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Next generation downstream process – manufacturing of biologics in a continuous way

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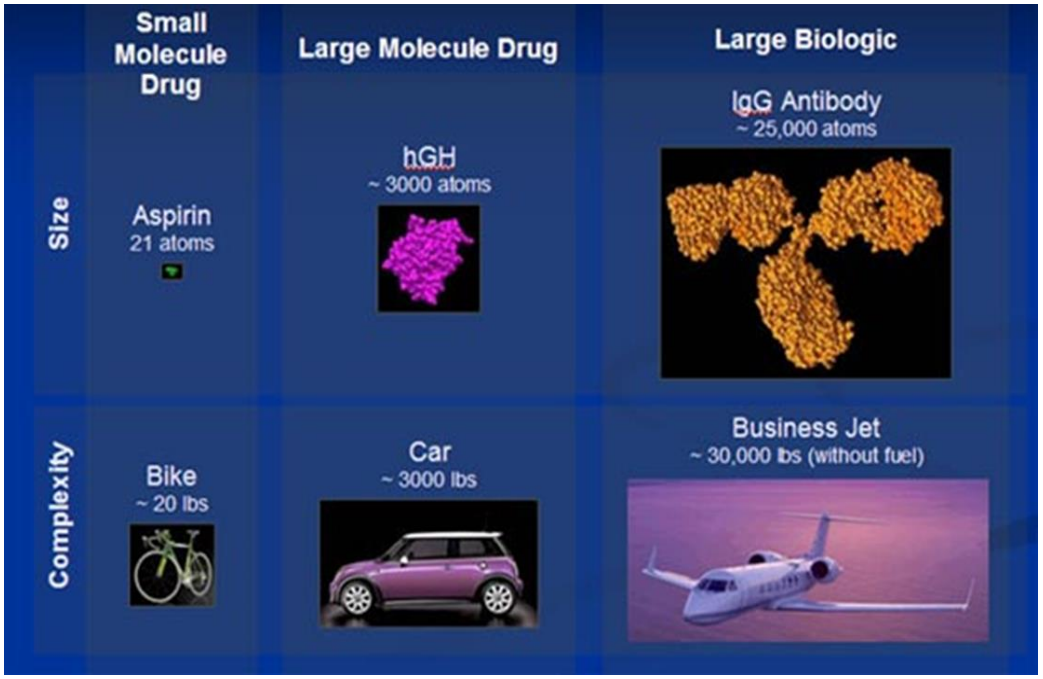
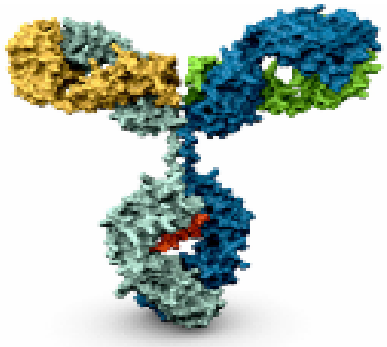
Biologics or biopharmaceuticals

Biopharmaceuticals are part of a broader category of therapeutic agents called biologics

Size and complexity



http://www.azbio.org/small-molecules-large-biologics-and-the-biosimilar-debate



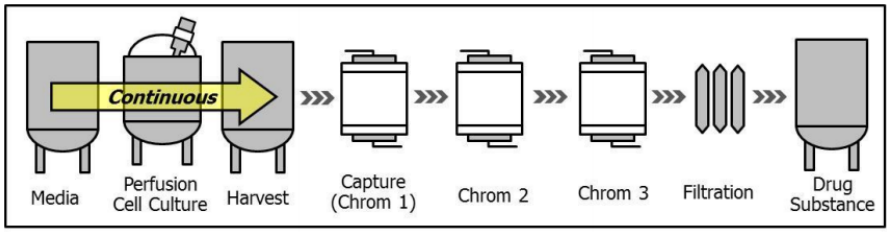
Highly specific and targeted medicines

Produced in living organisms

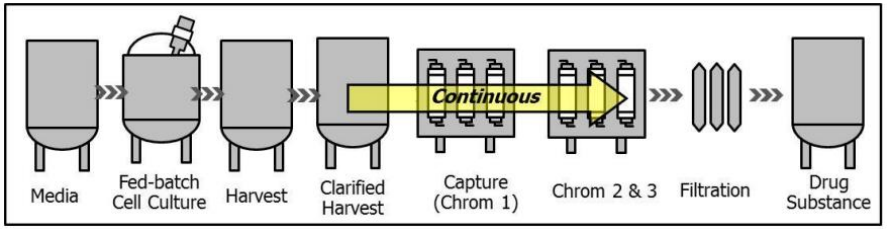
Strategies for manufacturing

Hybrid process

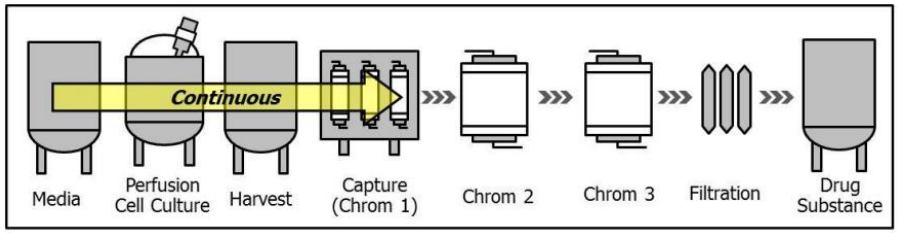
Continuous upstream with batch downstream



