Joint BWP / QWP workshop with stakeholders in relation to **prior knowledge and its use in regulatory applications**

Subteam 3. Using Prior Knowledge in Process Development & Manufacturing Strategy

London, Nov. 23, 2017

Case study #3. Prior knowledge to streamline viral safety and resin lifetime studies

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efpia
European Federation of Pharmaceutical Industries and Associations

ebe
european biopharmaceutical enterprises

Vaccines Europe
An industry for healthy lives

medicines for europe
better access. better health.

Viral Clearance studies & Resin lifetime

Case Study is inclusive of the following:

Monoclonal Antibody Case Study –

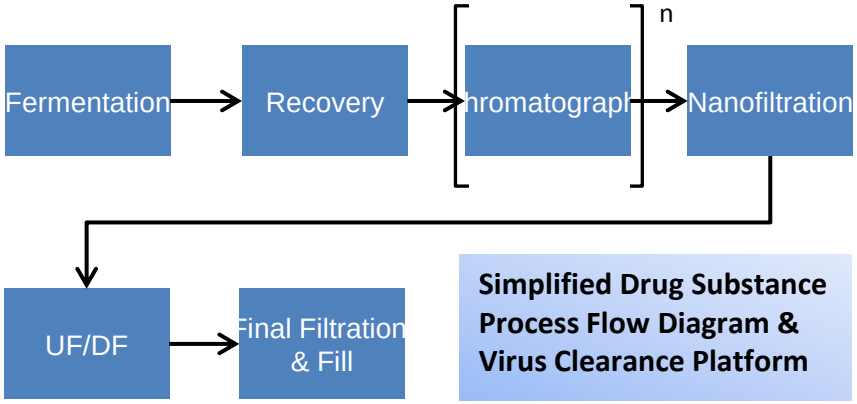
Use of Prior Knowledge for small virus filters to support testing of *worst case* small virus *in lieu* of large viruses

Use of Prior Knowledge on Affinity Capture Resins to support resin age evaluation criteria

Vaccines Case Study –

Use of Prior Knowledge to Support Resin Reuse Across Vaccine Serotypes (chromatography step)

Viral Clearance Platform	Benefits of Platform-based Processing
Affinity Capture (e.g., Protein A)	✓ Orthogonal VC using Platform Unit Operations
Chemical Inactivation (Detergent, S/D)	✓ Early-Phase data provide baseline expectations
Low pH VI	✓ Streamlined Unit Operations + Process Parameters
2nd Column	✓ Robust ranges for Manufacturing
Viral Filtration	✓ Standardised risk assessments
	✓ Continued Improvement & Sustainability Initiatives



Simplified Drug Substance Process Flow Diagram & Virus Clearance Platform

EMA Prior Knowledge Workshop

n°3.2.9; Virus Safety Case Study from EBE Consortium

Marie Murphy, Microbiologist, Technical Services, Eli Lilly & Company

on behalf of EBE Viral Safety Consortium

Nov 2017

1. Nano-filtration – Virus Retention Claim for Large Viruses based upon *worst case*, Small Virus only

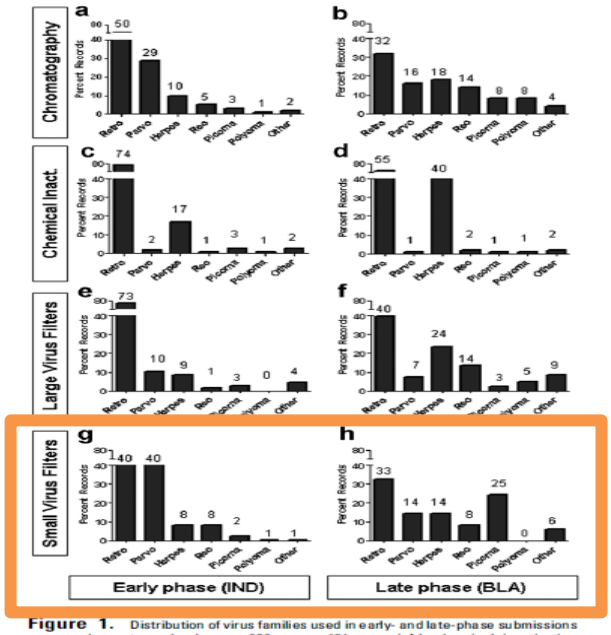


Figure 1. Distribution of virus families used in early- and late-phase submissions among chromatography ($n_{early} = 926$, $n_{late} = 451$; **a** and **b**), chemical inactivation ($n_{early} = 350$, $n_{late} = 225$; **c** and **d**), large virus filters ($n_{early} = 69$, $n_{late} = 81$; **e** and **f**), and small virus filters ($n_{early} = 296$, $n_{late} = 49$; **g** and **h**), respectively. Values represent percent total records.

