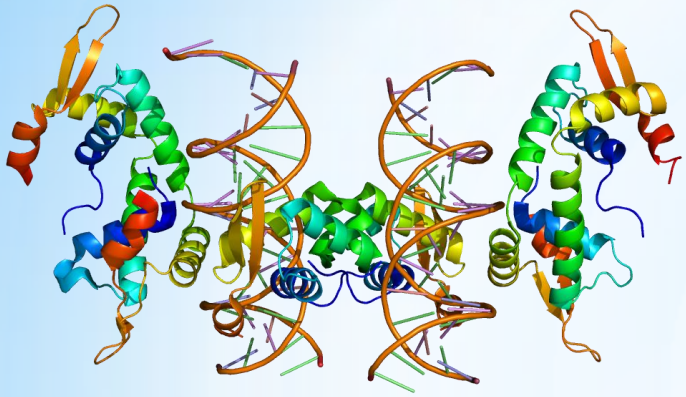

Technical and economical challenges in downstream processing

Adebiotech – Paris – 28, 29 & 30 October, 2013

Pierre Lepage

Content

- Biotech’s economical aspects
- Challenges in biotech industry
- Future
- Conclusion

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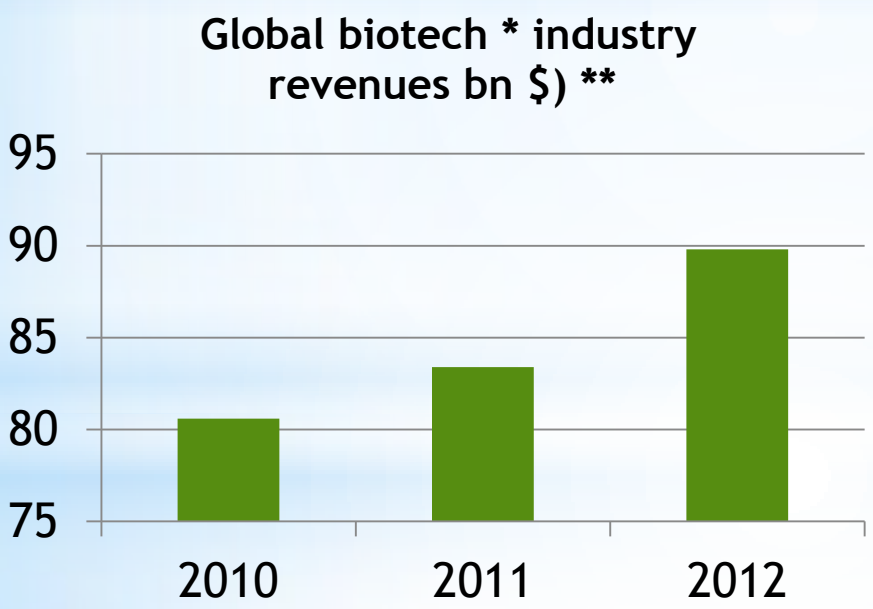
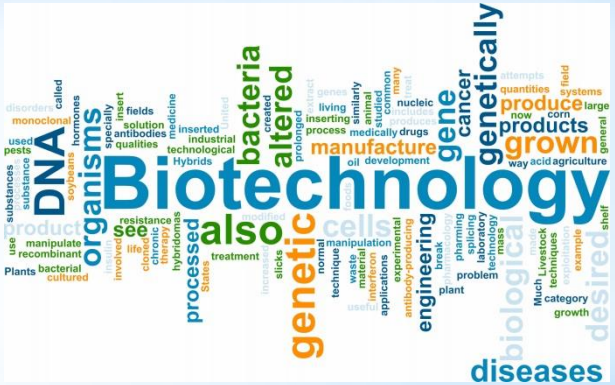
Biotechnology: a growing industry





* Biotech industry:
- Agriculture – genetically-modified seeds
- Manufacture of enzymes (food processing, éthanol,...)
- Phamaceuticals (Ab, Inteleukins, Vaccines,…)