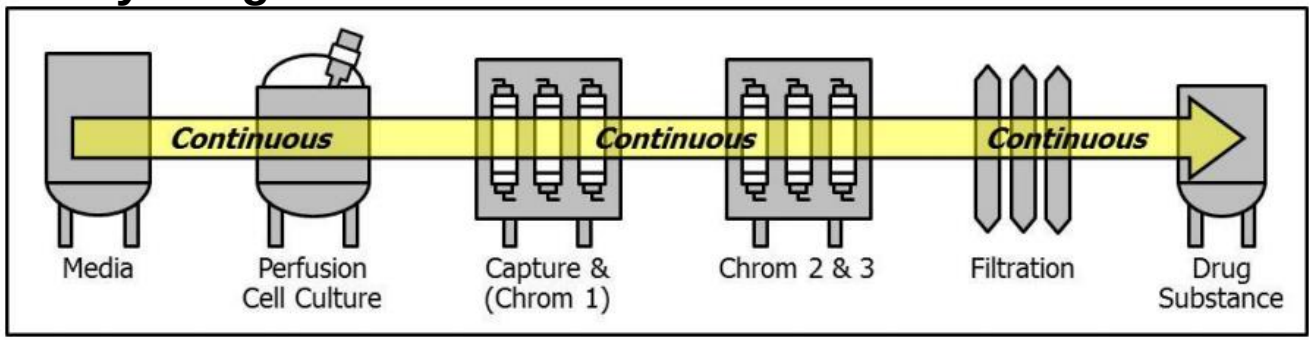
Batch upstream with continuous downstream



Continuous upstream + capture, batch downstream



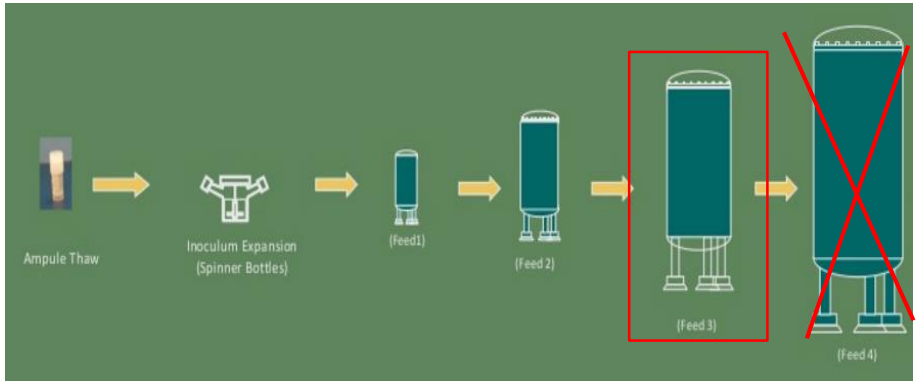
Fully Integrated Continuous Process

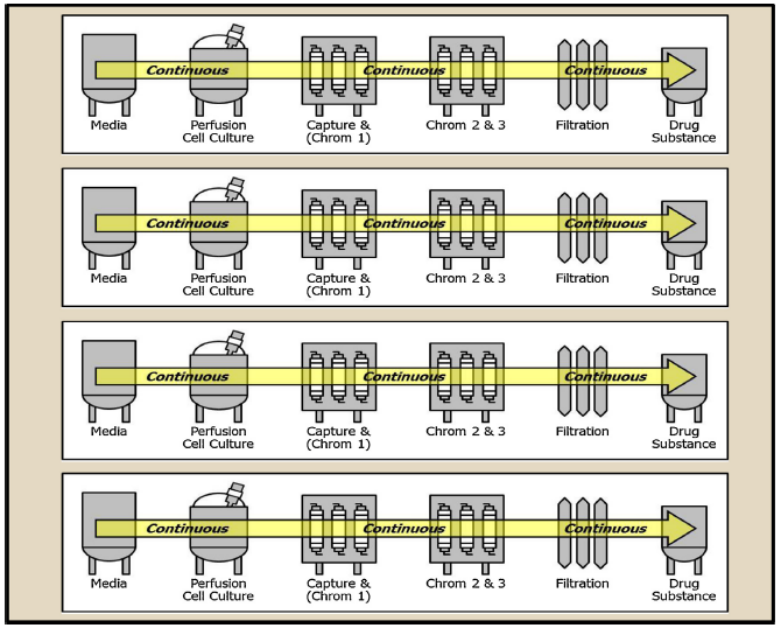


Konstantinov K.B. and Cooney C.L. – White Paper on Continuous Bioprocessing; J. of Pharmaceutical Sciences: 104:813–820, 2015

Scale out or numbering up instead of scale up

- Pilot scale becomes a final scale – speed to market
- 500L – 2000L BR vs 10.000L - 25.000 L BR – with same productivity
- Multiproduct facilities – fit facility to product not vice versa
- Same process for clinical and final manufacturing
- Following market demands
- Flexibility / modularity
- Local manufacturing - decentralization
- One time validation

