Development of an Integrated Manufacturing Process: The iSKID™

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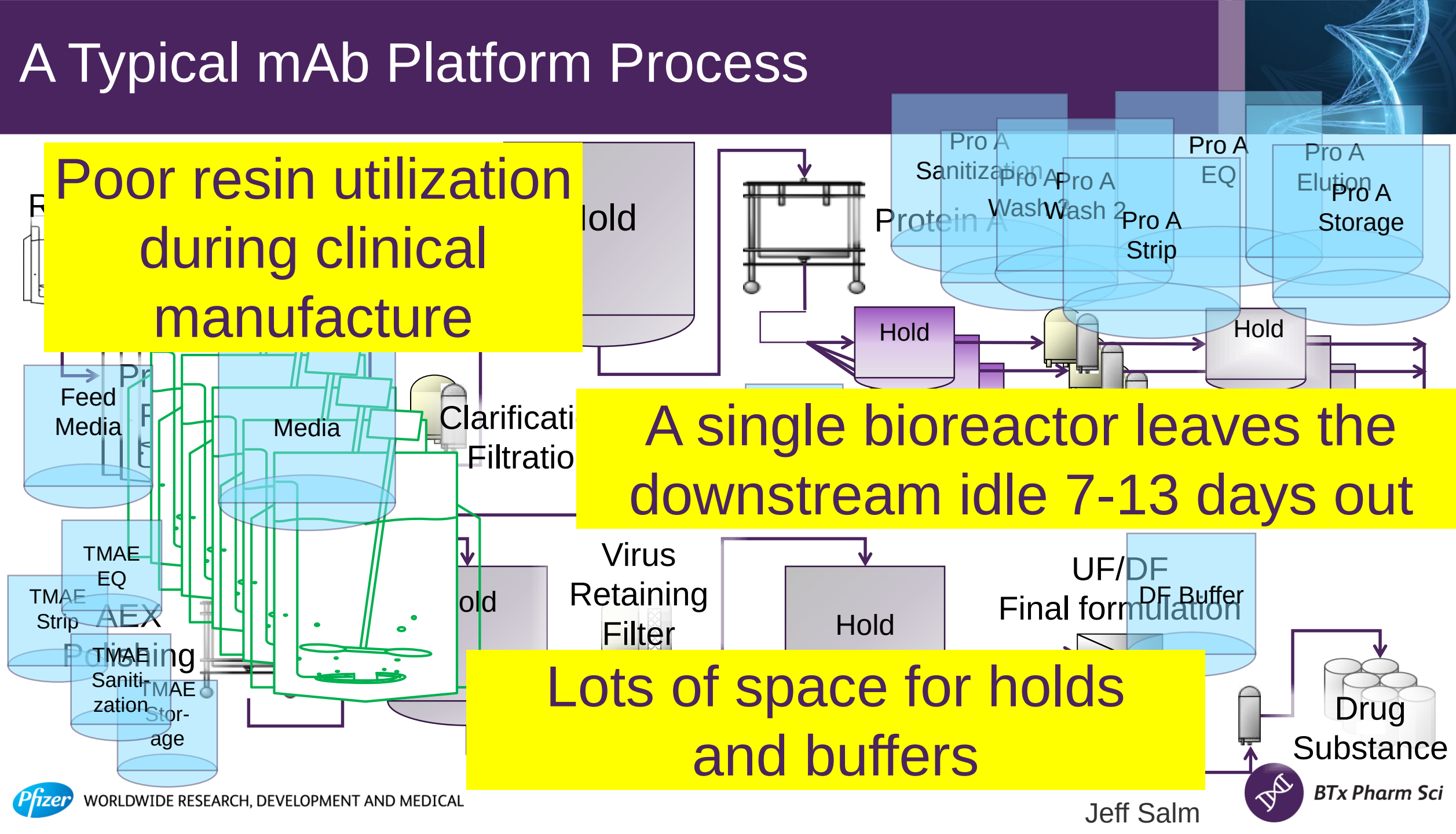
BioTherapeutics Pharmaceutical Sciences

Pfizer WORLDWIDE RESEARCH, DEVELOPMENT AND MEDICAL

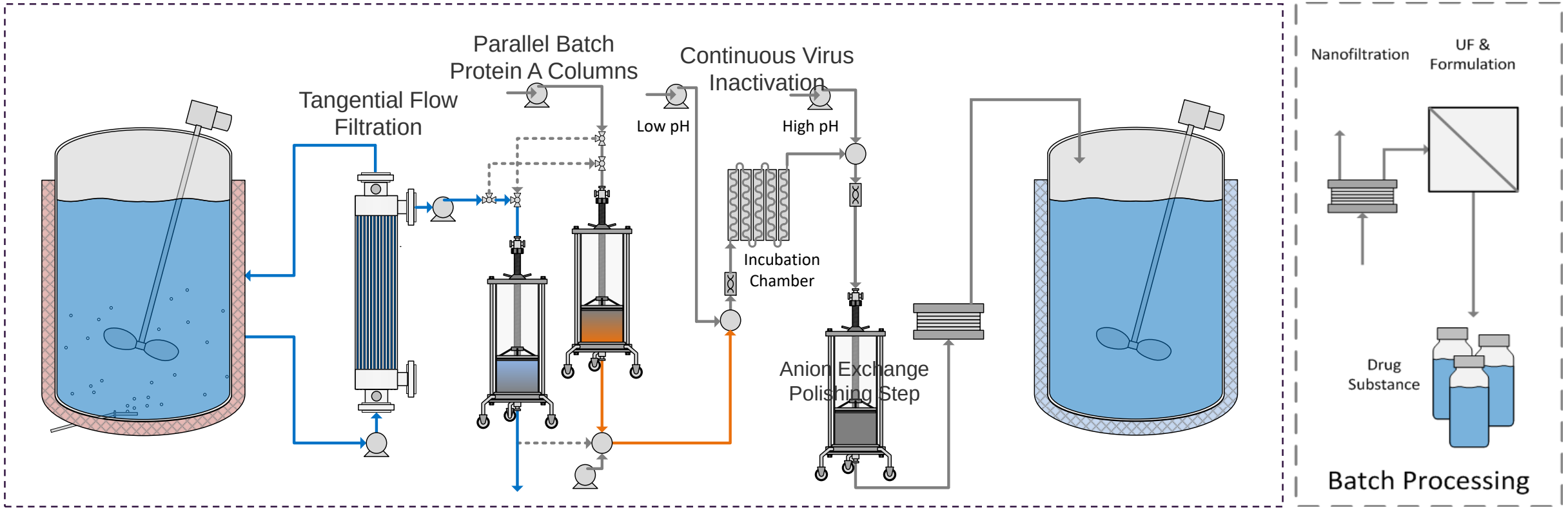
Introducing the ISKID™
An integrated approach to manufacturing