N_{early}= 296; N_{late} 49 records[1]

- Small virus (e.g., Parvovirus) is considered *worst case* contamination to be removed by a size-based nano-filtration
- Prior knowledge (sponsor & published data) demonstrate robustness of small virus filters to retain larger viruses[1 - 5]
- Early phase & commercial applications include LRF claims for both large and small model viruses

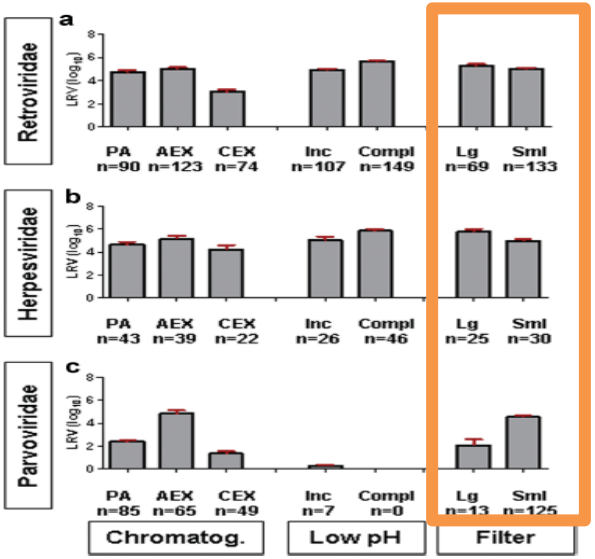


Figure 2. Mean clearance values (expressed as LRV) and standard error among unit operations commonly validated for clearance of retroviridae (**a**), herpesviridae (**b**), and parvoviridae (**c**). Shown are data for protein A, flowthrough anion exchange, and bind/elute cation exchange chromatography operations, low pH chemical inactivation ("incomplete" vs. "complete" clearance), and large and small virus retentive filters. [Color figure can be seen in the online version of this article, available at www.interscience.wiley.com.]

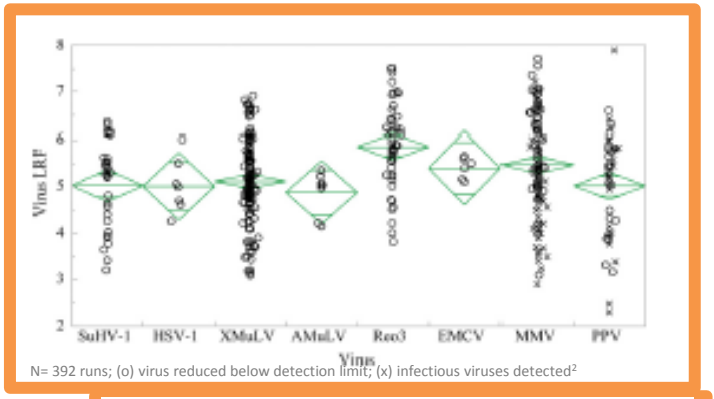
- Using Prior Knowledge, virus clearance studies completed using *worst case* virus could be extrapolated to "larger viruses", *in lieu* of product-specific large virus clearance studies
  - *Small scale model extrapolation to larger viruses has been already demonstrated for IMP's*
- The achieved LRV for the *worst case* study could be used for the "larger viruses", even though they in theory could achieve higher safety factors

Model Virus Family	Large Viruses			Intermediate Size				Small Viruses	
	Retroviridae	*Herpesviridae*	*Paramyxoviridae*	*Togaviridae*	*Orthoreoviridae*	*Papovaviridae*	*Flaviviridae*	*Picornaviridae*	*Parvoviridae*
Size (nm)	80 - 120	150 - 200	150 - 200	60-70	60 - 80	40-50	40 - 70	25 - 30	18 - 24