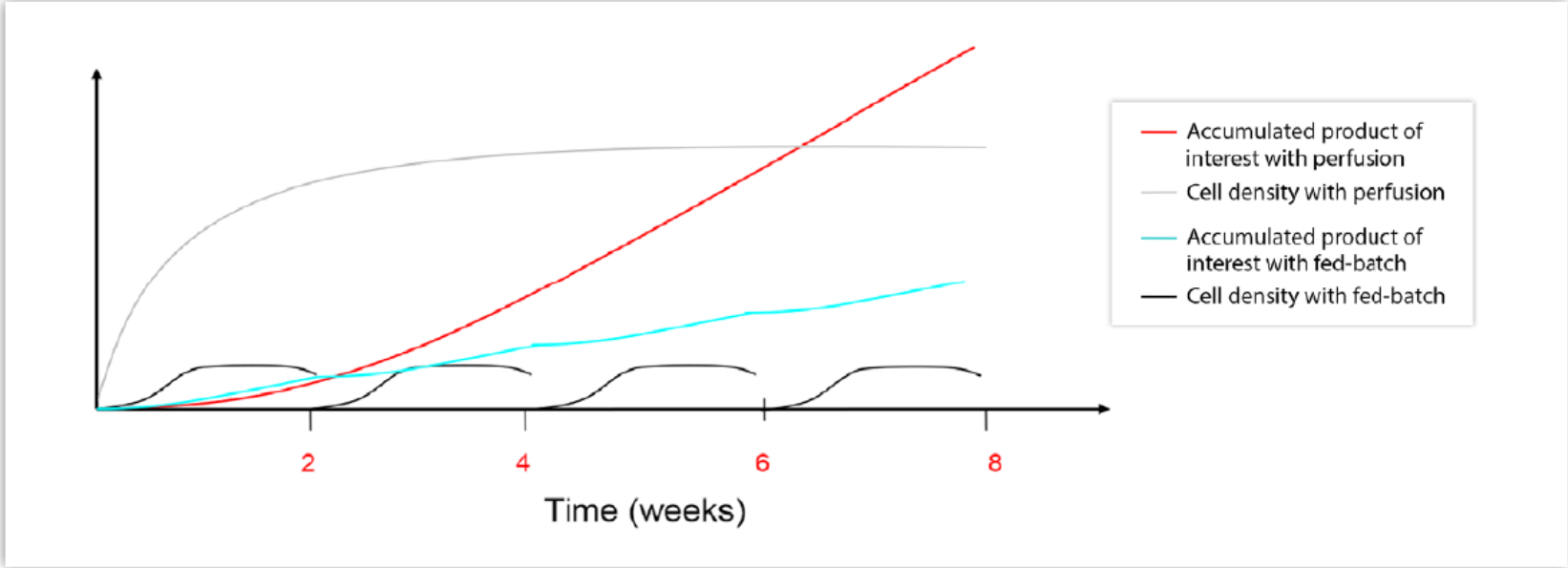




Godawat R et al: End-to-end integrated fully continuous production of recombinant monoclonal antibodies. J Biotechnol. 2015; 213:13-9.

USP: Productivity comparison

- Much higher cell densities (10x)
- Higher product content per L of media
- Shorter time – resulting in smaller bioreactors
- **There is a need for more efficient DSP!**

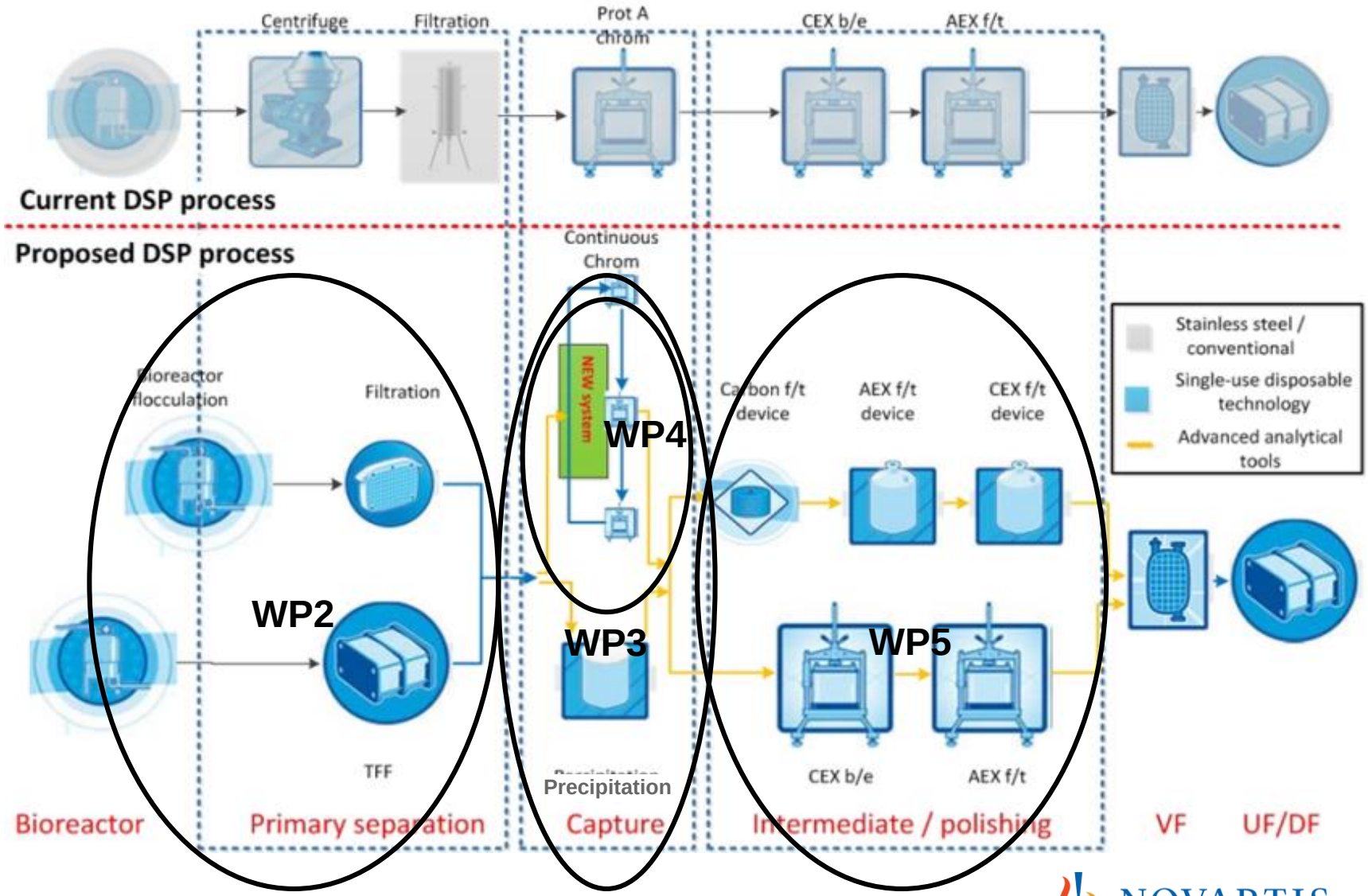


Continuous Bioprocessing and Perfusion: Wider Adoption Coming as Bioprocessing Matures
By ERIC S. LANGER and RONALD A. RADER

