**Case Study Draft Scenarios for ICB Workshop:**

1. ***Legacy commercial production site retrofit***

A moderate scale fed-batch commercial production site is migrating its legacy commercial product to be supplied primarily from another larger-scale site and thus the existing 6x5kL scale facility will soon be available for other clinical and/or low volume commercial product production. The timing is good because after a gap of several years in clinical candidates, the early portfolio is very promising and has a number of candidates which could enter Phase 1 trials in the next 12-18 months. The facility is older and was designed for low titer processes prevalent at that time especially for a low volume product: e.g., capture column is 50 cm and was run for 7 cycles because of limitations on buffer storage tanks. The current process standard for the early clinical development portfolio is ~10 g/L so certain capital upgrades are anticipated

A small amount of the legacy product will need to still be manufactured here but a request has been made to increase facility throughput, reduce consumable raw material investments for small batch campaigns, and decrease COGm overall. As the technical project lead, you see the facility as an opportunity to modify and create a space for fully integrated continuous bioprocessing for those clinical assets and have generated the following options for specific unit operations upgrades:

Unit ops proposed for continuous processing approaches include:

* + N-1 perfusion
  + Continuous capture column
  + Continuous/on-demand buffer preparation (eliminate/reduce buffer hold tanks)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Detail |  | Legacy | Fed-Batch upgrade | Fed-Batch + MCC capture | N-1 Perfusion + MCC Capture |
| N-1 Seed Bioreactor | L | 1x500 | 3x500 | 3x500 | 3 x Perfused 500 |
| Bioreactor Vol | L | 6x5000 | 6x5000 | 6x5000 | 6x5000 |
| Titer | g/L | 2 | 10 | 10 | 10 |
|  | kg/batch | 10 | 50 | 50 | 50 |
| Bioreactor Duration | days | 18 | 15 | 15 | 12 |
| Harvest Cadence | days | 6 | 3 | 3 | 2 |
|  |  |  |  |  |  |
| # | columns | 1 | 1 | 4 | 4 |
| diameter | cm | 50 | 120 | 50 | 50 |
| Column volume | L CV | 39.3 | 226.2 | 39.3 | 39.3 |
| target load | g/L resin | 40 | 70 | 90 | 90 |
| target load | g/cycle | 1572 | 15834 | 3534 | 3534 |
| # | cycles | 7 | 4 | 15 | 15 |
| flow | cm/hr | 150 | 150 | 150 | 150 |
| flow | L/hr | 295 | 1696 | 295 | 295 |
| buffer/cycle | CV | 25 | 25 | 20 | 20 |
| Buffer/batch | L | 6,878 | 22,619 | 11,781 | 11,781 |
| active flow time | hrs | 30 | 16.3 | 17.0 | 17.0 |
|  |  |  |  |  |  |

Clinical assets have all been developed using the updated platform fed-batch process format up to this point which yields ~10 g/L after 15d or 12d if a perfused N-1 seed bioreactor is employed. How would you prioritize process upgrades to maximize facility output with minimal/no impact on facility footprint or utilities? 

1. ***Clinical legacy site moving to commercial (unstable product)***

Your Business Development team has just in-licensed a clinical product with outstanding potential (“can’t miss blockbuster” they said) but it also has a demonstrated susceptibility to degradation via deamidation across the process, especially during upstream production. FIH clinical supplies were produced via a shortened, low titer upstream process and rapid handling of the low volume downstream process since the molecule is sensitive to elongated hold times at low pH as well.  As the program moves into late stage clinical and commercial manufacturing, much larger volumes are anticipated so certain decisions need to be made now: do you lock into the low productivity fed-batch process used to supply FIH or do you follow the lead from one of the innovator company’s tech reports and pursue the results from a single development experiment which demonstrated almost no deamidation in a 25d steady state perfusion run at bench scale. You also see an opportunity to convert to a fully integrated continuous process at some point. Note that your company also has locked in options on some related candidates from the same innovator company which all have a similar motif in the structure making their susceptibility to deamidation highly likely.

The facility proposed for future manufacturing is traditionally a clinical only operations facility with 2x2kL SUBs with harvest by depth filtration and has experience in implementing and operating advanced PAT tools. It has an overall openness for new technology adoption however is only currently equipped with continuous unit ops of N-1 perfusion (200 L sub) and continuous multi-column chromatography for the capture step.

* + What development work would be required to support a change in manufacturing approach (fed-batch to perfusion/ICB)?
  + Assuming the N-stage bioreactors are converted to perfusion operation, what additional DSP upgrades would be useful for this product and also be applicable to a broader portfolio, e.g., continuous low pH viral inactivation or SPTFF?
  + What would a transition strategy look like for a switch to ICB including comparability studies?

1. **Facility Upgrade (if needed)**:  Select continuous bioprocessing unit ops only (Modernize an existing facility for throughput and COGm reductions with budget constraints in mind)
   * The site management team (operations, QA/QC, supply chain, etc) has requested increase facility throughput, reduce consumable raw material investments for small batch campaigns, and decrease COGm. You have asked for proposals to introduce continuous operations for specific unit operations only.
   * The facility proposed is an existing batch production (fed-batch for upstream N-stage) site used to run clinical and commercial products and is equipped with multiple trains of upstream and downstream equipment. Facility modifications need to fit within existing facility footprint.
   * Unit ops proposed for continuous processing approaches include:
     + N-1 perfusion
     + Continuous capture column for clinical programs only (to reduce clinical investment cost)
     + Continuous VIN step
     + Continuous buffer preparation

**Questions for each team to answer:**

1. Consider the following:
   * Facility fit engineering modifications required including data systems and automation
   * Workforce readiness wrt training required or new hires with new skills
   * Development work required to adapt current processes to proposed facility
   * Can development work/clinical manufacturing at a CDMO help mitigate any risks created by an accelerated timeline?
   * Vendor support for new equipment
   * Quality system modifications needed
   * Regulatory risks of making process changes
2. Create positions and arguments as if you are:
   * Team A: Technology engineers & scientists (SMEs) trying to advocate for the continuous process scenario implementation
     1. What justifications would you present to site leads for Quality and Operations for the modifications?
     2. How will you support implementation?
     3. Use technology and site readiness/adoption scorecard
        1. Document risk scoring and mitigations

* + Team B:  Upper Management (Devil's advocate/ Technology challenger) questioning the value and highlighting the roadblocks/barriers to implementing the continuous technology
    1. How is ROI for CapEx and OpEx needed for new equipment evaluated?
    2. What comparability protocols will be needed to support proposed changes?
    3. How applicable is new equipment across a product portfolio?
    4. Will batches need to be tagged for specific regions and for how long?
    5. Use technology and site readiness scorecard
       1. Document risk scoring and mitigations or arguments to support high risk