Interactive session:
Pitfalls in the development of a virus filtration process

Dr. Sebastian Teitz, Product Manager & Scientific Coordinator, Asahi Kasei Bioprocess Europe,
s.teitz@akbio.eu, www.ak-bio.com

Interactive Session

Material will be provided on-site

Bring your own case/topic/question/problem/challenge for discussion!

Participants have the opportunity to address real-life challenges during the implementation of a virus filtration process – from bench-top development through to commercial scale-up.

Interactive Session

Background

You are working for a manufacturer of several biopharmaceutical products.

Your position is in the process development department with close ties to the manufacturing as well as virus- & pathogen-safety department.

You are developing the purification process for a biopharmaceutical, with a projected market potential of several hundred million €'s and with competitors already selling similar products

Your role in the company

You have the overall responsibility for the DSP Development. Among the development of other steps, your task is to set-up an economic and safe virus filtration step. Should the DSP Development be holding up the commercialization…

→ **you are in charge**.

Current State of the Art Information

- Now it is year X. You have made your homework well up until now and the future process will look like this: (Preceding purification steps) … => chromatography => Filter A or Filter B (different vendors) => UF/formulation (5 g/L to 100 g/L).
- All commercial filters have been tested, the choice is between Filter A and Filter B
- Max desirable filtration time is 2h.
- The final choice about the filter should be made in year X + 1 and product commercialization should be in year X + 2

Interactive Session

Choice of filter

Filter A offers a price advantage of 7-30% (depending on filtration batch size) per gram of filtered product.

→ which filter do you choose?

→ Which other points could influence indirectly the filter price? Discuss in your group.

Interactive Session

Time: X + ½ year

- A decision is taken, mandating you to minimize the COGs → what do you do? Discuss in your group!
- Result: Both vendors independently say that the main possibility to lower COGs is to extend the filtration time → You have been able to convince management & process dev teams to accept this possibility
  - extend the max acceptable process time to 6h
  - undertake trials again for up to 8h (assisted by vendor)
- In some of the trials you are observing a mysterious flux decrease… what could be the reason? What do you do? Discuss in your group !

Interactive Session

Usual Root causes for lower flux or flux decrease:

- **Freeze/thaw** vs. Fresh
- Non efficient **pre washing** step (air removal, membrane wetting)
- Slight difference in the **feed solution composition** (impurities, aggregates, detergent)
- Higher **protein concentration**
- **Lower TMP** (air leak, leak on the line, wrong design, back pressure)
- **Lower temperature**
- Problem with the **prefilter** prior to the Planova filter (air, wetting, undersized)
- **Any deviations** in the previous purification steps (precipitation,, chromatography, depth filtration, UF/DF, etc…)

Interactive Session

Time: X + ½ year

- A decision is taken, mandating you to minimize the COGs → what do you do? Discuss in your group!
- Result: COG's for VF are lowered by >30%; lab-scale trials support the calculation Filter B is ~3% cheaper than Filter A.

Interactive Session

Time: X + ¾ year

If you go ahead pursuing a process with only Filter B → what is the next step? ?

and …

Scale-up trials are at 30% less capacity, compared to the lab-scale trials → what could be the reason? What do you do? Discuss in your group !

If you decided to keep both vendors for pilot-scale trials, testing the scalability of the virus filters. Filter A has similar but not identical reduction in capacity (capacity reduction is not as severe as with Filter B).

In depth discussion with VF vendors and internal FMEA finds that the lab-scale trials have been undertaken with ….. a different batch of product. One difference, found by analysis, is that the aggregate content is higher → this is impacting the performance of the VF. Furthermore different prefilters have been used in the different scales.

The major contribution seems to be the time of the pH adjustment. When you adjust in <10 minutes (compared to >1h previously) the filtration performance always seems to be better. More stringent QC strengthens this correlation.

Interactive Session

Time: X + 1 year

- Due to regulatory requirements to clinical studies (=out of your control) the commercialization is pushed back to X+3 years, giving you time to revisit the purification process with reduced time pressure.
- The results of the scale-up / pilot-scale trials seem to indicate that filter A is better able to handle process variations. → how does this impact your decision? Discuss in your group.

Interactive Session

Time: X + 3 years

Filter A and B are now validated and registered for your process.

Root cause for process variations: are due to the variation in the feed solution the performance may vary by about 100 %!

Summary

1. Virus Retentive Filtration is more than a singular DSP step in modern manufacturing strategies

2. VRF contributes
   - USP (Risk Mitigation)
   - DSP (“classical” virus removal as well as facility design considerations)

3. Additional viable applications
   - ATMPs Production
   - Microbial fermentation / USP Risk Mitigation