Next-generation biopharmaceutical downstream process

Title	▪ Next-generation biopharmaceutical downstream process ▪ Acronym: nextBioPharmDSP
General	▪ Grant No.: 635557 ▪ 4 year project (1st March 2015 - 28th February 2019) ▪ Webpage: www.nextbiopharmdsp.eu
Partners	▪ Industry: Lek Pharmaceuticals d.d. (Slovenia), Sandoz GmbH (Austria), Millipore SAS (France) ▪ Academia: University of Natural Resources and Life Sciences, Vienna (Austria), Karlsruhe Institute of Technology (Germany), National Institute of Chemistry (Slovenia) ▪ SME: National Systems srl (Italy)
Budget	▪ Total budget: 10,6 mio € ▪ EU funding: 8,4 mio € (70 % for industry, 100 % for academia)
Main goal	▪ Develop and implement a more **efficient**, **cost-effective** and **environmentally friendly** downstream process for the manufacture of monoclonal antibodies and biosimilars.

Scheme of the proposed process



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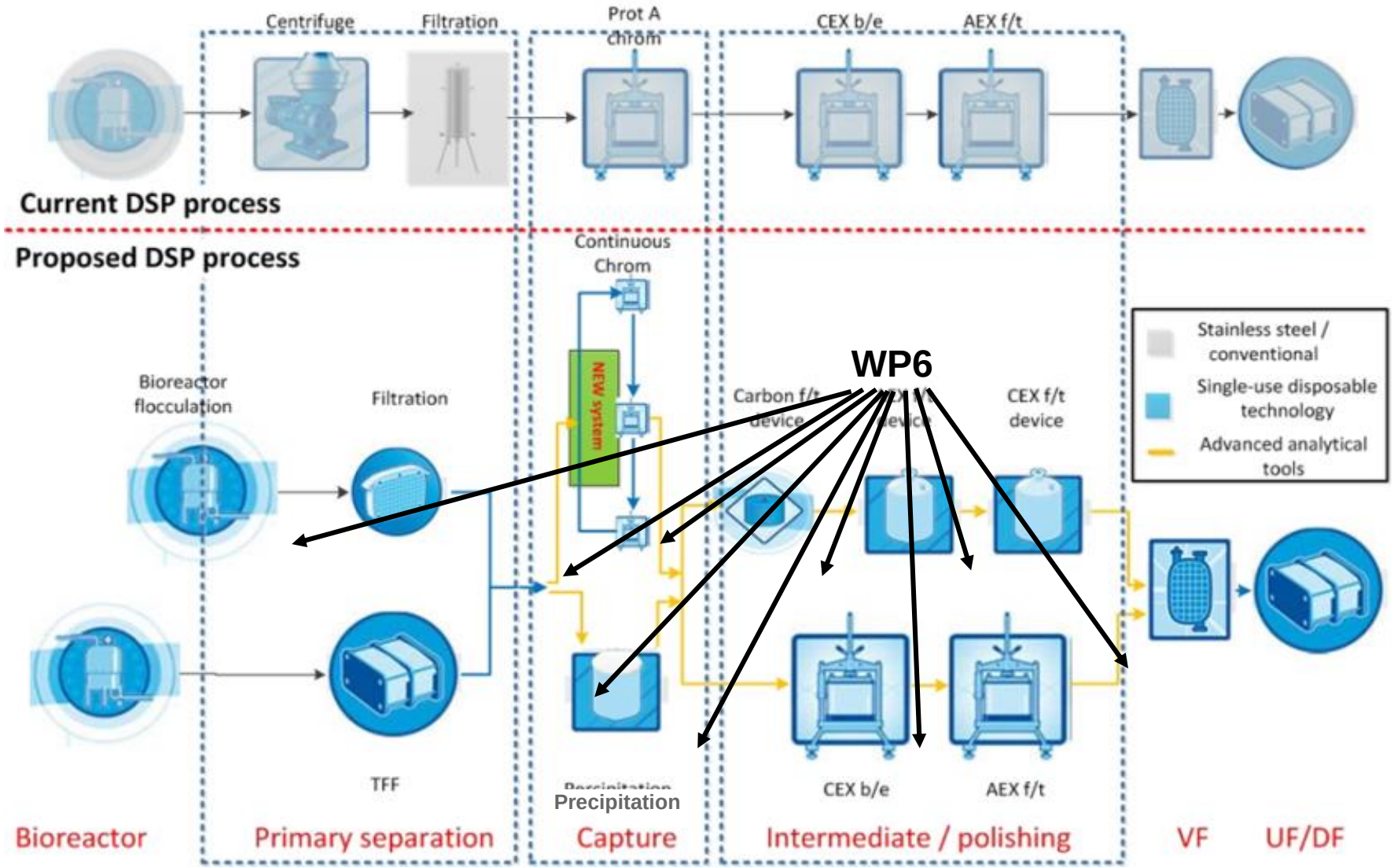
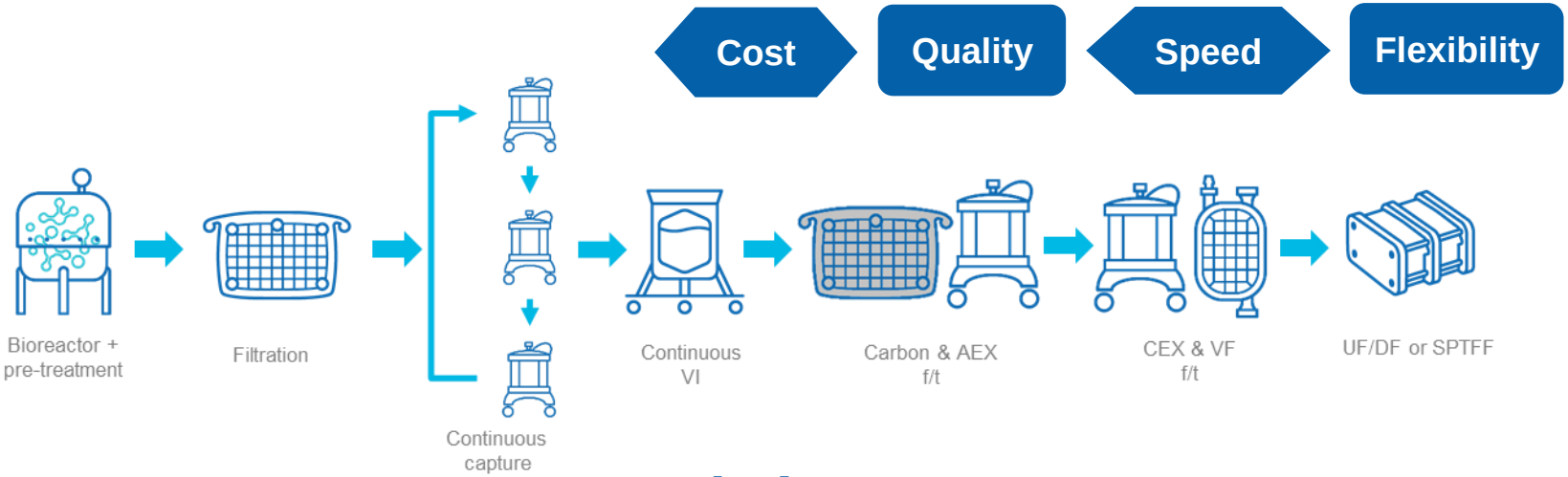
Scheme of the proposed process



