SARTORIUS

Simplifying Progress

Simplify Upstream Process Intensification From PD to Manufacturing

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1. Process Intensification Satisfies Key Business Drivers

Low Capex Investment	< 50%
Faster Buildout Time	< 2 years
Flexible Smaller Footprint	50 - 70%
Higher Productivity	2 - 3 ×
Lower COGS	> 30%

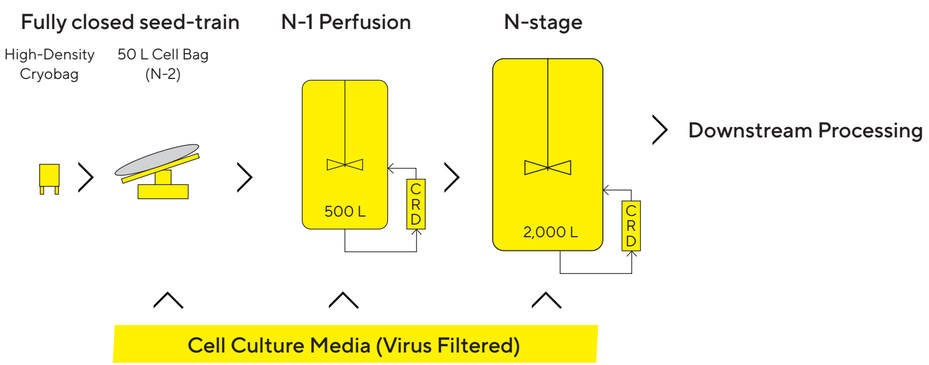
Process intensification is a holistic framework to maximize overall productivity of the unit operation(s), the manufacturing process and | or the facility output for biomanufacturing.

Benefits of Process Intensification:
- Enables faster drug development
- Increases the efficiency and productivity in GMP manufacturing
- Applicable to any process irrespective of molecule
- Can be step-wise (per unit operation) or end-to-end for maximum impact
- Other terms used in the same context: "continuous", "connected" and "integrated"

Source: Data derived from Biosolve modelling

2. Upstream Process Intensification Strategies

Requirements include robust cell line and media suitable for long culture durations & high VCDs of perfusion, scalable performance from clone screening to manufacturing along with recipes & PAT sensors for process control



Seed Train Intensification
- HCD cell banks | direct thaw in Rocking Motion (RM)
- RM **Perfusion** (before N-3) to skip N-2 (Fed-Batch)
- N-1 **Perfusion** using RM or stirred tank reactor (STR)

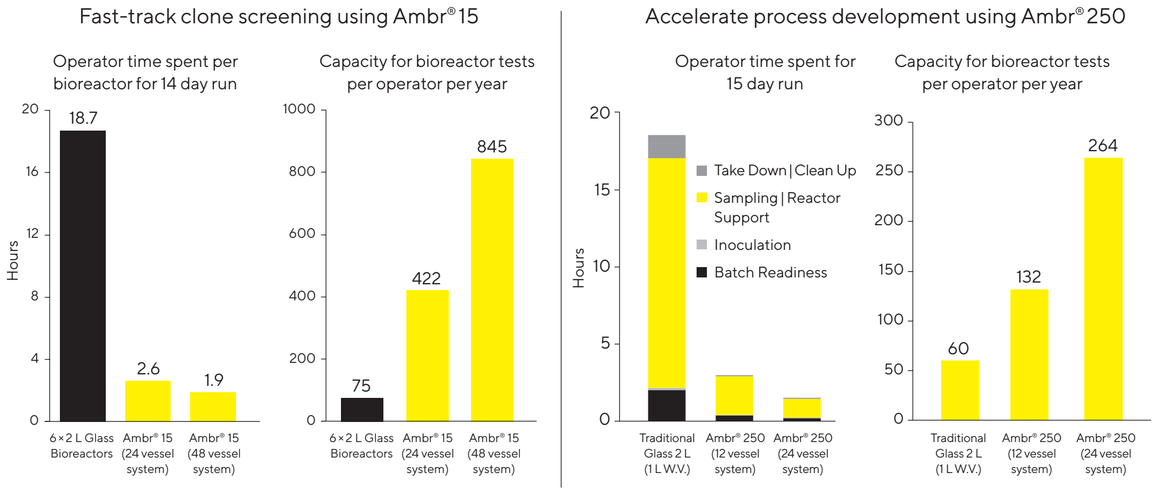
Main Bioreactor Intensification
- High inoculation FB from N-1 Perfusion
- Intensified Fed-Batch:
  a) **Concentrated FB** = Product in bioreactor
  b) (Dynamic) **Perfusion** = Product in permeate

Clarification Intensification
a) Single use centrifuge (e.g., Sartorius Ksep®)
b) Multi column chromatography (e.g., Sartorius BioSMB)

Ref: BPOG Technology Roadmap 1st edition, 2017; 3. Process Technologies Bio® BioPhorumOperations Group, Ltd.