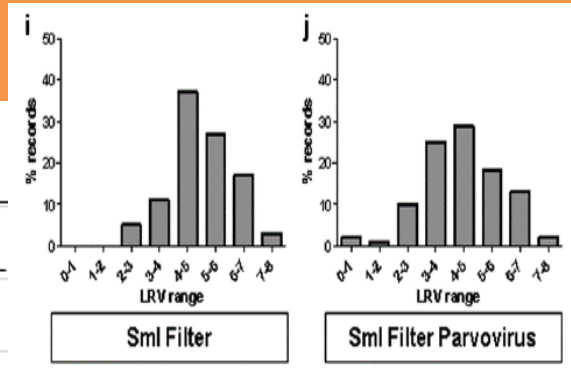
1. Consistency of process robustness; complete clearance of MuLV using small virus filters

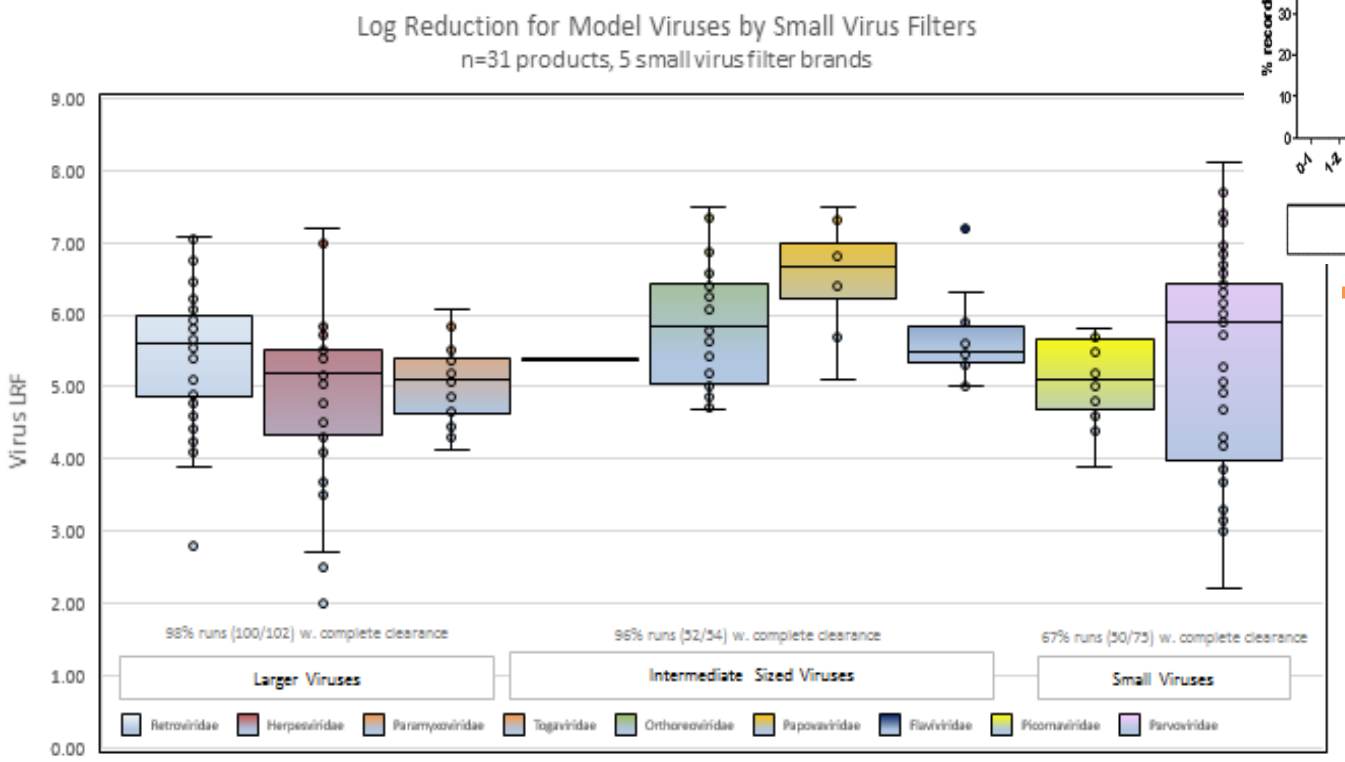
- ✓ Data encompasses a variety of product & virus filter types, buffer formulations
- ✓ Mechanism of action, retention is well understood
- ✓ Proven Acceptable Ranges for Key Operating Parameters
- ✓ Validations for *worst-case* conditions
- ✓ & Mitigation for Manufacturing events