Final process

Establish fully connected disposable continuous DSP platform for biologics production.



Process	Format	Analytics	Controls	Digital Plant
Batch	Stainless	Standard QC Methods	Stand-Alone	Pre-Digital
Int[illegible]sified	[illegible]id	Rap[illegible] QC [illegible]thods	Semi-Centralized	Digital Silos
C[illegible]cted	Single-Use	At-Line / On-Line	Full-Process	Connected Plant
Continuous	Single-Use / Closed	In-Line / Real-Time	Predictive	Adaptive Plant

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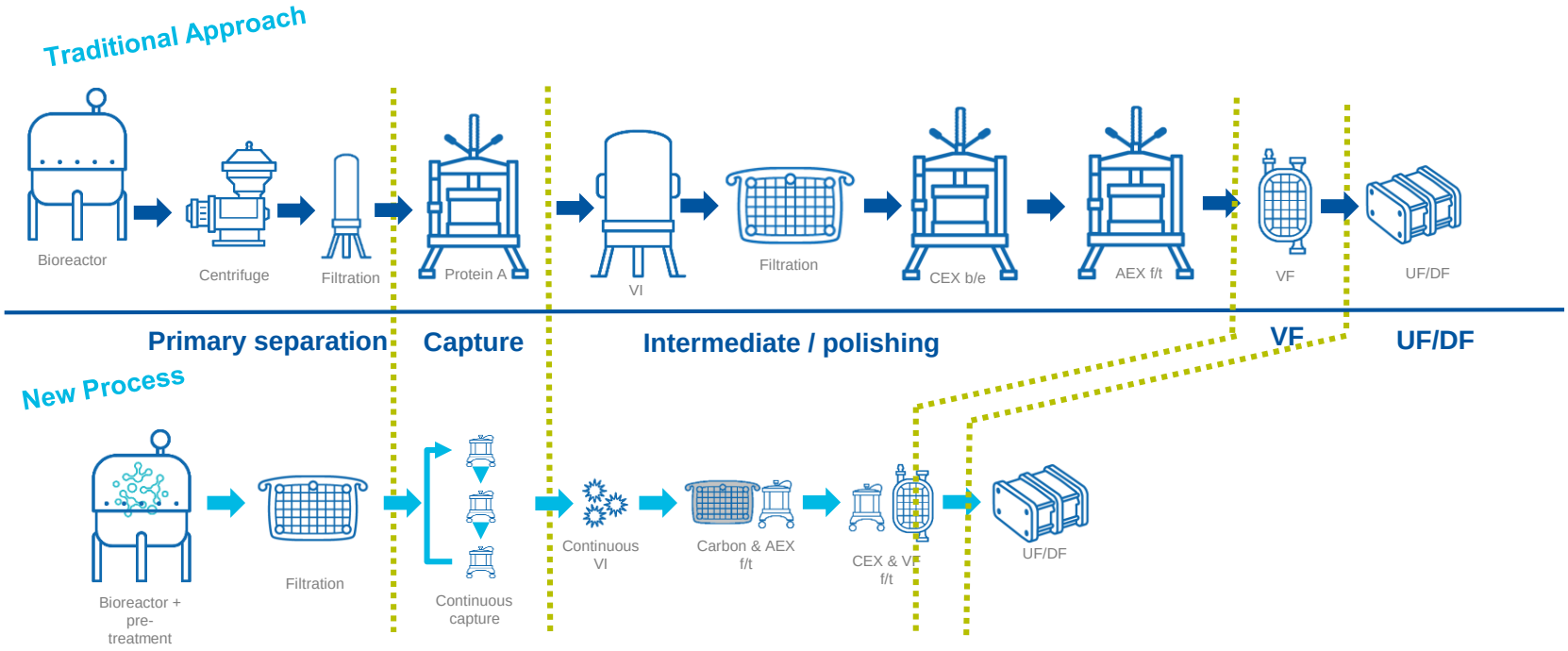
nextBioPharmDSP Gap/Benefit analysis