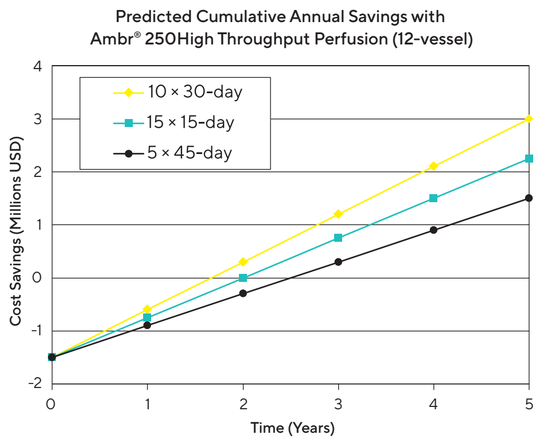
3. Clone Selection to Process Development

Save Time, Run More Experiments and Obtain Useful Data Using High Throughput, Multi-Parallel Ambr® Systems



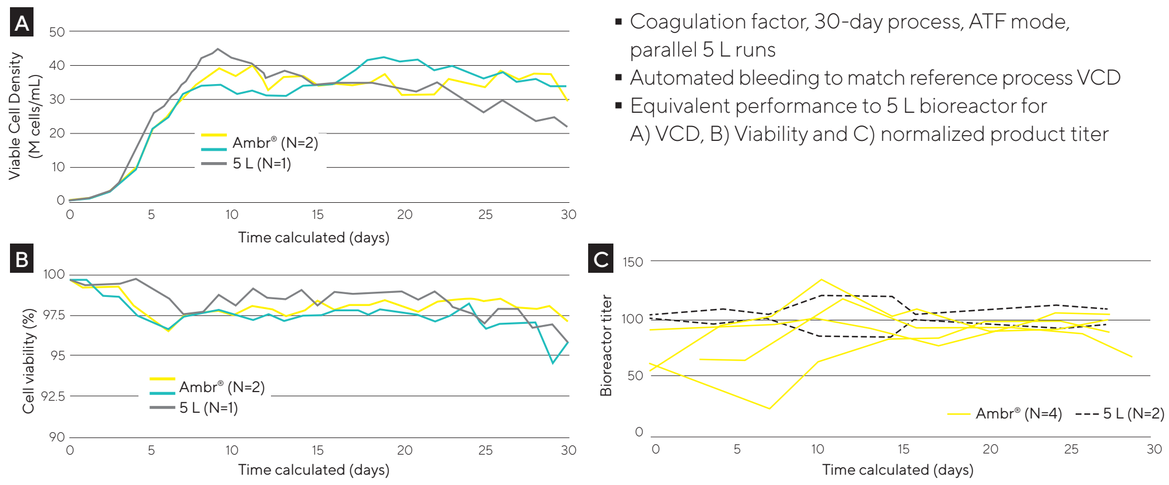
4. Process Development & Characterization

Ambr® 250 Perfusion is Efficient & Cost Effective Compared to Traditional Benchtop Perfusion



- System payback period 1 - 2 years
- The major source of cost savings is media cost reduction with Ambr® 250 High Throughput Perfusion
- Annual costs were calculated for three experiment capacity scenarios, for both:
  - 1× (Ambr® 250 High Throughput Perfusion – 12 vessels)
  - 2× (6 × 2 L benchtop bioreactors)
- Annual cost savings calculated as:
  - cost (12 × Ambr® 250) – cost (12 × 2 L)
- Cumulative annual cost savings include initial CAPEX investment

5. Ambr® 250 Perfusion: Good Match to 5 L for VCD & Titer



- Coagulation factor, 30-day process, ATF mode, parallel 5 L runs
- Automated bleeding to match reference process VCD
- Equivalent performance to 5 L bioreactor for A) VCD, B) Viability and C) normalized product titer

6. Flexible Seed Train Options

- Intensifying N-1 Seed Train is the easiest to implement with minimum change to the Fed-Batch process
- It results in upto 2 × higher titer, upto 50% increase in throughput & lower COGS compared to Fed-Batch

