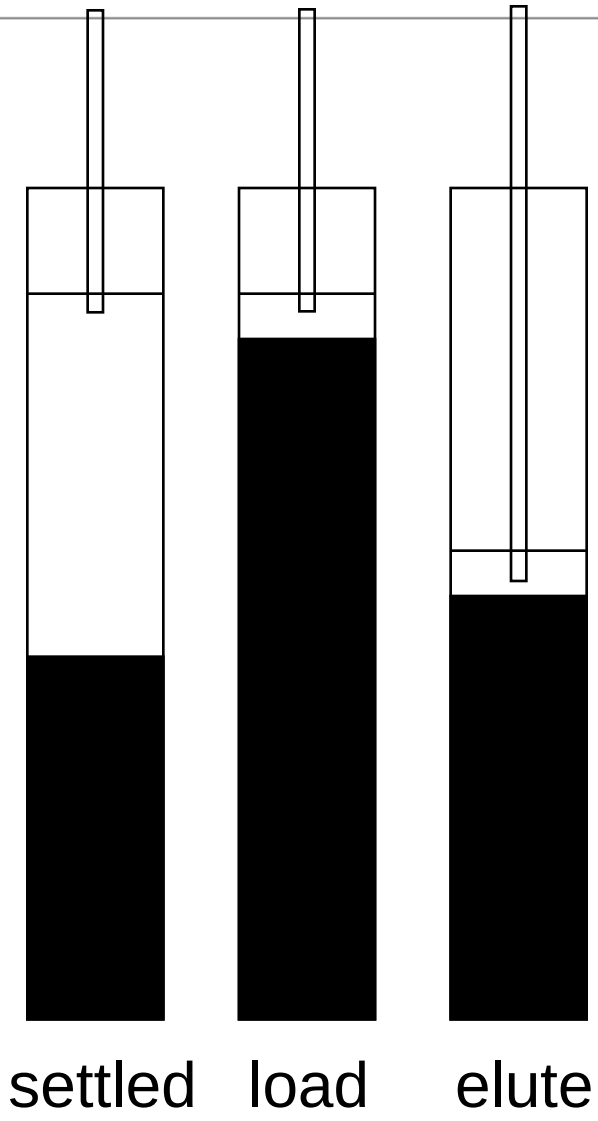

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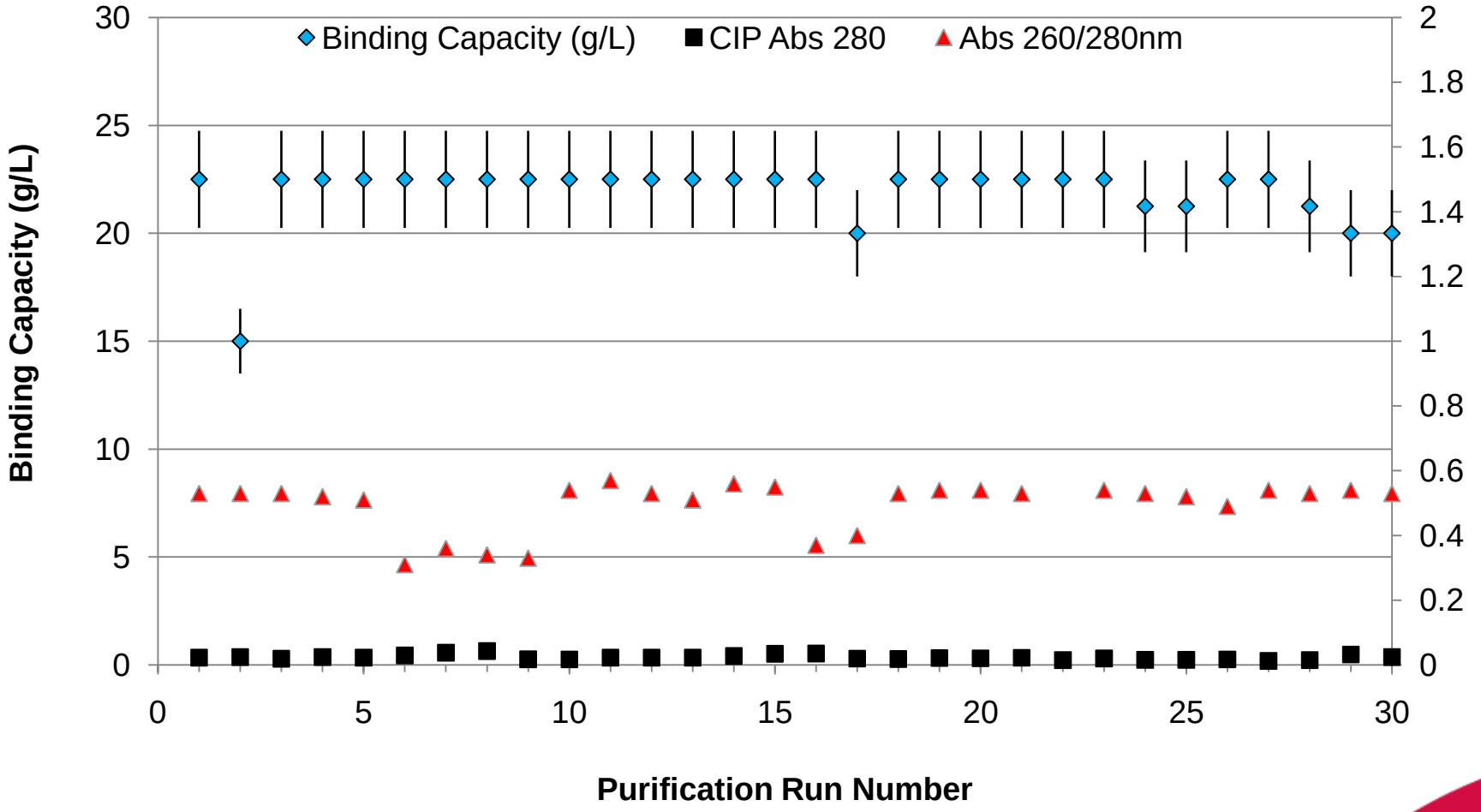
