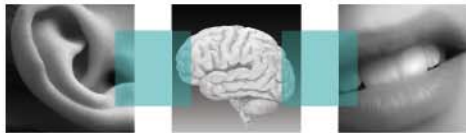




Microscale to Manufacture for Emerging Vaccine Technologies



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CONSULTING • DEVELOPING • MANUFACTURING



**Any questions are welcome and encouraged, they
can be asked by e-mailing:**

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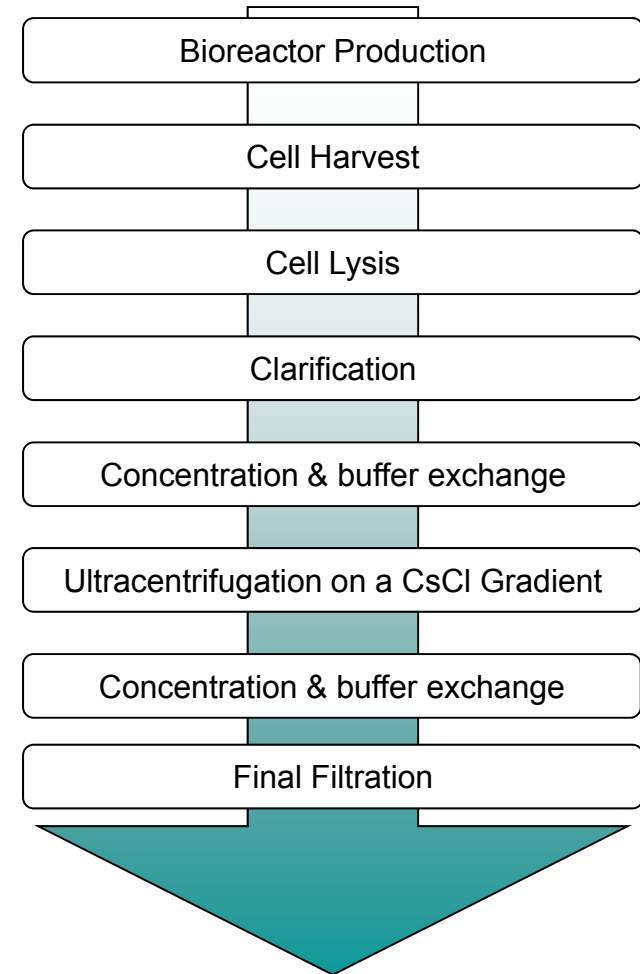
- **CMO offering:**
 - ▶ Expression system development
 - ▶ Process and analytical development
 - ▶ Cell banking
 - ▶ cGMP production services
- **Consultancy services in CMC issues, regulatory support, cGMP training, technical troubleshooting and clinical trial supply logistics.**
- **World class microbial, mammalian and viral process development and cGMP facilities located in Liverpool, UK.**
- **US subsidiary located in Research Triangle Park, NC.**
- **Now part of Watson Pharmaceuticals, Inc.**



Challenges



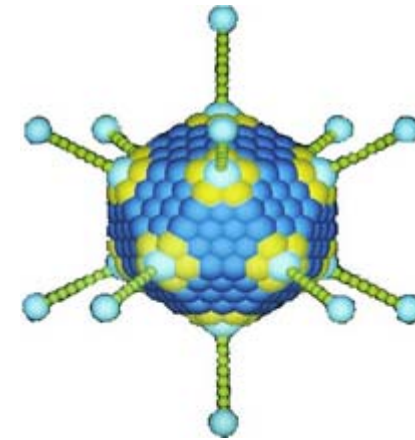
- **Increased demand in viral vectors**
 - ▶ Gene Therapy
 - ▶ Vaccines
- **High titres required**
 - ▶ Pre-clinical
 - ▶ Clinical
- **Complex and challenging product**
 - ▶ Low stability
 - ▶ Shear sensitive
 - ▶ Closely associated impurities
- **'Classical' Ad5 purification**
 - ▶ CsCl ultracentrifugation based
 - ▶ Process itself is an impurity
 - ▶ High capital expenditure outlay
 - ▶ Scale limiting
 - ▶ Time consuming/Laborious