Proposal to summarise such Prior Knowledge within MAA App. 3.2.A.2.3



N= 392 runs; (o) virus reduced below detection limit; (x) infectious viruses detected[2]





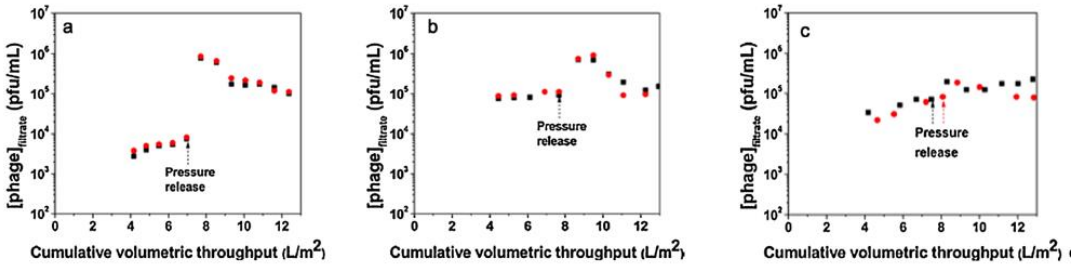
Published Data

Data: EBE Consortium

1. Nano-filtration – Virus Retention Claim for absence of impact of process interruption (pressure release) for insensitive nano-filters

- Filter qualification studies are performed in *worst-case* conditions based on an assessment of the potentially critical process parameters
- Process interruption is a parameter that must taken into consideration for its potential effect on filter efficiency

Figure 1: Concentration of bacteriophage in the permeate during filtration of a suspension containing 8x10^7 pfu/mL of ΦX174 through the (a) Ultipor® DV20, (b) Viresolve® NFP and (c) Viresolve® Pro filters[6]



Filters are known to be either sensitive or insensitive to process interruption

Proposal: To obviate the requirement for product-specific process interruption study, once prior knowledge on insensitivity of the virus filter to such interruption is assured.

2. Aged Affinity Capture Resins – Virus Removal studies using only Naïve Resin

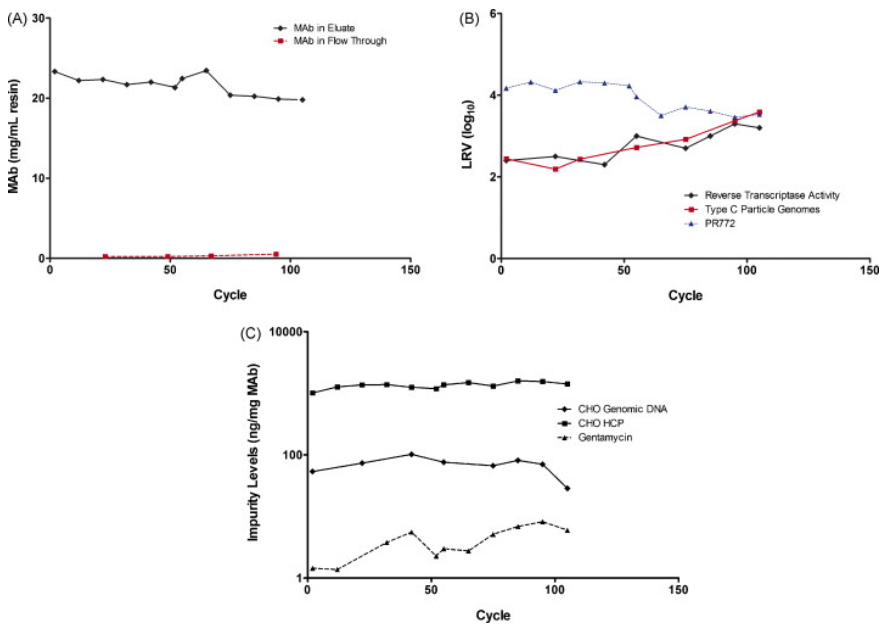


Fig. 4. Protein A MabSelect SuRe column run through 106 load/elution cycles with no cleaning. Back-pressure prevented further cycling. (A–C)[6]