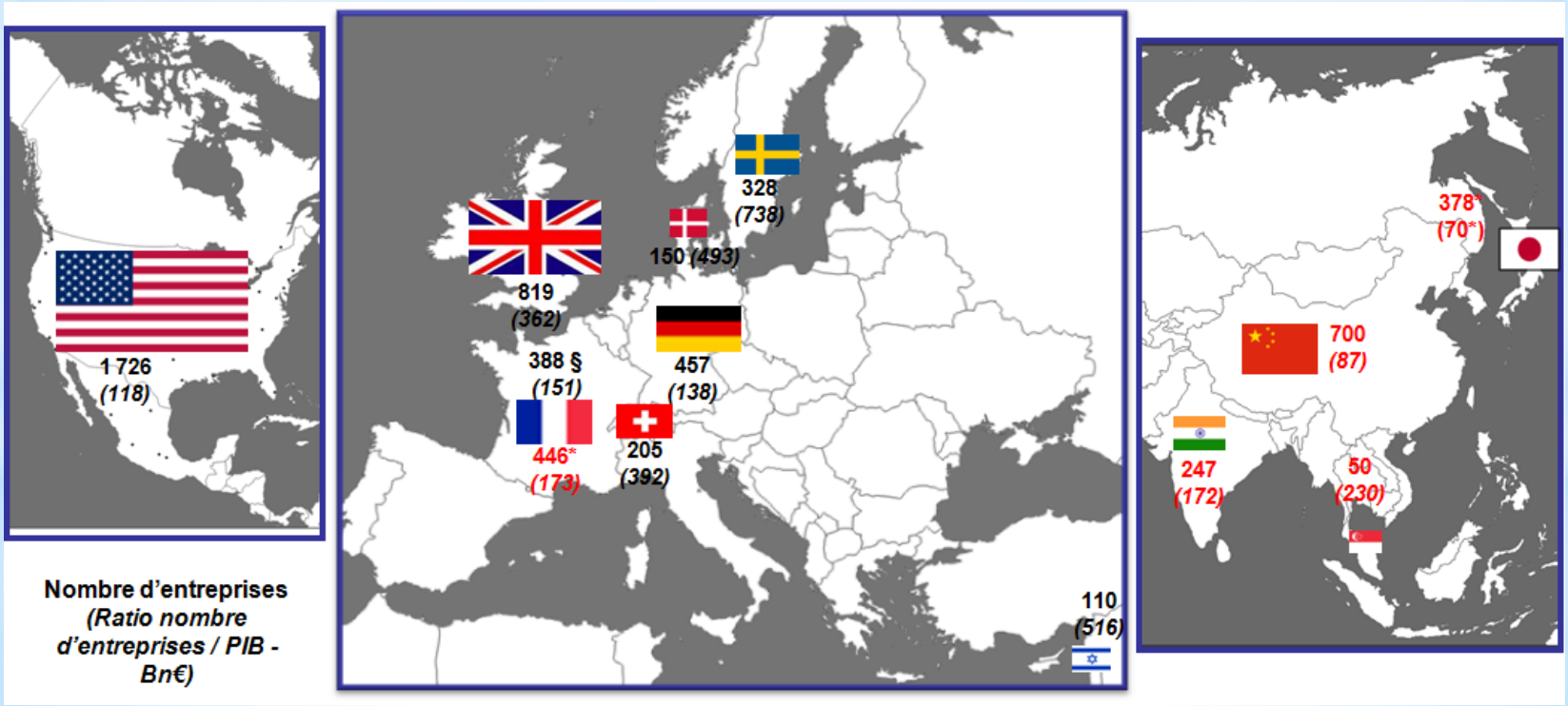
**: Ernst & Young

Global factors boosting biotech today

- Rapid aging of the population
- Renewed global focus to develop effective vaccines
- Major pharmaceuticals firms paying top prices to acquire biotech drug companies
- Increase dependence on genetically-engineered agricultural seeds
- Biotechnology research in Singapore, China and India
- Substitutes for petroleum-based fuels
- Ability of gene therapies to cure patients
- Drug market growth in emerging nations
- Focus on rare diseases or relatively small portions of the population.

Source: Plunkett Research, Ltd.

