Regulatory Gaps in Continuous Processing Workshop

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1 Objectives

To provide a forum for participants to discuss and share experiences relating regulatory approaches and challenges when implementing or considering ICB.

2 Topics

2.1 How do you define a batch for continuous & semi-continuous processes from a regulatory perspective?

- How did you/will you define a batch for continuous processes?
- What data did you use/would you use to justify the batch definition?
- What in-process pooling criteria did you/will you use for processes with variable PQ day to day?
- How much PQ variability is acceptable a particular release specification (e.g., glycosylation level, charge heterogeneity)? What data would you have to justify your stance?
- Are any of the above dependent on MOA (e.g., nuances in batch to batch consistency for a-fucose)?
- What are the implications of start up and shutdown

2.1.1

Outcomes Group a

For upstream

Batch definition based on time t = 0 to t = 30 flow dependent

Assumes PQ is consistent and that process is in steady state

Concentrated Intensified batch

1 bioreactor run = 1 batch

or 1 batch can be a fraction of the bioreactor batch

For downstream drug substance

1 downstream run = 1 batch

Post formulation volume product mass dependent

Drug product

This may have a different definition from drug substance define a pool based on a DS batch or batches

May have to test differently utilising RTRT

In process pool

Look for titre and glycoforms

Use PAT monitoring but not for pooling determination (this would be for development data, understanding process capability)

Multiple DS lots

What do you do with OOR [out of range]

Dev design space, set criteria before DS batching/pooling

Batches need to be at state of the control

Real time decision

USP out of control an issue even if the DS meets spec, this triggers investigations that covers design process characterisation additional IPC is need to determine pooling/batching challenges

Outcomes Group b

Definitions

1 end of 14 day

2 60-day break into multiple batches

3 multiple batches at the end of the continuous unit operations

Justification has to be based on traceability that address raw materials out of specification, deviations and situational issues

Other factors to consider are

PQ, Traceability and Integrity

2.1.2 Chairs Summary

Continuous processing is both end to end uninterrupted flow and the repetition of process step continuing over prolonged time.

Several of the Groups addressed batch definition as this has to be considered when discussing control strategy, validation, etc. Provided there is batch to batch consistency, and the criteria for pooling are pre-defined, the definition can be based on time or quantity, where 1 vial 1 batch is likely a component of the definition. Other GMP topics such as traceability of raw materials are not unique to continuous manufacturing

2.2 Validation of continuous processes how do we meet current regulatory expectations?

- Process characterization needs to account for the connectivity between steps. What is your approach for DOE – partition design vs testing isolated unit operations?
- How do you show the process is in a state of control?
- For instance, how do you demonstrate cycle-to-cycle consistency on downstream chromatography columns that are cycled 50-200 times?
- What data would you show to justify your stance?
- Are there different strategies for Upstream compared to Downstream

2.2.1 Outcomes Group a

Process control strategy

Per unit operation

Linking studies - SDM with links

Does not have to be like for like

- Accept engineering differences
- Test Interaction hypothesis
- Worst case scenario, intelligent wcs

PPQ

(3) Data analytics to measure and assure that CPP remain in spec.

(4) CPP out of specification can lead to product segregation and deviation analysis, though it may be released later.

Outcomes Group b

How do you show the process is in a state of control?

- Intentional consideration of time impact & dynamic conditions
- Appropriate sensors in the correct locations with the needed resolution [challenge, sensor resolution, response time & technology is not available]
  - Flowmeters are very important
- Predefined criteria to make decisions RTD criteria, pH criteria, etc.
  - Cannot wait for QC

Approach to Validation

- This depends on CPPs with QbD and how much you know about your process (it depends on how well you understand the platform and manufacturing)
- If parameters are to impact on subsequent UOs then characterize and validate

Drawbacks of the approaches for

- Integrated
  - More work and cost
  - Larger factorial analysis
- Single UOs
  - May miss variables that impact on CPPs

How do you demonstrate cycle to cycle consistency

- Upstream
  - This is more like batch where PQ already changes over time
- Downstream
  - Transition analysis to show that process parameters are within range
- Batch to batch has to consistent but cycle to cycle may be eliminated in some cases i.e. slipstream, intermediate pools
- Consider surrogates such as transition analysis

2.2.2 Chairs Summary

In the context of continuous processes, it was noted that this discussion was forward looking and somewhat theoretical as none of the assembled participants has validated a continuous process yet.