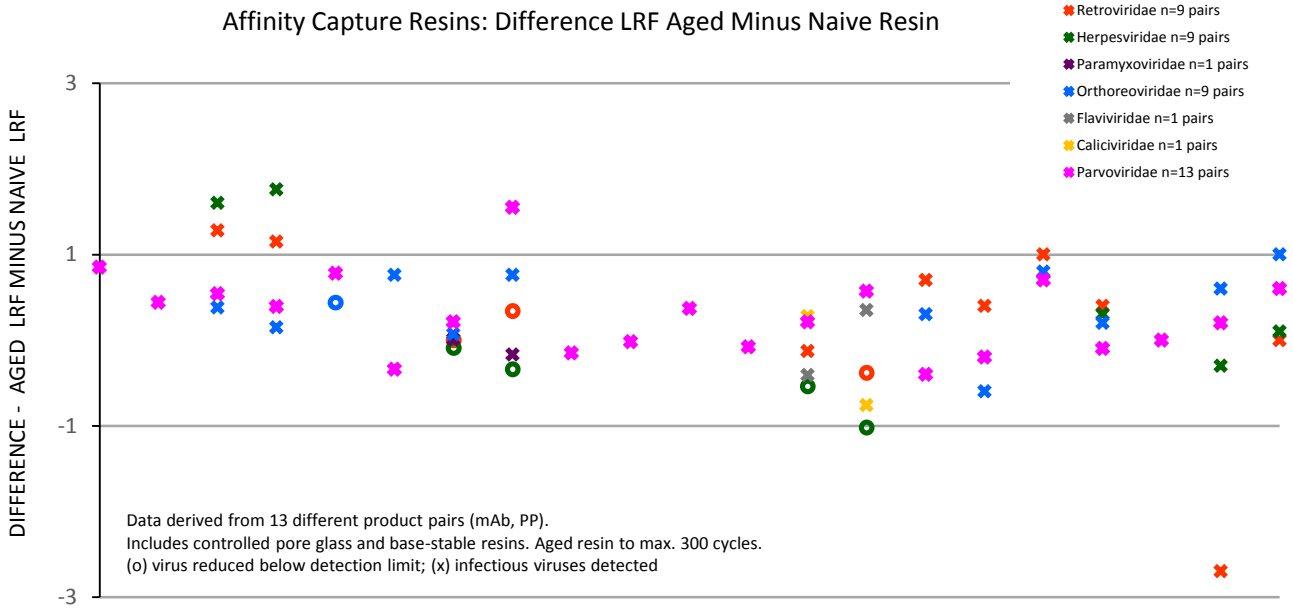
- Affinity Capture (e.g., Protein A) unit operations clear viruses by allowing them to flow uninhibited through the column during Ab capture.
- *"Some estimate of the stability of the viral clearance after several uses may provide support for repeated use of such columns"* (ICH Q5A). This guidance may be interpreted as need to measure virus reduction by used resin on a product-specific basis.
- Prior knowledge (sponsor & published data) demonstrate robustness of Affinity Capture-mediated clearance; which is not impacted by typical resin multi-cycling[7-9].
- "Because antibodies share similar biochemical attributes and antibody feedstocks are mostly bioreactor harvests, these performance attributes are more likely to depend on the particular media and cycling (i.e. cleaning) conditions in question, than on a product-specific attributes"[7]

- *Proposal: Using Prior Knowledge and robust process monitoring; measuring virus LRV using multi-cycled resin on a product-by-product basis may be obviated.*

2. EBE Viral Safety Consortium Data

- Consistency of process robustness; no impact to retrovirus clearance over resin lifetime

- Both published & consortium data demonstrate that virus clearance performance using aged Protein A resins is on PAR with new resins[7-9].
- Cleaning and cycling procedures are well-developed and typically applied in consistent manner throughout resin lifetime.
- Ab step yield and breakthrough could be proposed as surrogate performance attributes for resin performance over time
- *Proposal to summarise such Prior Knowledge within* MAA App. 3.2.A.2.3