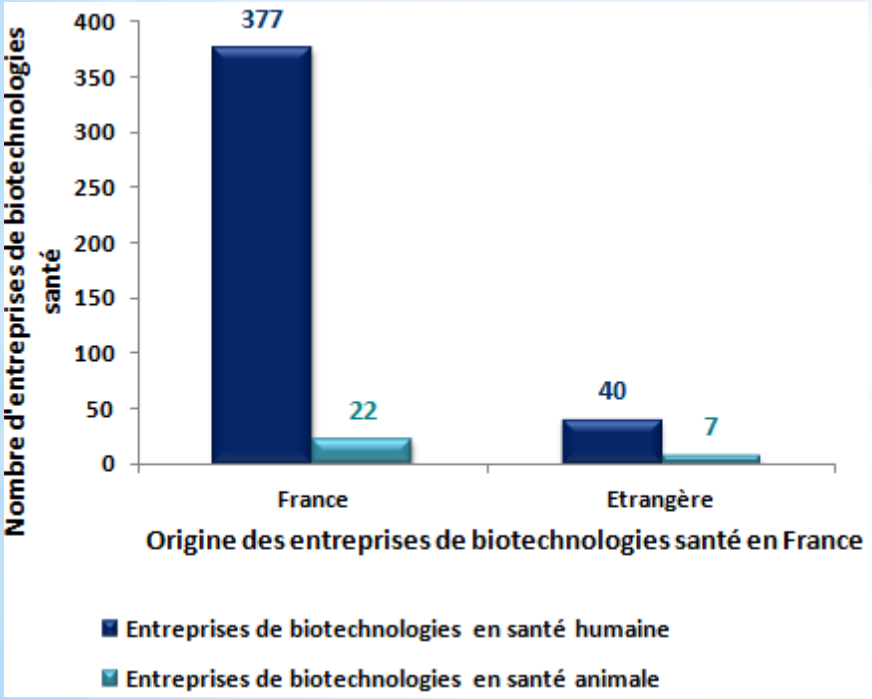
Repartition in the world and in Europe

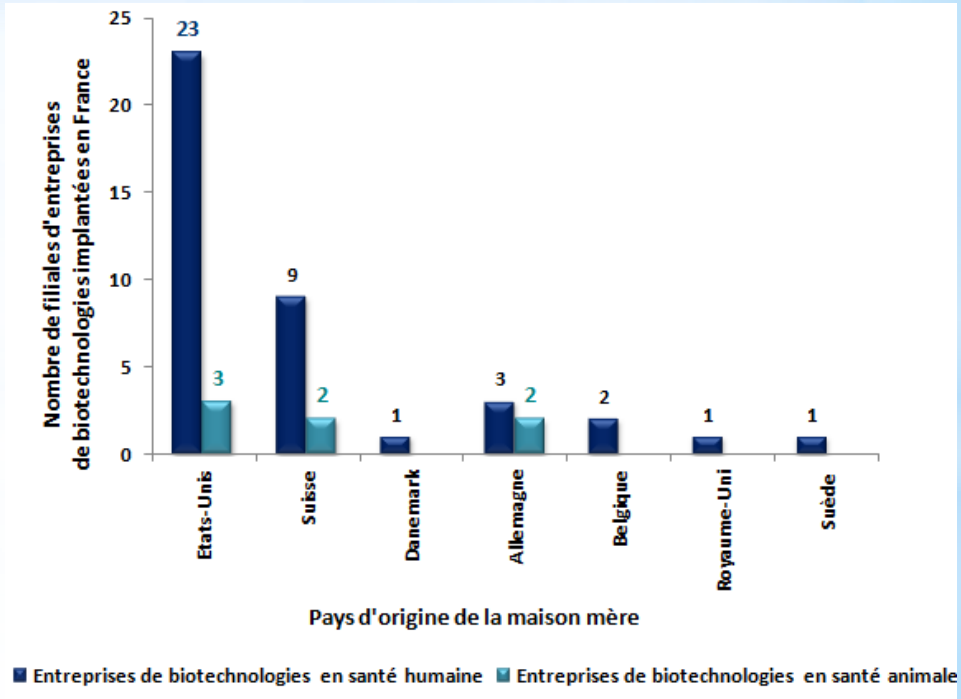


§ Base comparative de 388 entreprises de biotechnologie de la santé
* Base comparative de 446 entreprises actives en biotechnologies de santé
Pour le Japon, les seules données disponibles datent de 2005

Source:
Comité biotechnologies de santé du LEEM – Développement & conseil - 2011

Biotechnology : Status in France





Biotechnologies de santé: 1,5 Md€
11 000 personnes.

Source:
Comité biotechnologies de santé du LEEM – Développement & conseil - 2011

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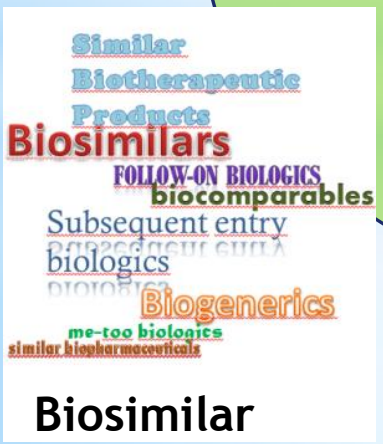
Challenges in biotech industry

Quality

Efficiency

Cost



Biosimilar

Financial crisis

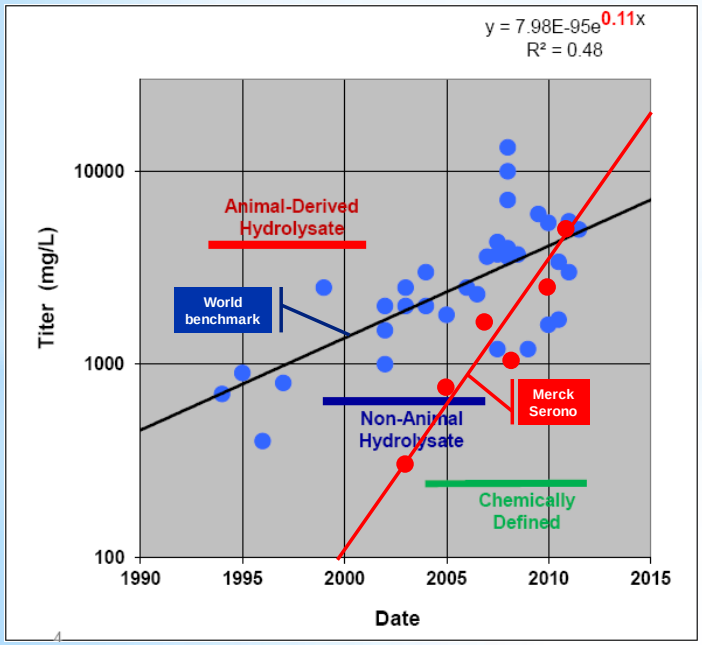
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA
U.S. Department of Health and Human Services
Food and Drug Administration