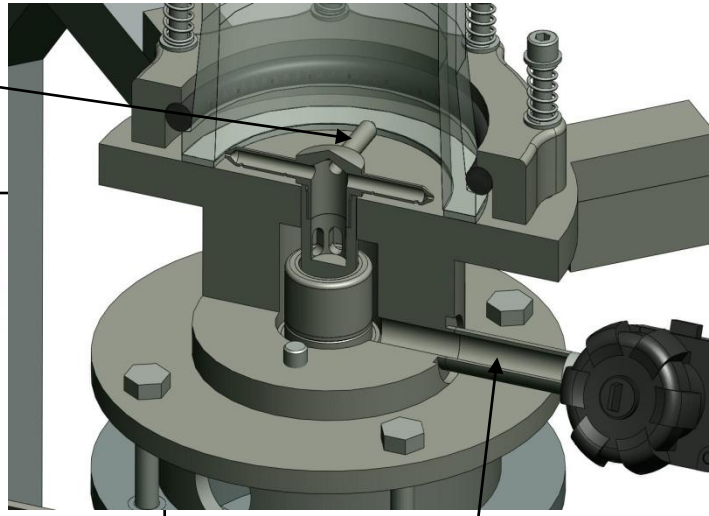
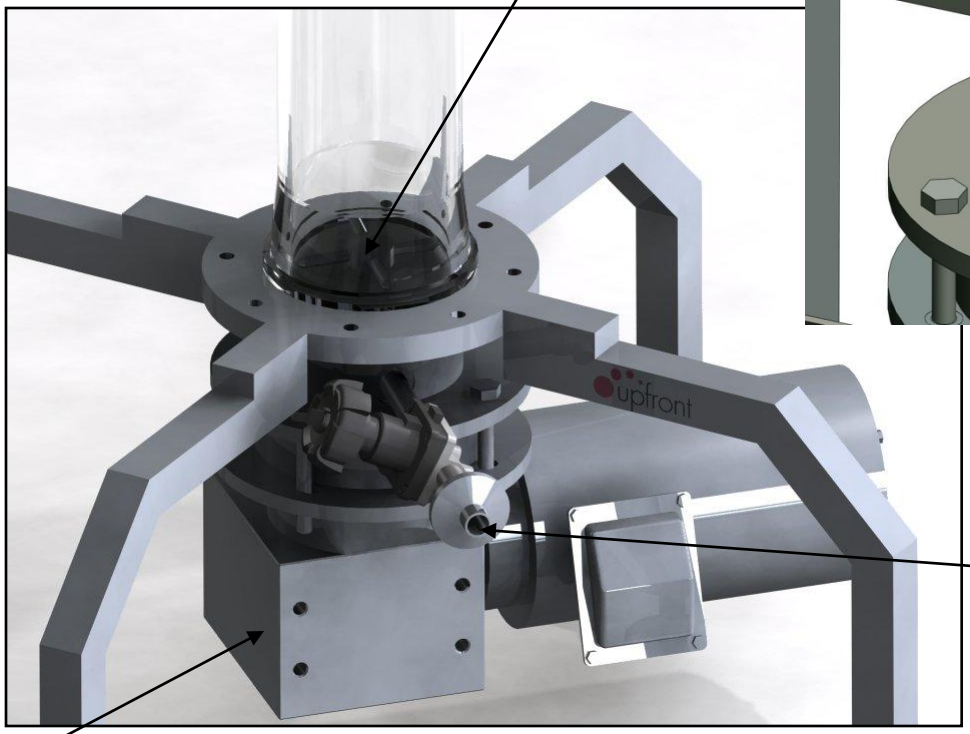
Repeated Cycles Data – 5% w/v Yeast Homogenate, 1g/L IgG (50mM NaOH, 1M NaCl CIP)