The consensus is that validation will be a mixture of approaches for different unit operations. The goal of upstream PV is to show batch to batch consistency, with cycle to cycle measurements focusing on process performance and not necessarily product quality *(vote was not to measure CQAs per cycle).*

2.3 How do we meet regulatory requirements requiring us to demonstrate viral reduction throughout the process?

- How do you validate continuous virus inactivation?

- How do you validate VRF in a continuous process?
- How do you demonstrate viral clearance in a continuous chromatography column
- Do you use one membrane system continuously for 14-60 days?
  - Or do you change membranes every day?
  - What are the criteria to be used for changing them?

2.3.1 Outcomes Group a

Viral Inactivation

- Understand the residence time and maybe do it in batch as much as possible
- Plug flow reactor can treat as a batch run
- Leverage reaction kinetics
- Spot on pH is really important. Doing a best case and worst case
- Narrow pH to control to 3.6 +/-0.1

Viral Filtration

- Protein loading and flux and which is worst case
- Throughput is worst case. The disruption of flow can impact.
- increase the surface area (which can also impact flux, risk assessment needed)
- The column before can impact the protein concentration
- oversizing is costly and you can also impact the filter integrity testing

Spiking studies for VI and chromatography

- Small scale studies
- Life cycle of resin
- Using simulations to show how things change and then recreate.
- Leveraging historical knowledge and experience

Outcomes Group b

Same fundamentals as traditional batch [Low pH VI, Anion IEX VRF & Protein A]

- Regulators require 2 orthogonal methods industry uses 3

Challenges scale down

- Time
- Max total load
- Flux AEX and VRF

Strategies

- VRF swap out
- Spiking studies beginning, middle, end
- AEX cycle or oversize
- "worst case" model

Challenges connectivity

- Surge tanks sizing
- Depends on technical solution
  - Repetitive cyclic process or
  - Continuous flow

2.3.2 Chairs Summary

Concepts applied to demonstrate viral clearance are the same as those for batch-process. Typically, validation of performance (VLR) is achieved "commonly" with 3 orthogonal steps and the use of scale down models to address worst case per unit operation.

Generally, while nanofiltration may be absolute, reactive steps like low pH and depth-based steps are probabilistic; thus, when you compare batch and continuous validation you need to consider what influences the probability of an increased challenge. It is typically greater volume through the step and one must adjust the probability accordingly (This has been done for decades in batch vs. continuous thermal sterilization).

For plug-flow systems, the residence time distribution will be critical. Valid small scale models for all steps are needed, including strategies for virus spiking and also to evaluate range of protein concentrations in different cycles.

For plug flow systems there will have to be defined operating flowrate range as this is linked to residence time.

2.4 What PAT technologies are needed to support robust in-line monitoring?

- How do you show the process is in a state of control?
  - For normal steady state, start-up and shutdown considerations
- For instance, how do you demonstrate cycle-to-cycle consistency on downstream chromatography columns that are cycled 50-200 times?
  - What data would you show to justify your stance?
- Can we use PAT to adjust process perturbations in real time steering process to a optimum?
- How do you manage process deviations?

Outcomes:

Monitor trends of parameters from a column unit operation

- A combination of monitoring process and product quality maybe required
- Use of PAT (capacitance) to control cell bleed rate for steady state cell density
- Is a mechanistic model required for biologics?
- Challenges in the of VCD control
  - Is the protein conc. in a state of control?
  - We rely on scale down models

Use of PAT for product diversion

2.4.1 Chairs Summary

PAT would be used to measure process performance rather than CQAs. RTR is still an aspiration by many but there is no a complete consensus on sensor validity, sampling strategy and use of process data relative to direct measure of CQAs on- or at-line.

2.5 What are your in-process bioburden control strategies?

- What are your in-process bioburden control strategies for processes that operate continuously for 14 – 60 days downstream?
- Do you sanitize everything daily?

- Do you rely on sterile materials and filters and forgo sanitization?
- How do you change non active SU components (bags tubing)

Outcomes

From experience:

- Keep as much of the process closed as possible
- Risk assessment for testing (business risk)

Theory:

1. Keep it open and sanitise/sterilise
2. Sampling worst case end of hold

- Swapping out components similar to USP
- Sterile components
- Functionally closed
- Need to understand (all components) the residence time in the process

Options:

- Prep front end work (engineering controls) vs. monitoring and control
- Functional closed or fully closed system
- Add filters at high risk points (after protein A)
- Sanitise/sterilise where open

Challenges:

- Swapping out components/filters
- How to test for functional closure (integrity test, etc.)
- End of process very high risk
- Sampling in a closed manner

2.5.1 Chairs Summary

It was noted that FDA typically requests data on microbial control beyond that needed based on risk assessment and scientific principles, so this needs to be planned for. There was much variability between participants regarding use of closed systems, reliance on sterile components/sanitization. e.g. there are few standards of practice. for instance some processes incorporate sterile filters between each step and others do not use filters at all (depending on tolerance for risk).