Adenovirus Serotype 5 (Ad5)



- **Ad5 benefits**
 - ▶ Well characterised
 - ▶ Transduce many tissue and cell types
 - ▶ High transduction yield
 - ▶ Easy to produce in culture
 - ▶ DNA readily manipulated to insert transgene of clinical importance
- **Ad5 particle properties**
 - ▶ Non-enveloped
 - ▶ 80 – 110 nm diameter
 - ▶ ~150 MDa
 - ▶ Icosahedral symmetry
- **Platform purification process**
 - ▶ Reduced costs
 - ▶ Minimised risks
 - ▶ Improved quality



Eden's Platform Purification



■ Rapid deployment and technology transfer

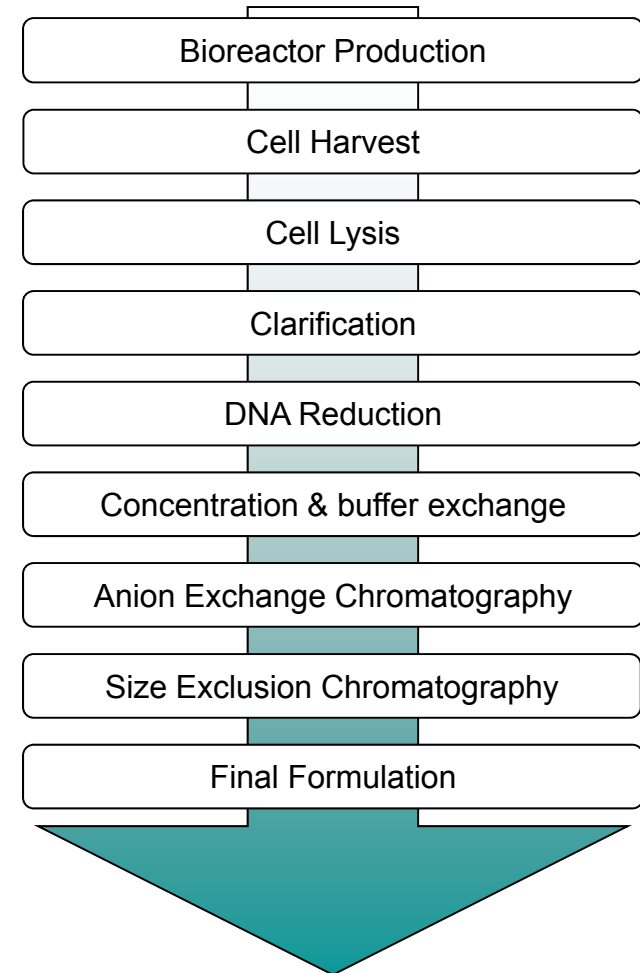
- ▶ Sighting ⇔ Scale ⇔ Manufacture
- ▶ 'Plug and play' – minimal development
- ▶ Robust
- ▶ Scalable

■ Chromatography based purification

- ▶ Reduced processing times
- ▶ Appropriate impurity profile
- ▶ High recovery
- ▶ Scalable