Regulatory constraints

Capabilities of low cost countries

Downstream processing – What is new ?
Antobody production

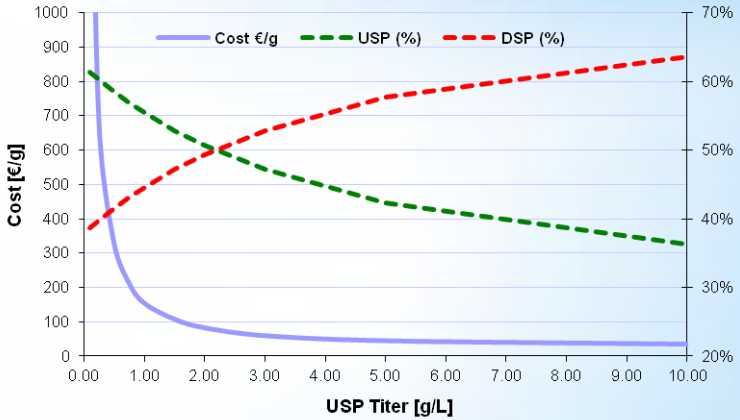


State of the art: 3-5 g/l

En 2010 DSM announced very high levels of McAbs (10 to 27 g/L) using XD production

← Cell Culture Mode of Manufacturing →

Fed Batch	XD™	Perfusion
Feed concentrate	Medium Feed	Medium Feed
Build up Metabolites	Wash out Metabolites	Wash out Metabolites
Osmo increase	No Osmo increase	No Osmo increase
Changing environment	Constant environment	Constant environment
Reducing cell viabilities	High cell viabilities	High cell viabilities
Concentrated Harvest batch identification	Concentrated Harvest batch identification	Dilute harvest Large harvest



DSP Challenges

Capacity mismatches between USP & DSP

Need to adapt DSP by addressing

- Purification step Performance, Quality & Cost
- Manufacturing efficiency and removal of non value added activities
- Evaluate Capex & investments for economical running cost

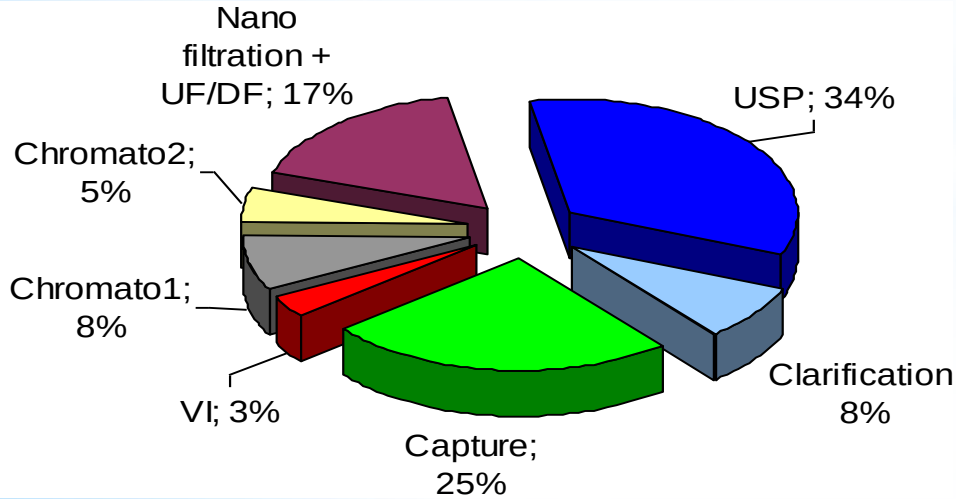
Downstream processing challenges

- **Purification step Performance, Quality & Cost**
- Manufacturing efficiency and removal of non value added
- Economical running cost considering Capex & investments