Second Generation – EBA v 2.0

Rotating fluid distribution arm





Rotation speed 0-70rpm, direction reversed every 10-350 sec (adjustable)

Fluid inlet

Motor driven fluid distribution unit

Second Generation – EBA v 2.0

One Campaign !!

Scale-Up, Robustness, Ease of Operation

- Industrial technology came first
- 1cm – 150cm scale up

Process Development Tools

Process Development Tools

Rhobust Flex Operating System & Production Scale

cGMP *Rho*bust™ EBA Features

FEATURE	PROCESS BENEFIT
Increased Density Beads	High flow rates Stable bed High inertia to changes
No porous plates	Processing crude or unstable feedstocks without clogging
Mixed mode affinity ligands	Increase selectivity, reduce non-specific binding
Inherent positioning of beads	No column packing/repacking

cGMP *Rho*bust™ EBA Features

FEATURE	PROCESS BENEFIT
High temperature (60 °C) 1M NaOH ***facilitated***	Thorough clean-in-place facilitated Long adsorbent lifetime
High Fluid Velocity Cleaning (spray balls, flow distribution jets)	No low flow areas, no dead spots Easy to remove adsorbent
Proprietary dual pump operation	Inside of column equilibrated with atmospheric pressure
Tall (1 m, 2 m, 3m), large columns (1,5 m diam. = 1,700 L-7,000 L)	Minimise wash & elution volumes Minimise number of cycles

UFC Process Technology - Practise

- ✓ ISO 9001 certified since 2003
- ✓ Provide regulatory support file data
- ✓ Clean room manufacturing
- ✓ Present production capacity of 1000’s litre per customer
- ✓ No animal raw materials
- ✓ FDA food approved since 1998