■ cGMP manufacturing considerations

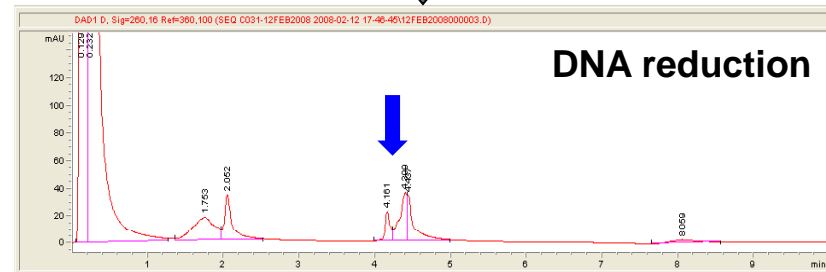
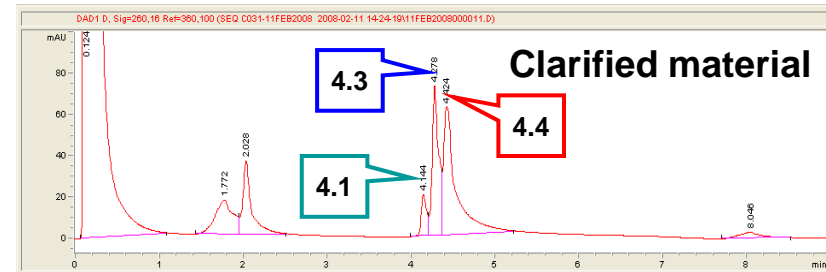
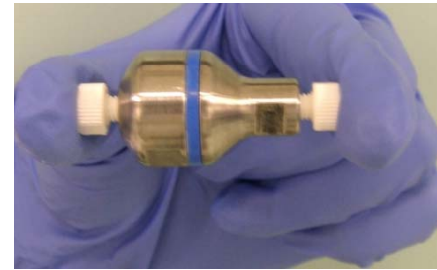
- ▶ Reduced COGs
- ▶ Well defined unit operations
- ▶ Eased equipment and plant cleaning
- ▶ Facilitated logistics



Primary Separations



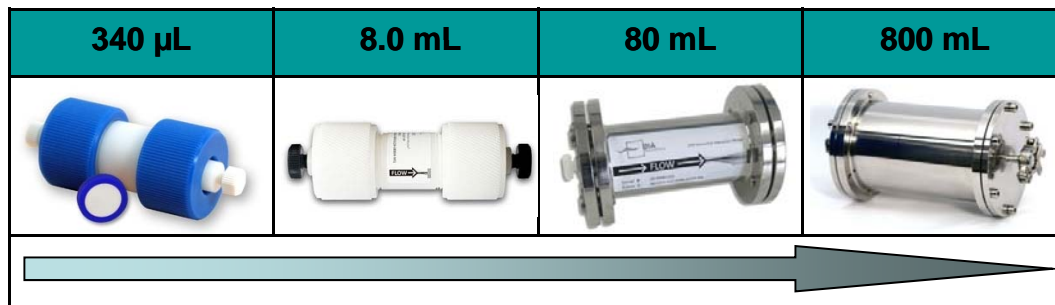
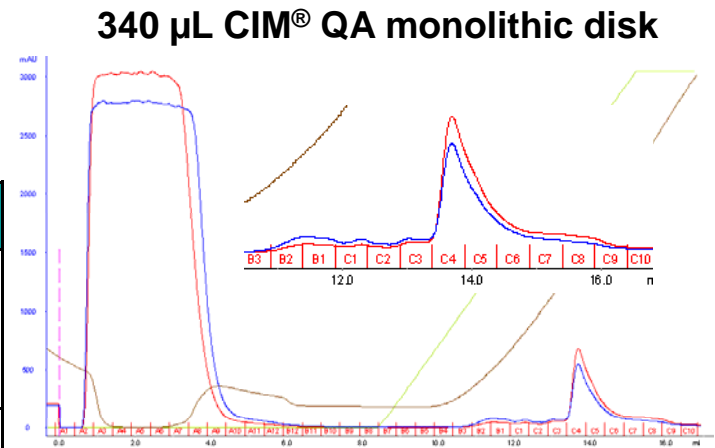
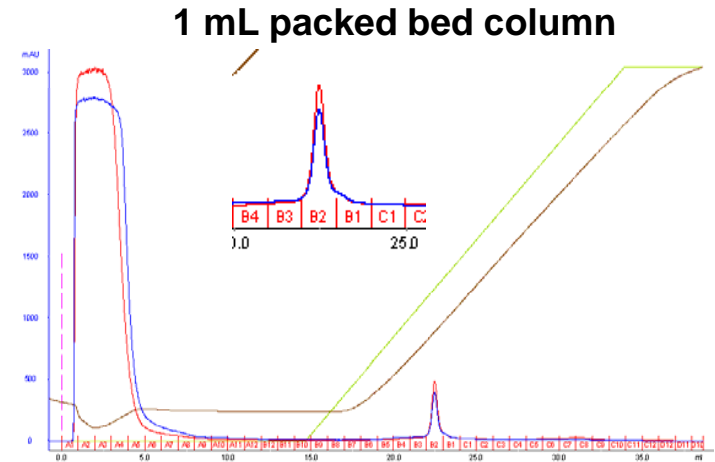
- **Cell harvest**
 - ▶ Centrifugation
- **Cell disruption**
 - ▶ Freeze thaw
 - ▶ Chemical lysis
- **Clarification**
 - ▶ Depth Filtration
- **DNA Reduction**
 - ▶ Enzymic degradation
 - ▶ Benzonase Endonuclease
 - ▶ Temperature controlled incubation
- **Concentration and buffer exchange**
 - ▶ Crossflow filtration – UF/DF
 - ▶ × 5 volume reduction
 - ▶ Benzonase reduction
 - ▶ Low molecular weight HCP reduction