FROM *Current DSP standard*		TO *nextBioPharmDSP*	
High cost of DSP	• Traditional large volume setups for biologics • Obsolete technologies resulting in high COGS	**Continuous processing**	• Smaller investments in equipment and facility • High volumetric productivity • High equipment utilization • Less footprint • Elimination of intermediate tanks • Elimination of intermediate hold steps - reduced risk of product degradation • Decreased residence time in the process
Quality	• Poor intermediate stability of certain products		
Low flexibility of manufacturing	• Product dedicated facilities • Stainless steel setup with low flexibility • Limited possibilities for capacity expansion	**Single use operation units**	• Reduce bioburden risk - single use assemblies • Smaller and mobile equipment - lower footprint • Easy transfer to other manufacturing site • No carry over issues
Speed to market	• Delayed market entry due to scale-up activities, product allocation strategies, lack of proper manufacturing options	**Scale out instead of scale up**	• Eliminated scale up activities • Eliminated transfer risks • Clinical production scale is final manufacturing scale

Establish fully connected disposable advanced DSP platform for biologics production.

Final process

Establish fully connected disposable continuous DSP platform for biologics production



Connected & Continuous processing

Innovative Technologies

Single-use operation units

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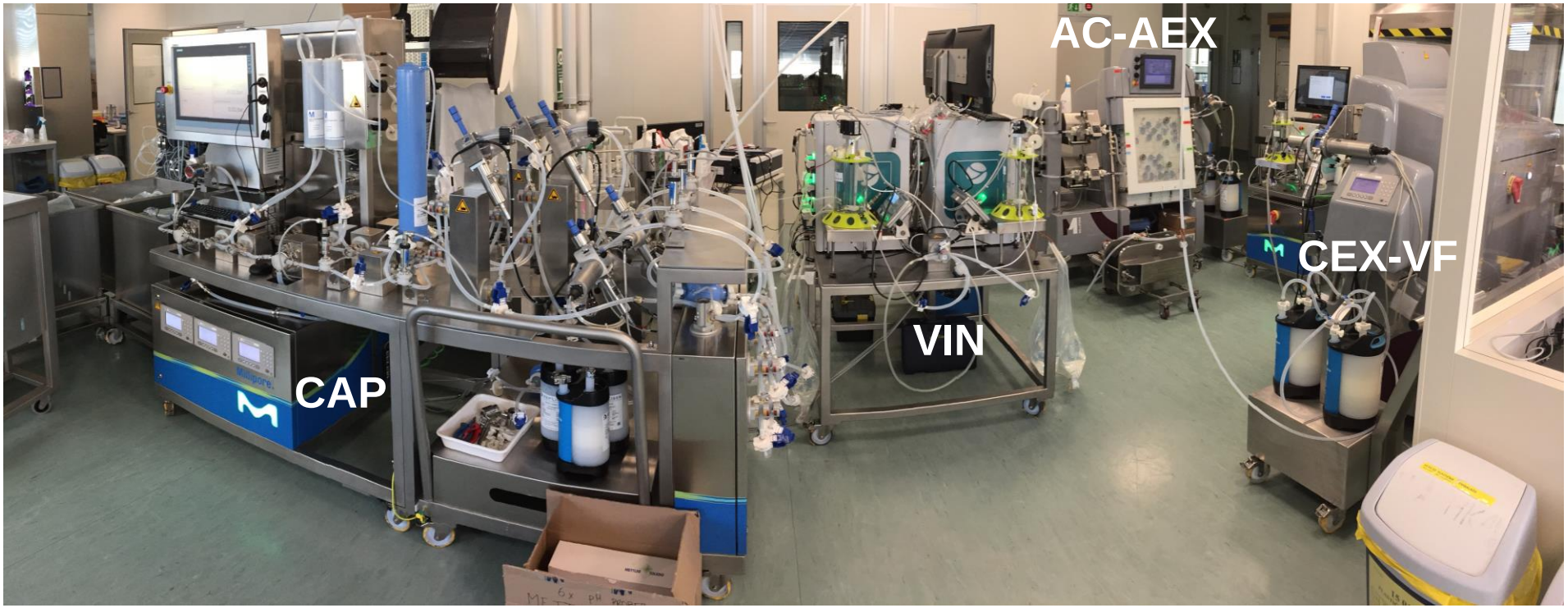
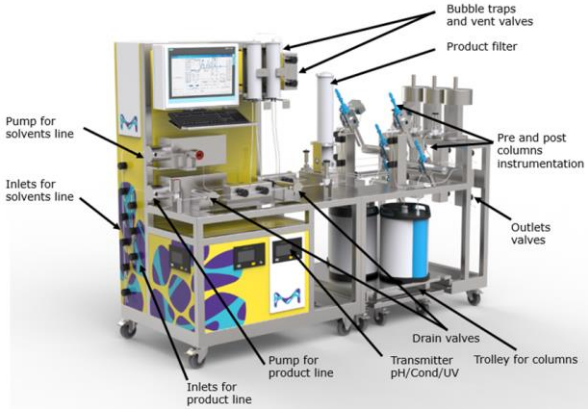
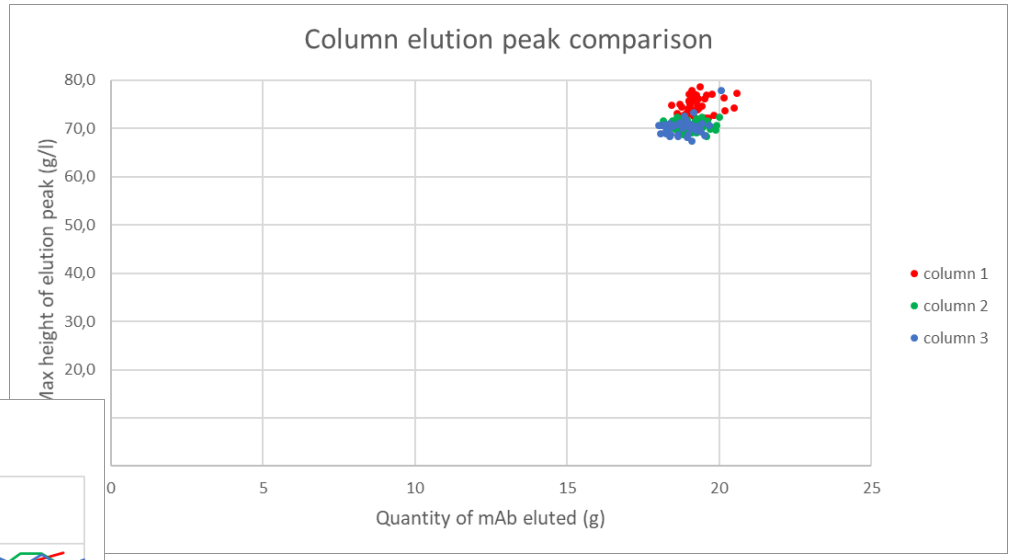
Connected DSP setup overview