Production cost

Market needs:
Several tons due to large dosage over long period

100 kg / Batch

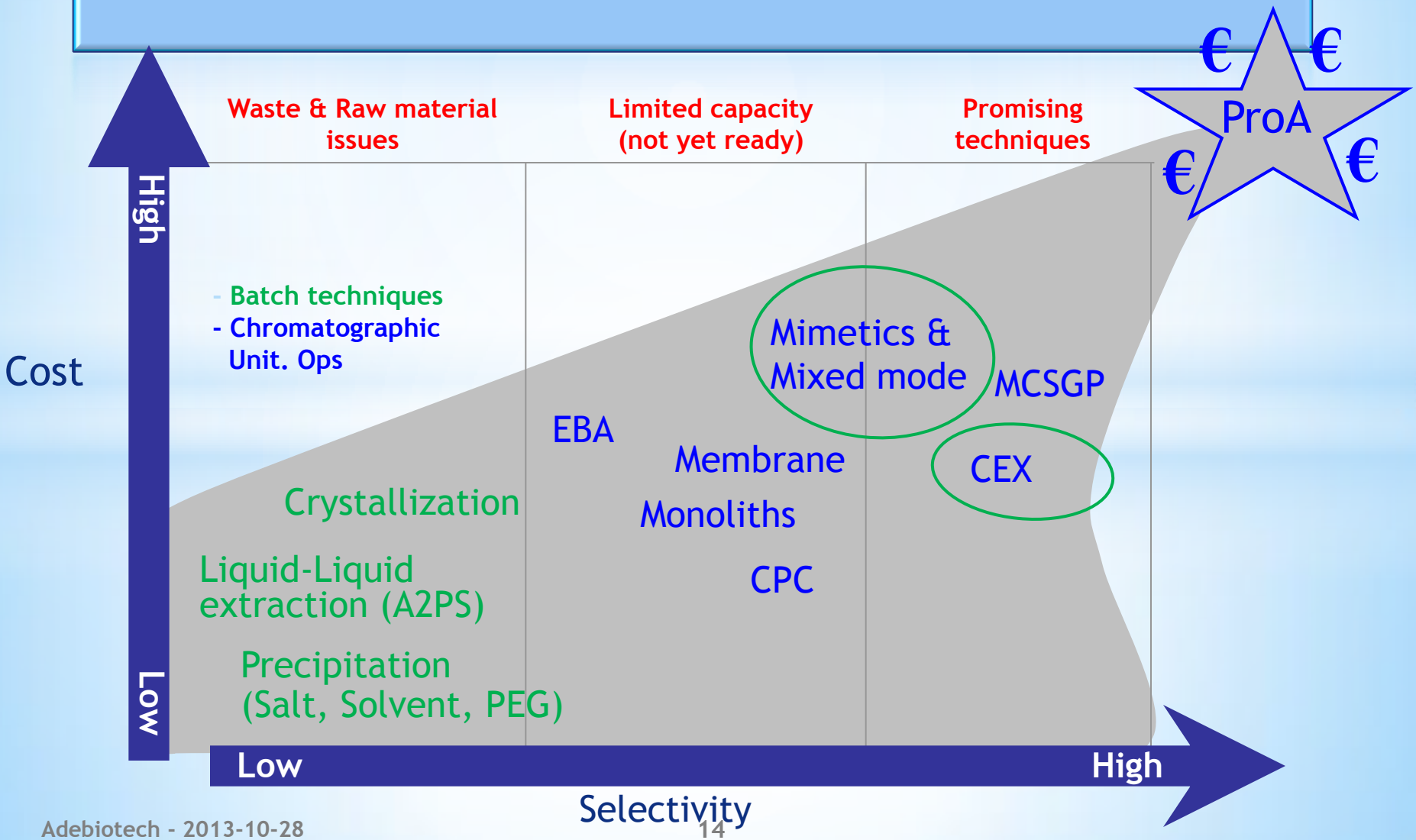


Capture step: 25 %

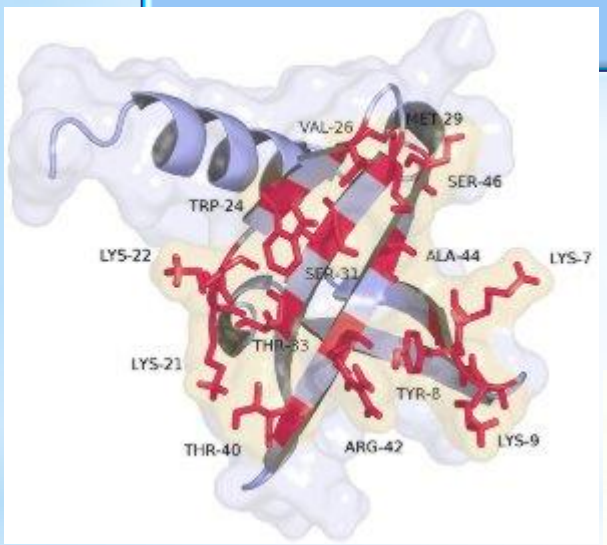
Viral filtration: 17%

Chromatography: 13%

USP volume & capture step

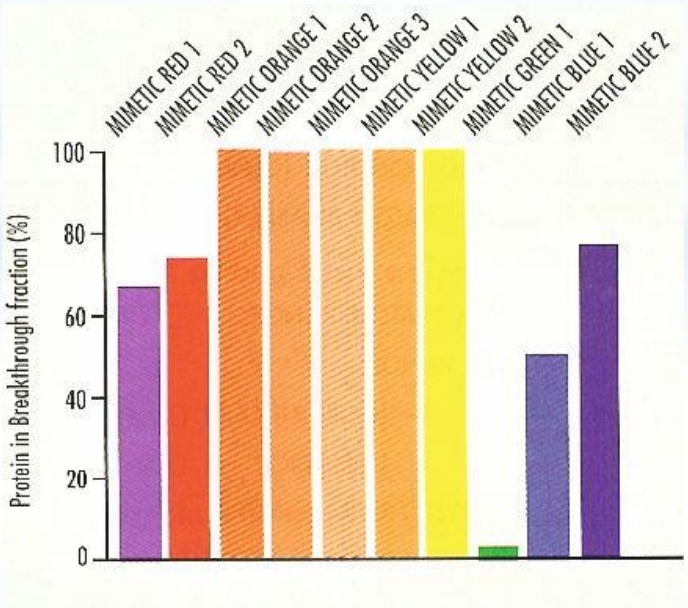


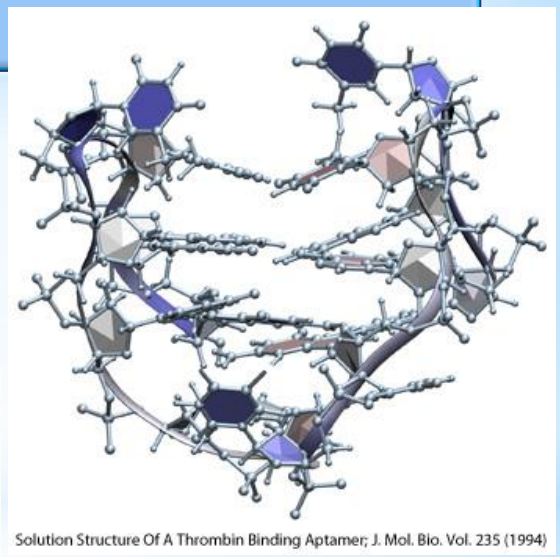
Capture step with mimetics agents



Nanofitins
Affilogic

Conventional Mimetics dyes




Solution Structure Of A Thrombin Binding Aptamer; J. Mol. Bio. Vol. 235 (1994)

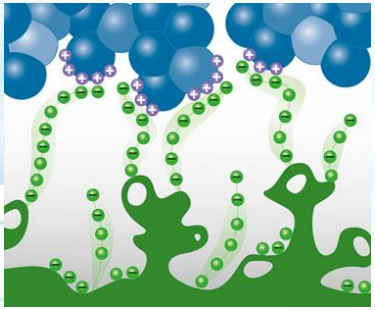
Aptamers

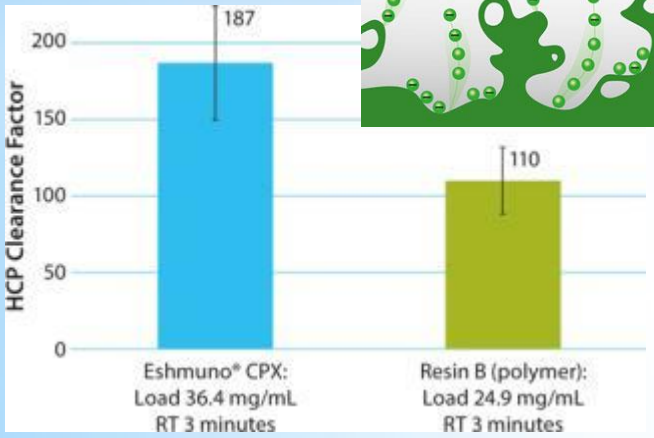
New generations of resins & membranes

NEXT GENERATION CEX:

- Improve selectivity: To address issues on Dimers/Aggregates – Charged variants – Truncated forms – HCP - DNA
- Improve capacity : >100 mg/ml

Eshmuno® CPX
EMD Millipore





POROS® XS
Applied Biosystems