Intensified Stirred Tank N-1 Seed Train

- N-1 perfusion enables high inoculation of production bioreactor
- Reduce culture length of production bioreactor (~40%) –17 seed train days (25 - 29 total USP days)

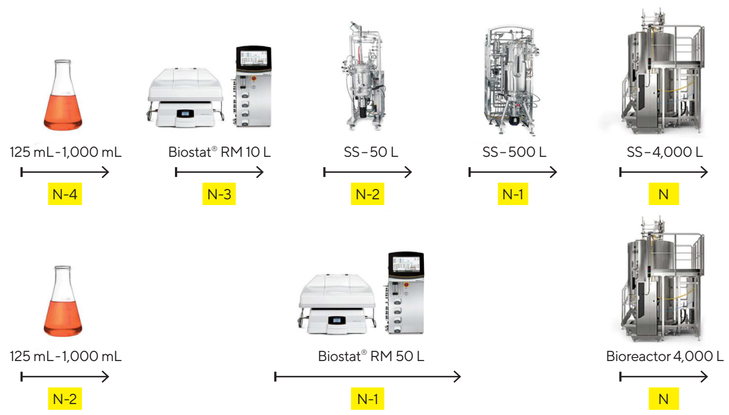
Intensified RM 200 N-1 Seed Train (Economical)

- Upto 25% reduction in investment cost
- 50% lower consumables cost per batch
- Upto 20% reduction in production bioreactor culture length: 14 seed train days (22 - 26 total USP days)

3 Bioreactors & 3 steps (instead of 4 each in FB)
3 - 6 more batches / year / train

7. Intensified N-1 Seed Train: 10 × Productivity Increase

Traditional Batch (Top) Versus Perfusion (Below) Seed Train Cell Culture Process Workflow at Intas



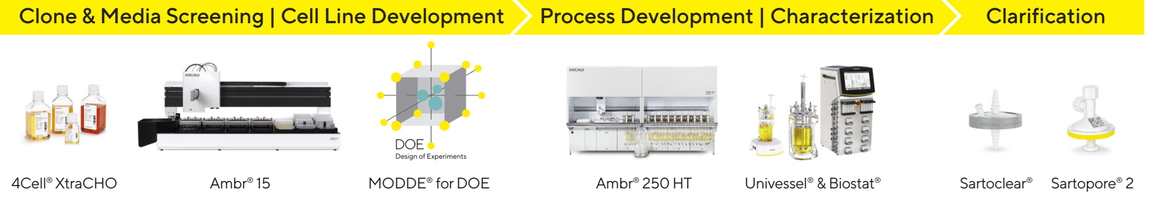
- Reduced seed train from 5 to 3 steps saving time and cost
- N-1 perfusion increased cell culture productivity 10 × with a smaller manufacturing footprint
- Showed comparable growth kinetics and yield with a control process at 50 L scale
- Target VCD reached with > 98% cell viability in 6 – 8 days of fed-batch culture

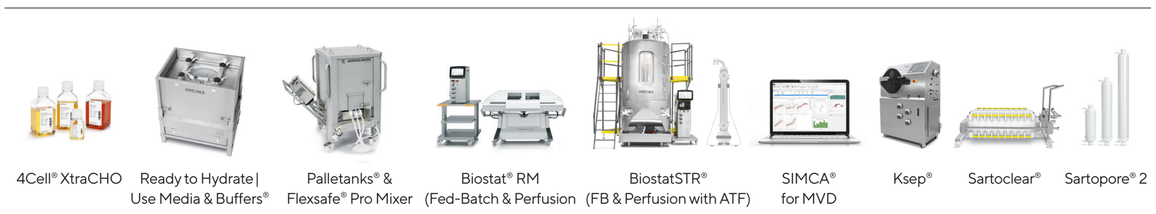
Source: Malla R et al., BioProcess J, 2021; 20.

8. Process Scale-up & Summary

Sartorius Upstream Process Intensification Platform: PD to Manufacturing

Clone & Media Screening | Cell Line Development | **Process Development | Characterization** | **Clarification**





Media | Buffers | **Seed Train | Production** | **Clarification**

Summary

- Process Intensification maximizes productivity and flexibility and can be implemented step-wise or end-to-end
- High throughput Ambr® systems fast-track biopharm perfusion process development saving time and money
- N-1 Perfusion results in upto 2 × high titer, lower COGS and is the easiest to implement in an existing facility
- PAT sensors enable culture monitoring, automated inoculation of subsequent cultures & better process control