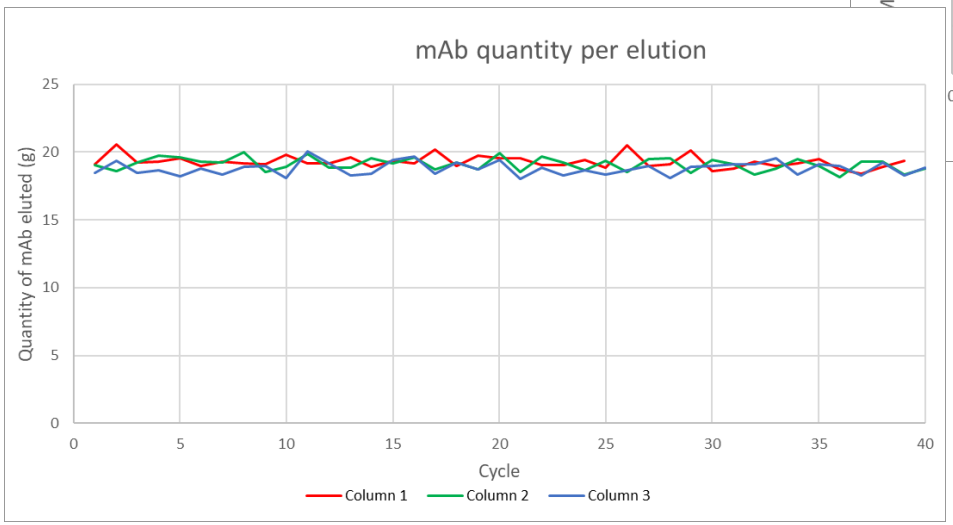


Continuous capture performance

- Continuous multi-column chromatography with real time monitoring of product content