High capacity > 100 mg/ml +
high resolution +
high salt tolerance

Membrane adsorbers
Sartorius Stedim

Virus filtration optimisation

17% DSP cost

- To achieve highest throuput without compromising
  - Flow rate
  - Log reduction value
- Challenge
  - Higher concentration and viscosity
  - Viruses smaller than 20 nm
  - Hydrophilic and hydrophobic properties of the Ab, isolelectric point, tendency to aggregates
- Possible solutions:
  - New generation of filter with better flow properties
  - New generation of pre-filters decreasing sub-particles content
  - Virus stock used for spiking => higher purity and concentration available

Downstream processing challenges

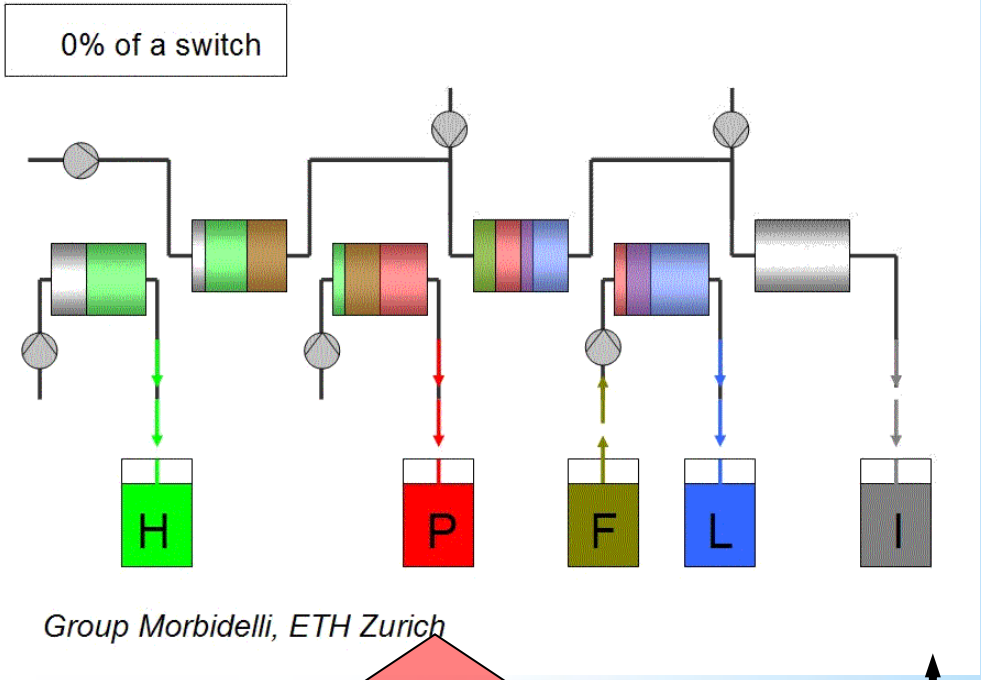
- Purification step Performance, Quality & Cost
- **Manufacturing efficiency and removal of non value added activities**
- Economical running cost considering Capex & investments