Anion Exchange Chromatography

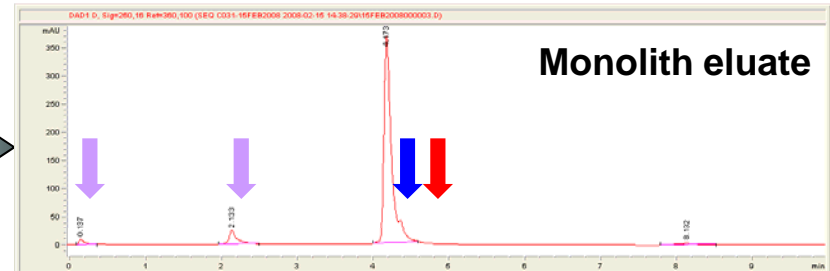
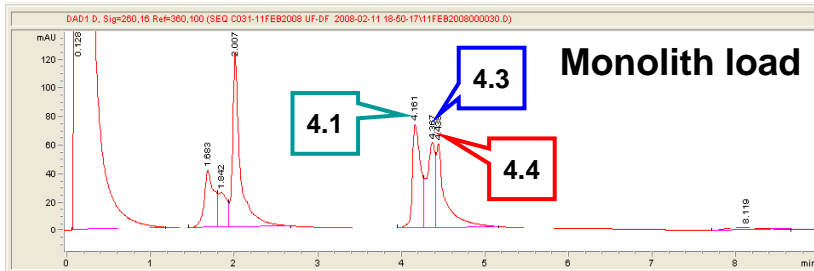
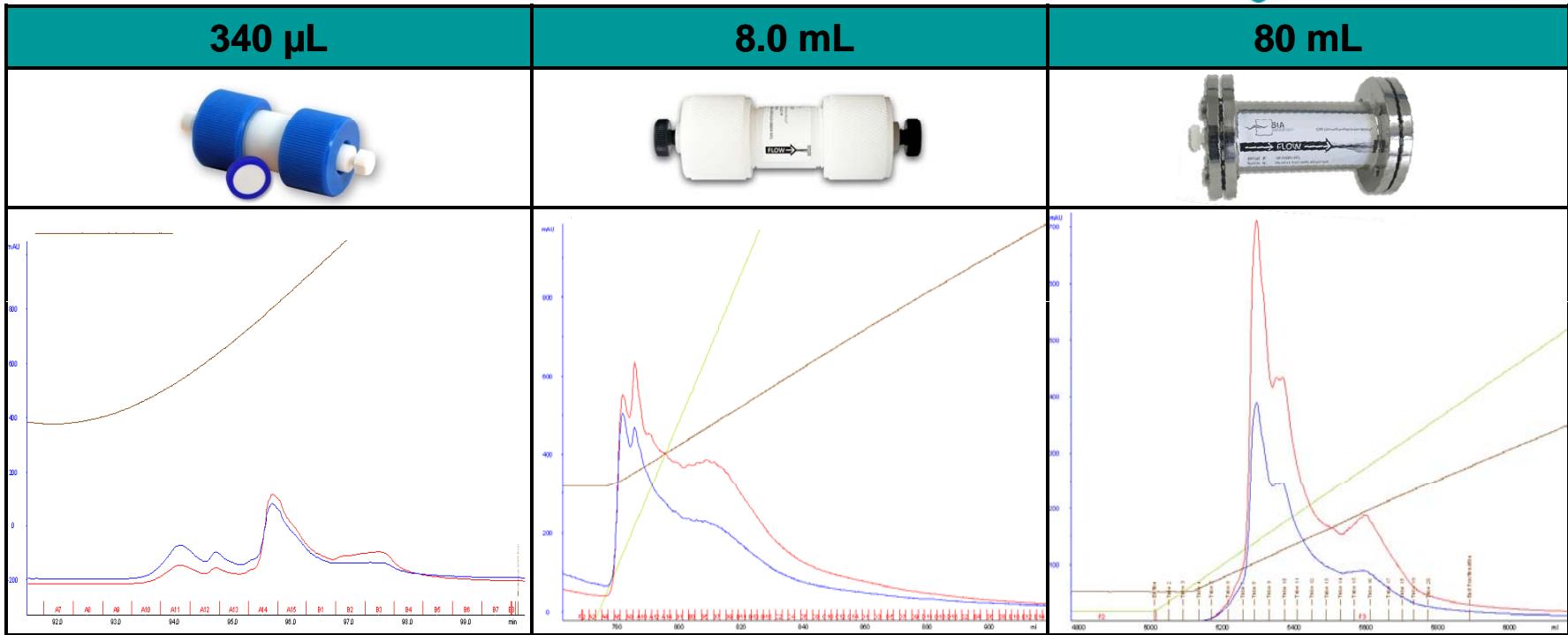


- **Monolith Technology (QA CIM®)**
 - ▶ Scalable to commercial application
 - ▶ Microscale down capabilities
 - ▶ High viral binding capacity
 - ▶ High recovery
 - ▶ High purity
 - ▶ High flow rate – accelerated processing
 - ▶ Low shear – improved product integrity
 - ▶ Robust technology