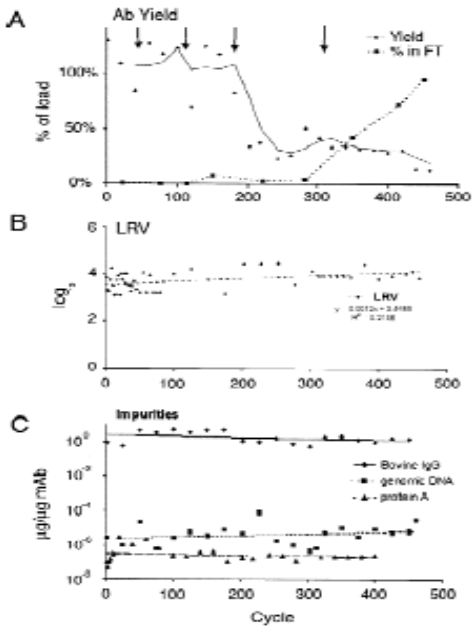


Fig. 1. Protein A column run through 461 purification/cleaning cycles with 100 m*M* NaOH cleaning. (a) IgG step yield in eluates measured every 10–15 purification/cleaning cycles are represented by diamonds. The solid line represents the moving average (n=4) of step yield. Squares indicate breakthrough in the pooled flow-through of purification/cleaning cycles 1–45, 46–105, 106–120, 121–180, 192–252, 253–311, 312–389, 390–441, and 442–461. Arrows indicates cycles where the column was re-packed. (b) LRV of RT activity (diamonds) measured every 10–25 purification/cleaning cycles. Equation and R^2 value is calculated from the line fitted to the data (dashed). (c) Levels in µg/µg of protein A (triangles), mouse genomic DNA (squares), and bovine IgG (diamonds) measured every 25 purification/cleaning cycles.

Published Data[8]

Data: EBE Consortium

Conclusion / Q&A

- EBE consortium group acknowledge the importance of appropriate virus safety strategies, and how they must ensure safety to the patients

- EBE call for feedback on the proposed approach to utilise the concepts of prior knowledge to help develop more streamlined viral safety studies:
  - Nano-filtration for parvovirus filters
    - – test *worst case* small virus; and remove product-specific large virus clearance studies
    - – once a nano-filter has been determined insensitive to process interruption, this parameter is not tested in later virus clearance studies
  - Aged Protein A resins
    - – measuring virus LRV using multi-cycled resin on a product-by-product basis may be obviated

- To best determine minimum expectations in these cases:
  - Technical rationale based on published data or requirement for in-house platform data?
  - Reproducibility across number of product types
  - Expectation for commonality of process parameters and conditions
- How can we continue the dialog?

Thank you to Consortium Members involved

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ebe european biopharmaceutical enterprises

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Vaccines Case Study - Use of Prior Knowledge to Support Resin Reuse Across Vaccine Serotypes

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Nov 2017

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Acknowledgements:
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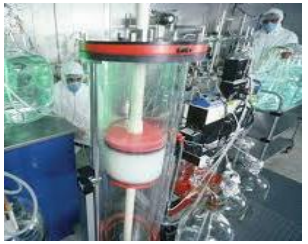
Dave Wohlpart

Vaccines Case Study - Use of Prior Knowledge to Support Resin Reuse Across Vaccine Serotypes

- Background
  - Several polyvalent vaccines utilize **chromatography as part of the purification** of drug substances
  - These manufacturing processes **typically utilize resins dedicated by antigen serotype and for a relatively limited number of uses**
  - This practice has resulted in the **discard of costly** resins and **inefficient utilization** of manufacturing facilities

Resin chromatography for clearance of impurities for multivalent vaccine
Prior Knowledge