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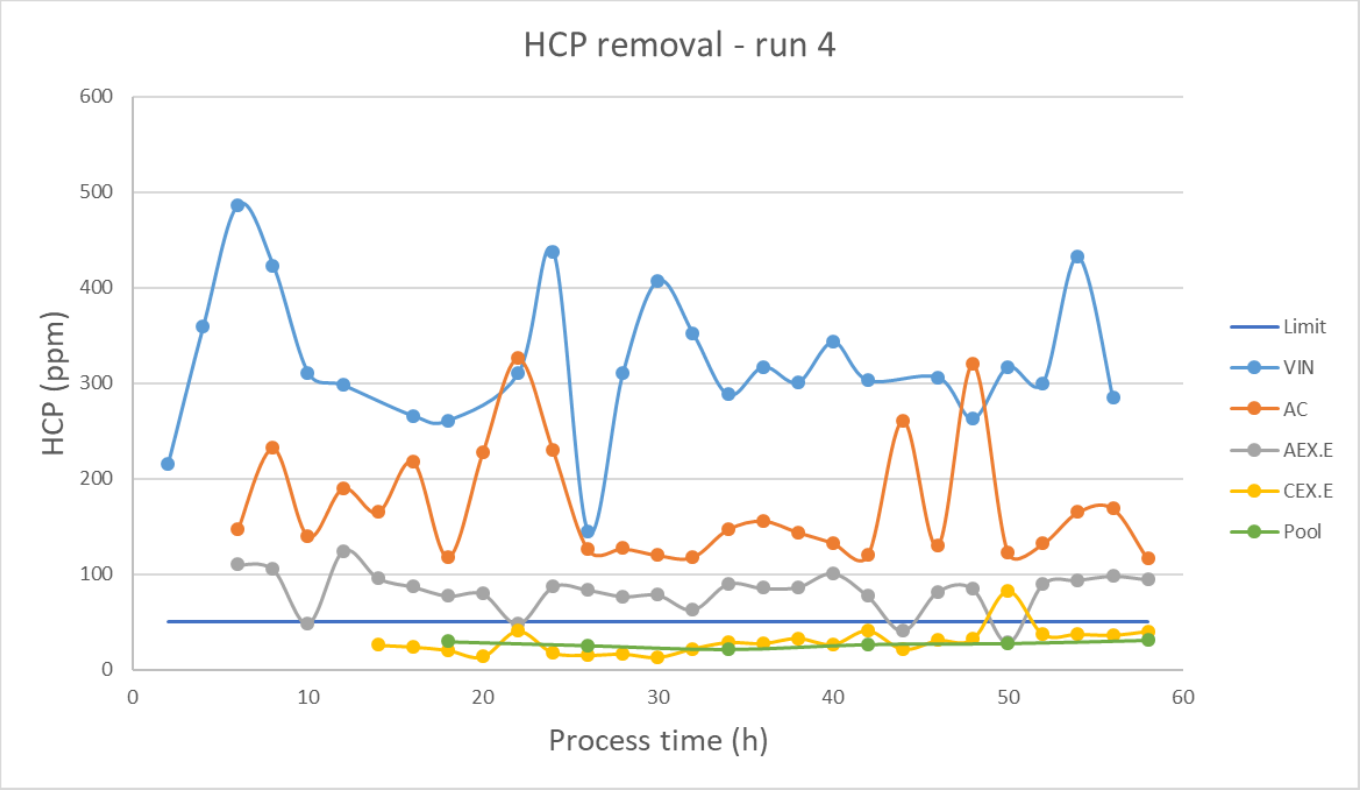
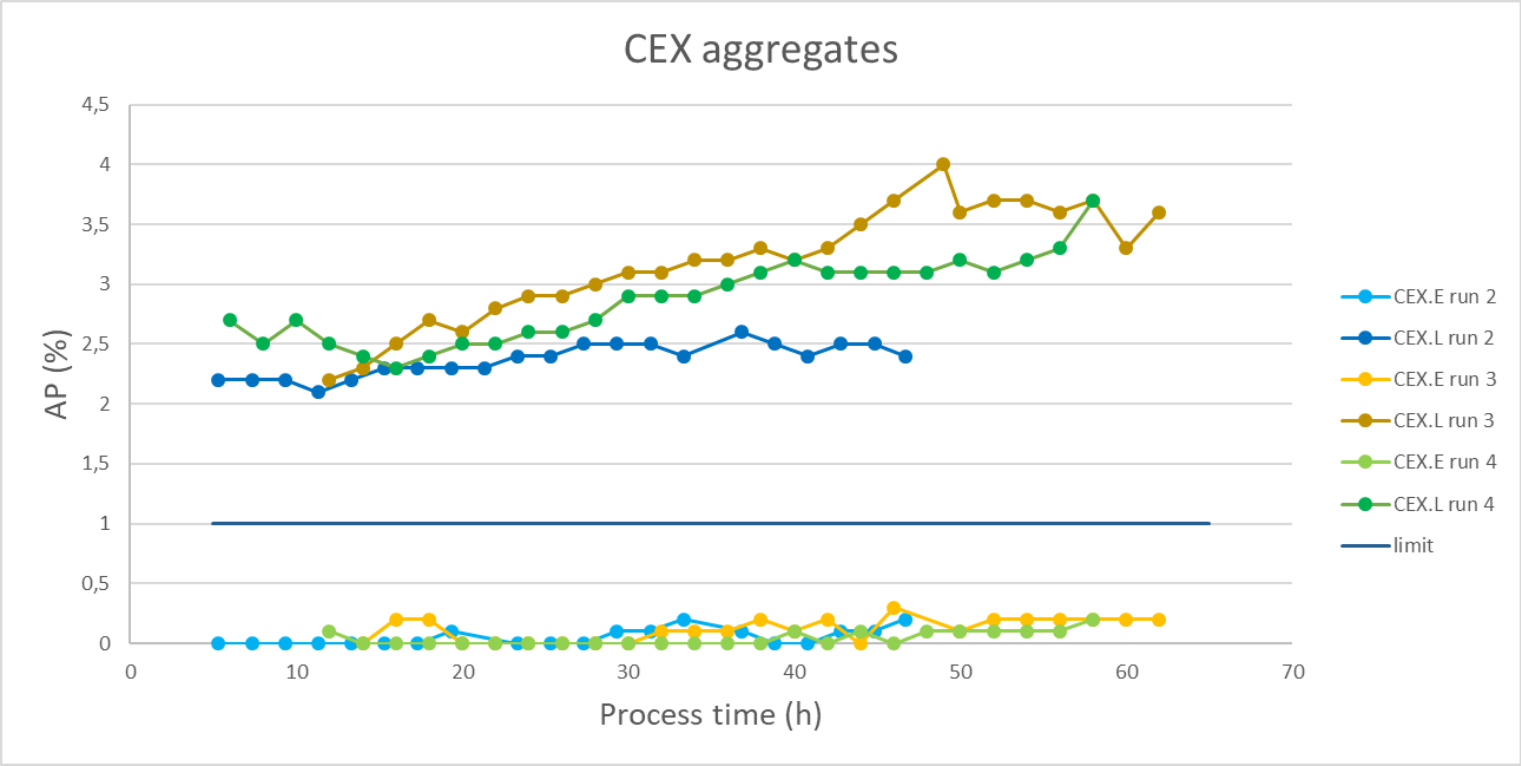
Impurity removal - HCP

- Efficient removal of HCP in different steps of DSP
  - Initial amount around 150.000 – 200.000 ppm



Impurity removal - aggregates

- Efficient removal of impurities – CEX flow-through step for aggregate removal



Main advantages

Productivity

- Capable of processing 3000L harvest in 24 hours (12 kg of mAb)

Footprint

- Complete DSP in 30 m^2 (10-15x smaller)
- Elimination of large intermediate hold tanks
- Smaller buildings & lower facility footprint

Single-Use

- Flexibility (mobile equipment)
- Reduce bioburden risk
- No carry-over issues
- No cleaning, regeneration, steaming
- Rapid change-over

Economics

- Facility investment: ↘ 35%
- Running costs: ↘ 30%
- Cost of materials: ↘ 50%

Environmental

- CO_2 emissions: ↘ 25%
- Reduced water, buffer, resins consumption (water ↘ 10x)
- Decreased energy consumption

Acknowledgements

lek
član skupine Sandoz
a Sandoz company

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KIT
Karlsruhe Institute of Technology

NSYS
Growing together

MERCK

NATIONAL INSTITUTE OF CHEMISTRY

SANDOZ A Novartis Division

next BioPharm DSP

www.nextbiopharmdsp.eu

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