Reducing volume
Sequential Multicolumn Chromatography

BioSC® from Novasep

Expected reduction in :

- **Buffer consumption**
- **Resin consumption**
- **Process time**



Single use technology

15,000	drug compounds in pre-clincal
15	in clinical study
3	on the market
1	product with revenues to cover their cost

- Need to test many concepts
- Least amount of cost
- Capital expenditures

Flexibility – Speed - Safety

Why single use ?

USP Class VI Certified

Single use in Biotech manufacturing

ISO 10993-5

Single use technology – Downstream application

Pall – Mustang Membrane chomatography

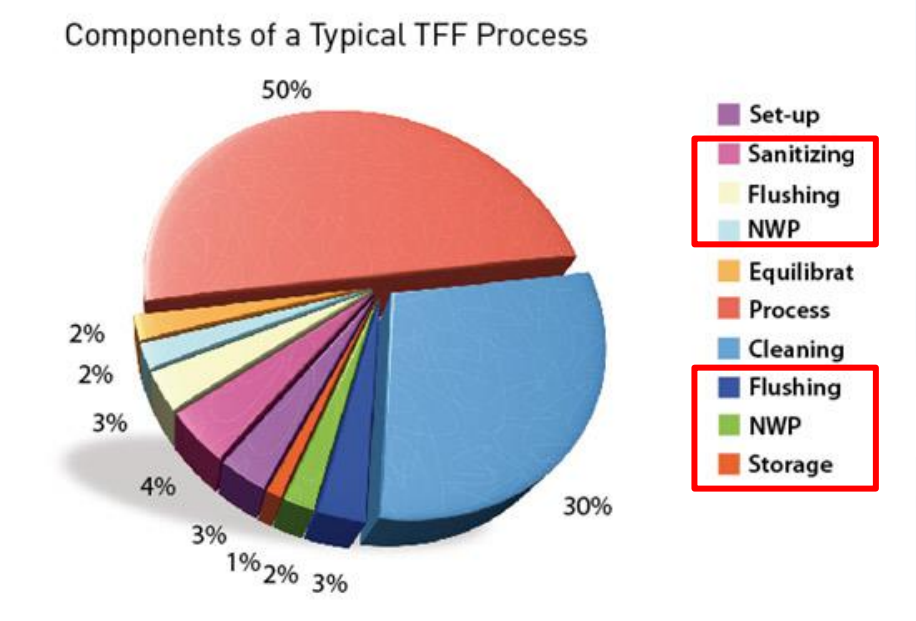
Milipore ® - Depth filtration

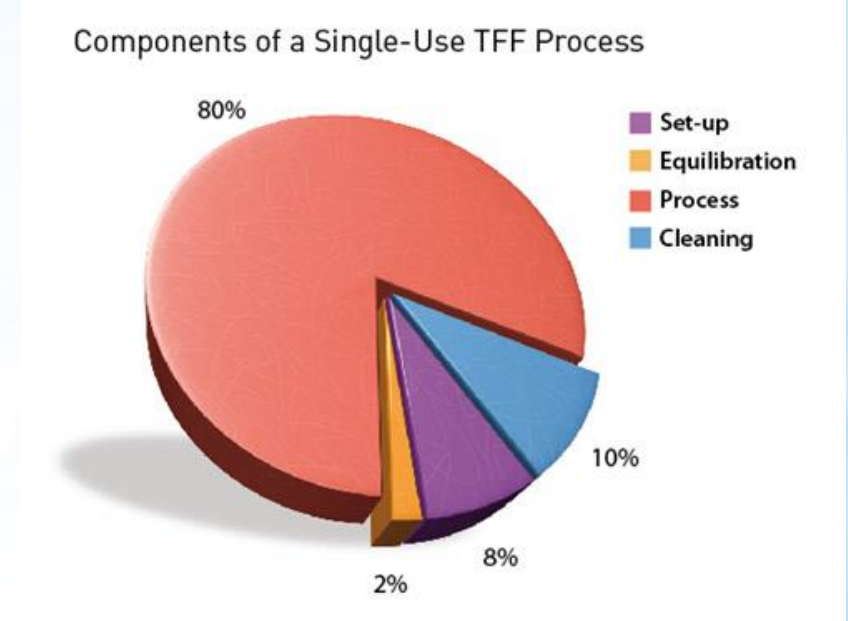
Asahi
Viral Filtration

Sartorius Stedim – Single-use mixing systems

Bioflex ™
Single-Use Tubing And Filter/Tubing Assemblies

Single use technology – Time saving efficiency (Data from Novasep)