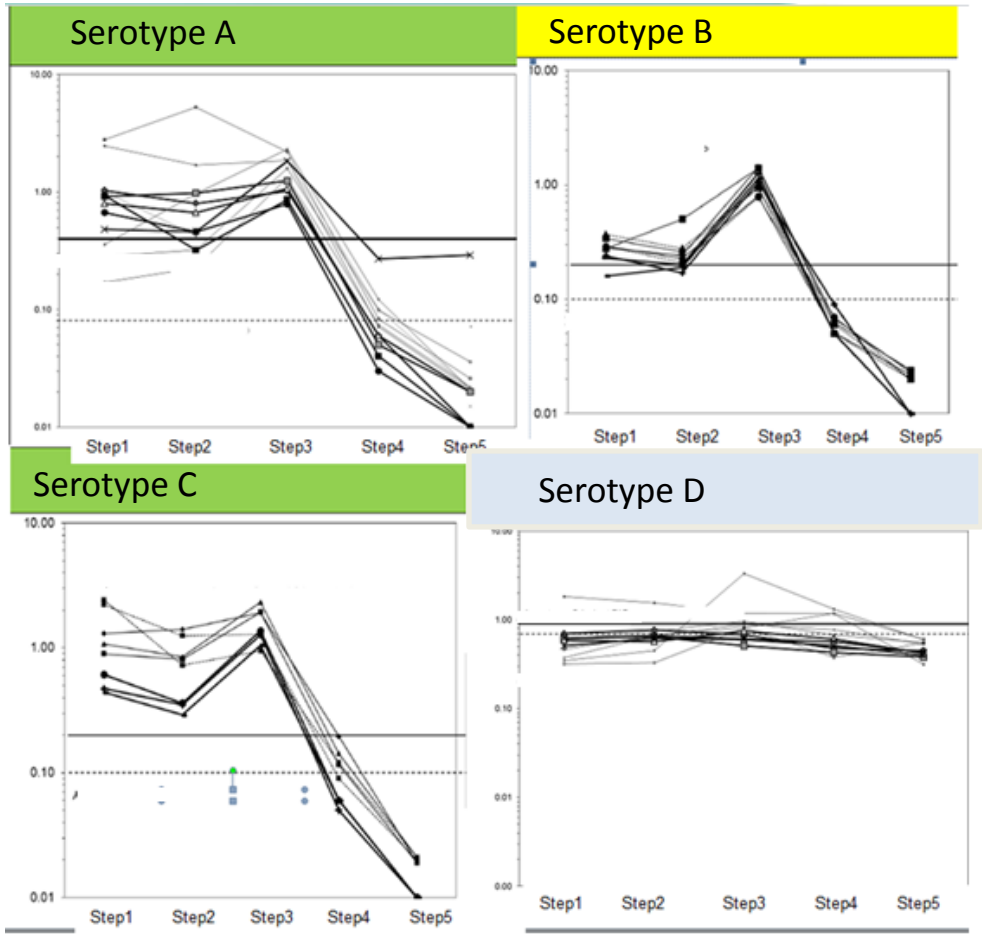
- **Development Studies**
  - Physico-chemical properties of the serotypes are similar
  - Manufacturing process – unit operations and process conditions nearly identical for all serotypes
  - Small scale model for several process changes shown predictive of commercial scale manufacturing

- **Commercial Manufacturing History**
  - CPP and CQA data
  - Knowledge gained from comparability assessments from prior changes
  - Continued Process Verification Data
  - Clearance of process & product related impurities have been shown to be similar

Prior Knowledge in the Re-Use of Resins

- **Use** process stream data from **serotype specific** commercial scale data (historical data) **to evaluate qualitative and quantitative characteristics of impurities across serotypes**

Example Process Stream Data



- Process Stream Data:
  - Host Cell Protein (HCP)
  - DNA, RNA
  - Carbohydrates
  - Lipids
  - Process Additives (e.g. enzymes, antifoam, etc.)
  - Purity

Comparable results – Data are similar and of same order of magnitude

Similar results – Data appear slightly different but evaluation concluded that difference is by less than 1 order of magnitude and thus comparability is confirmed.

Different results – greater than 1 order of magnitude different. Further evaluation or justification indicates serotype can be discounted for further studies in resin reuse.

Proposal to Apply Prior Knowledge in the Re-Use of Resins

- Use historical commercial scale process data from individual serotypes to **select the antigen serotypes for which resin reuse could be feasible**
- **Feasibility of resin reuse across serotypes to be further confirmed in a small scale resin reuse study** (using a qualified model predictive of commercial manufacturing)
- Proposal to submit and gain Health Authority approval based on the **prior knowledge,** supplemented with data derived from the **small scale model to use resins across serotypes,** but still dedicated to a specific product, and **monitor** the performance at scale under the company **Pharmaceutical Quality System (PQS)**

With increased knowledge from individual serotypes (product and process knowledge, small scale and historical commercial scale), use of resins across serotypes within a specific polyvalent vaccine and for extended uses may be justified