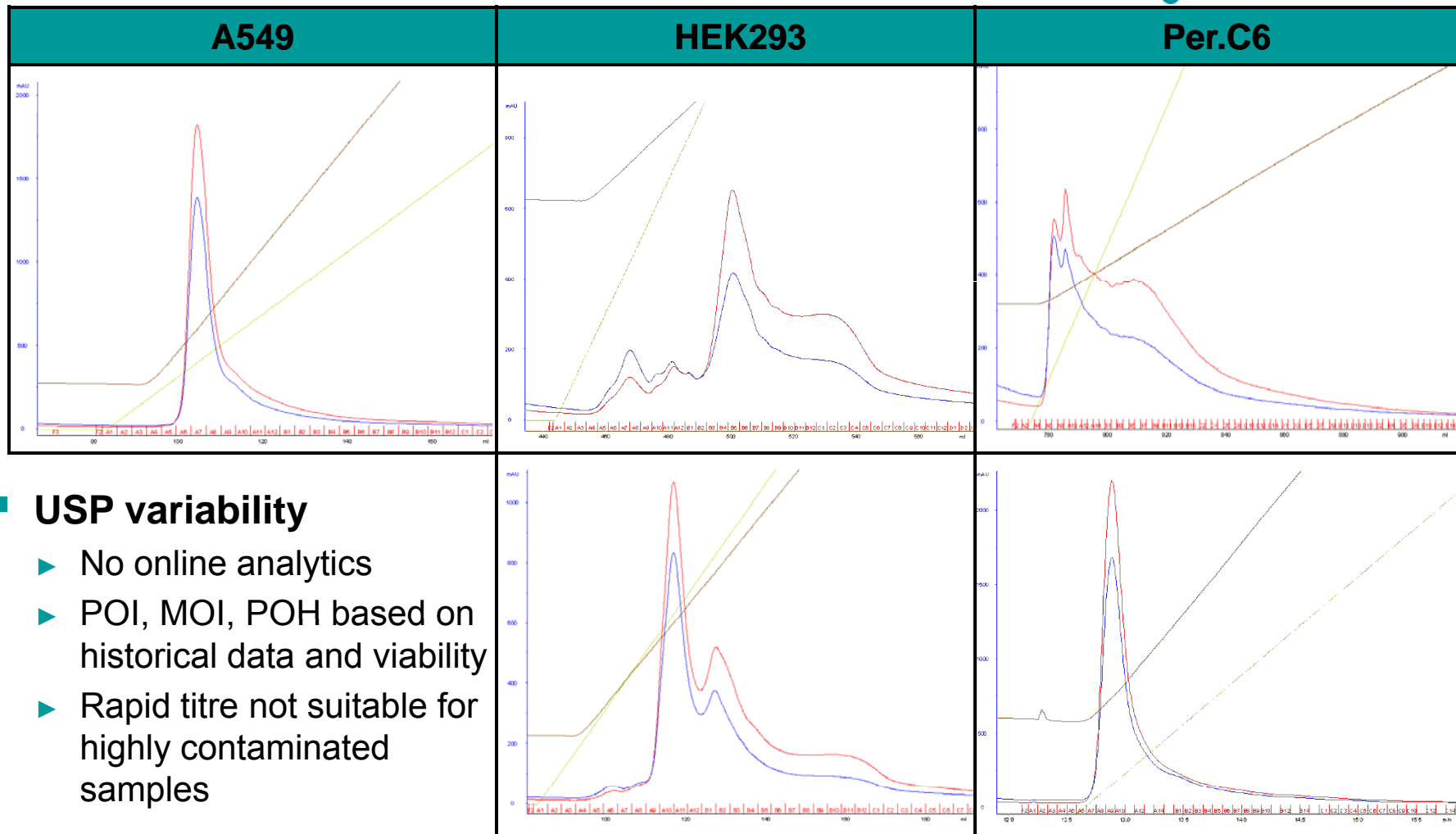
DESIGN • DEVELOP • DELIVER

Scalable Technology



DESIGN • DEVELOP • DELIVER

Robust Technology



Final Polishing / Formulation

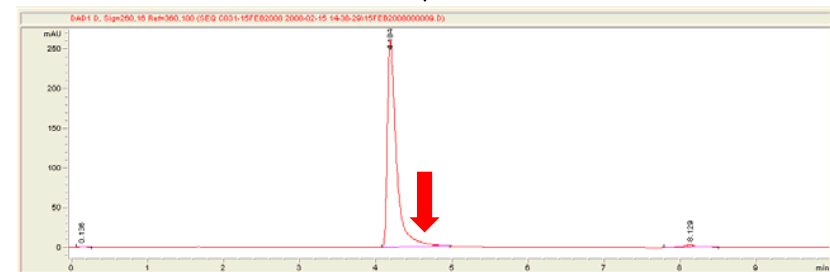
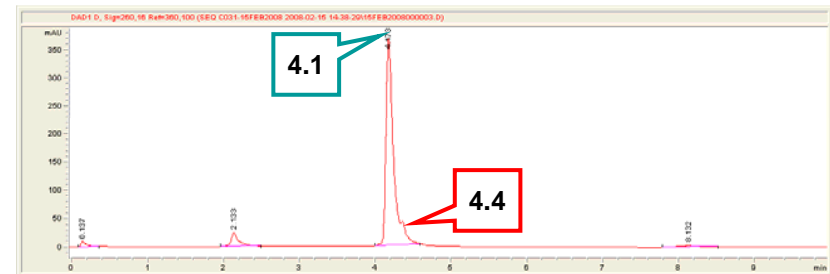