2.6 How and where are samples taken in a continuous process?

- Methods for taking a sample
- Frequency
- Device and controller delays
- Uniformity
- Start up vs. steady state

Outcomes

Where to take samples

- At the end of the process
- At surge tanks and intermediate points

How

- Novoseptum, sterile bags
- Periodic point samples

When

- Depends on batch definition
- Risk management to determine the frequency (e.g. 2 h or 8h)

Challenge

- Taking samples vs. sterility

2.6.1 Chairs Summary

Sampling strategy aka "testing" is built into the risk mitigation strategy. Regulators are often expecting data, particularly for microbial control, even when there is a scientific rationale for not sampling extensively.

2.7 What are implications of system integration from a regulatory perspective?

- Do we need increased understanding of the interaction between linked unit operations?
  - To ensure stable operation
  - Resident time distributions
  - Implication for feedback/feedforward control
- Are there data management issues
- How do we deal with changes and disturbances?
  - Raw materials
  - Changes in process conditions (titre from the bioreactor)

2.7.1 Outcomes

We need increased understanding of interactions in terms of

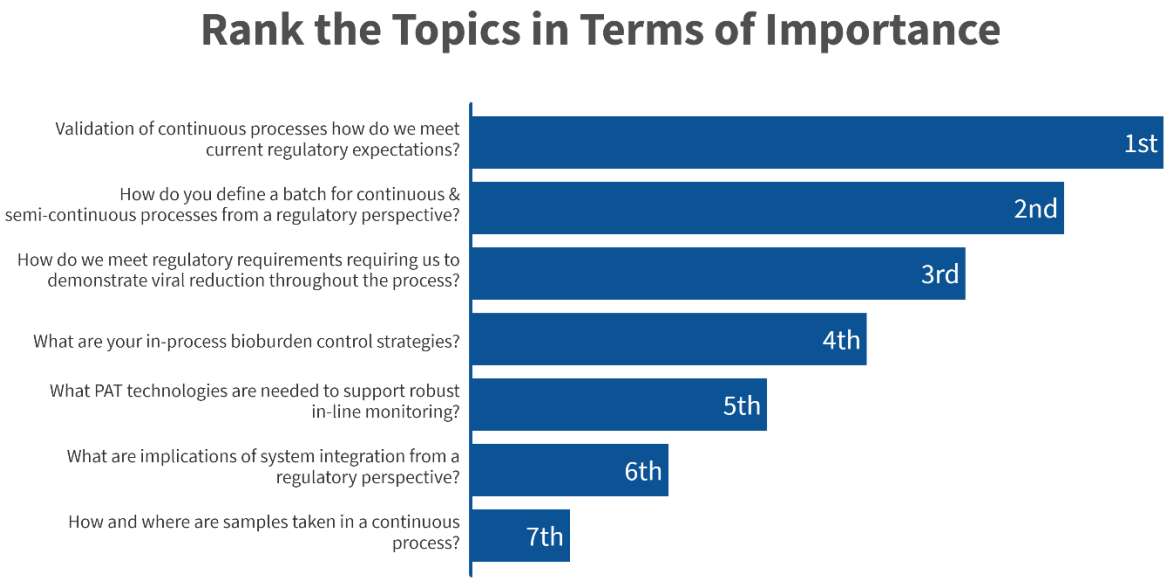
- Charge variants (perfusion conditions)
- HMW
- Implications on downstream
  - One perfusion batch = 1 DS slot
  - Multiple lots
- Feedforward or back is implemented on a case by case basis
- RTD is critical
- Strategy for a sublot

2.7.2 Chairs Summary

There was a recognition that increased process understanding is required when directly connecting unit operations. This is used to demonstrate to the regulators that there is an understanding of the interactions that can be utilised in controlling the process leading to a stable operation and consistent residence time.

3 Audience Feedback

The audience were asked the topics in order of importance we had a total of 29 responses



We had feedback from a workshop participant who stated that the topics listed mirrored the list of topics they put together for discussion with the FDA

4 Observations

There currently there are many different interpretations of some of the key terms/concepts used when describing key aspects of continuous processing. Consideration would be given to an appropriate forum for industry to discuss and build a consensus as it relates to definitions and terminology and regulatory approaches that are relevant to ICB.