Downstream processing challenges

- Purification step Performance, Quality & Cost
- Manufacturing efficiency and removal of non value added activities
- **Economical running cost considering Capex & investments**

Investments & Flexibility

- Investment considerations
  - Which scale ?
  - Product's forecasting
  - Location
- Flexibility
  - Clinical production
  - Multi products facility - changeover

Single use technology – Downstream application

kSep® - Centrifugation Up to 6000 L

GE – ReadyToProcess chromatography

Single use technology – Mobius Platform from Millipore

Clarification | Chromatography | Virus clearance | Ultra Diafiltration

Buffer/Media preparation

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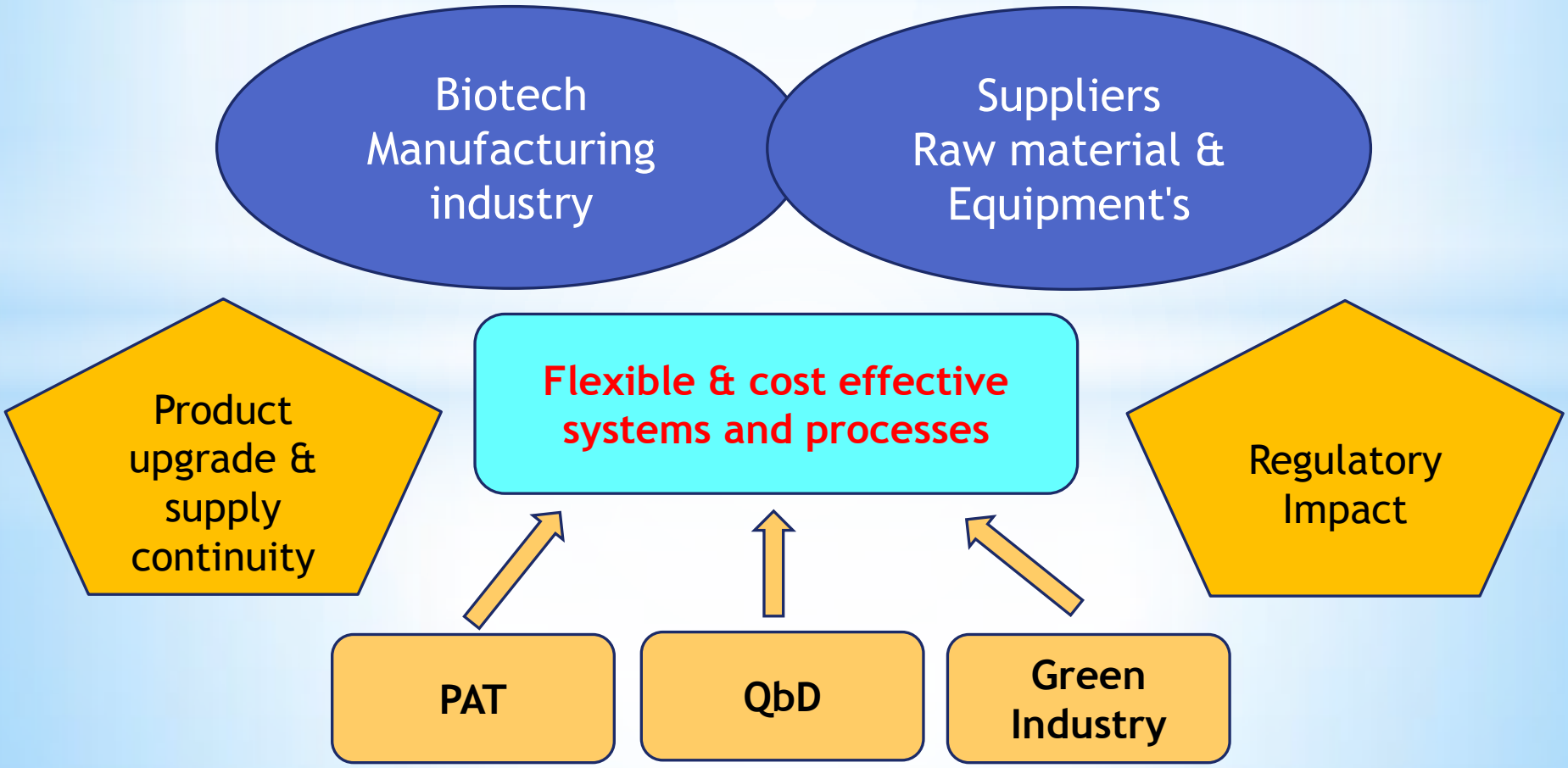
Future – challenge with rationalisation & innovation



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Conclusions

- Economic pressure to reduce cost, improve efficiency, keep quality
- Need to appropriately adapt DSP to USP performance
- Drivers for DSP improvements:
  - High selectivity and low cost for capture and nanofiltration
  - Capacity increase : resin and membrane
  - Increase proces performance time with continuous purification
  - Eliminate non value activities by using single technology
- Reinforce synergy and close collaboration between manufacturers and suppliers

Thank You