■ Size exclusion chromatography

- ▶ Group separations
- ▶ Sepharose CL 6B
- ▶ Simple, cheap and effective

■ Final formulation

- ▶ Concentration and buffer exchange
 - ▶ Crossflow filtration – UF/DF
 - ▶ Appropriate for route of administration
 - ▶ Ad5 poor storage stability
- ▶ Bioburden reduction filtration – 0.2 μm



Conclusions



■ Scalable DSP technology

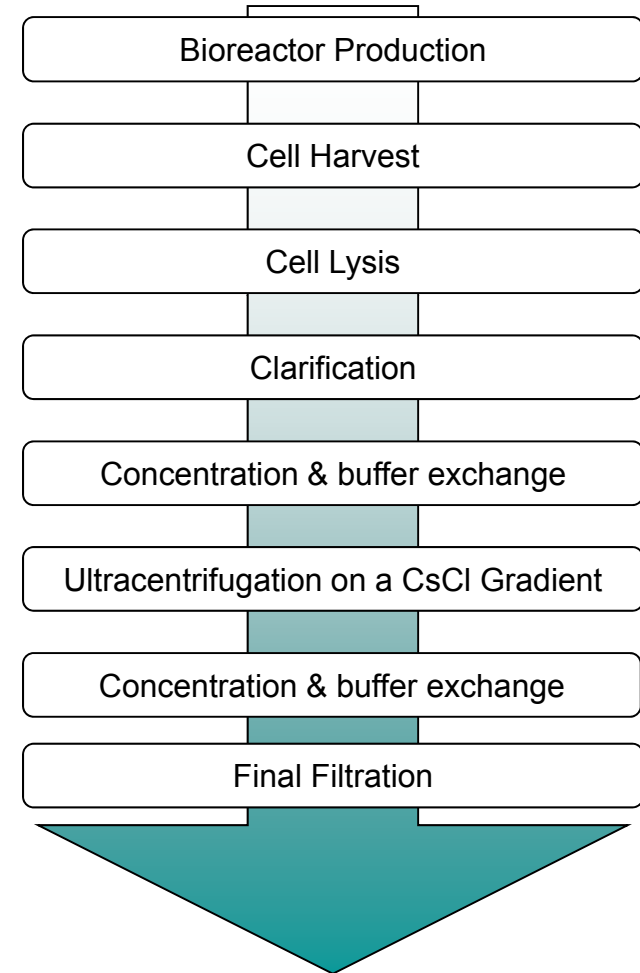
- ▶ Reproducible from microscale to manufacturing.
- ▶ Micro scale-down capabilities accelerate process development, optimisation and sighting.

■ Robust platform purification strategy

- ▶ Tolerates variability in the feedstream (cell line, media and batch to batch).
- ▶ Identical impurity profiles also achieved at all process scales.

■ Rapid deployment of manufacturing solution for adenoviral therapeutics

- ▶ No optimisation required between cell lines and product types (Sighting ⇔ Scale ⇔ Manufacture).
- ▶ Platform analytics and USP also facilitate deployment to manufacture.



Acknowledgements



- **Eden Biodesign** ▪

- DSP Development Team
 - USP Development Team
 - Analytical Development Team

- **BIA Separations** ▪

- Aleš Štrancar
 - Miloš Barut



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