The iSKID™ initiative is a technology partnership between Pfizer and Boehringer Ingelheim (BI) focused on delivering transformative manufacturing efficiency and accelerated launch options for protein therapeutics (drug substance/DS).

A Typical mAb Platform Process



iSKID™ Integrated Manufacturing System
Thoughtful integration of process maximizes productivity

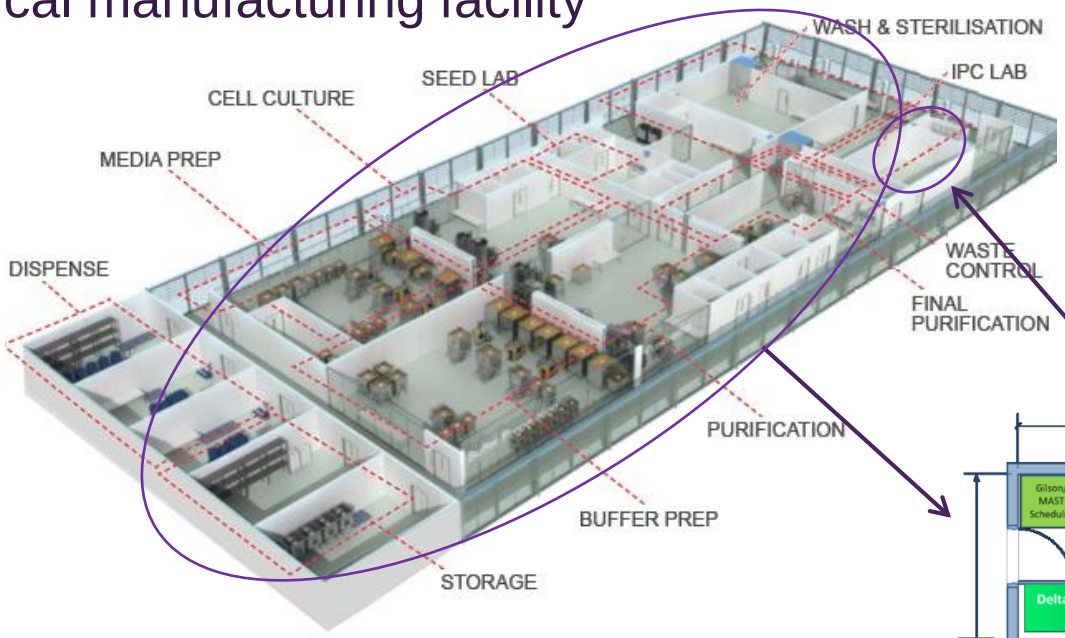


- Fully automated and disposable system
  - Highly productive short duration perfusion: 2-3 week cadence
  - “Simple” downstream design – Continuous, periodic, batch
  - Buffer and media concentrates

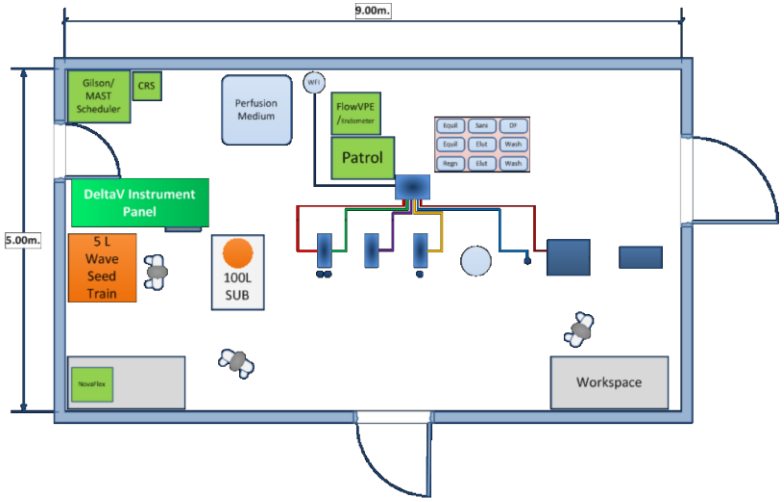
Re-Imagining Bio-Manufacturing

Current state of the art

Clinical manufacturing facility

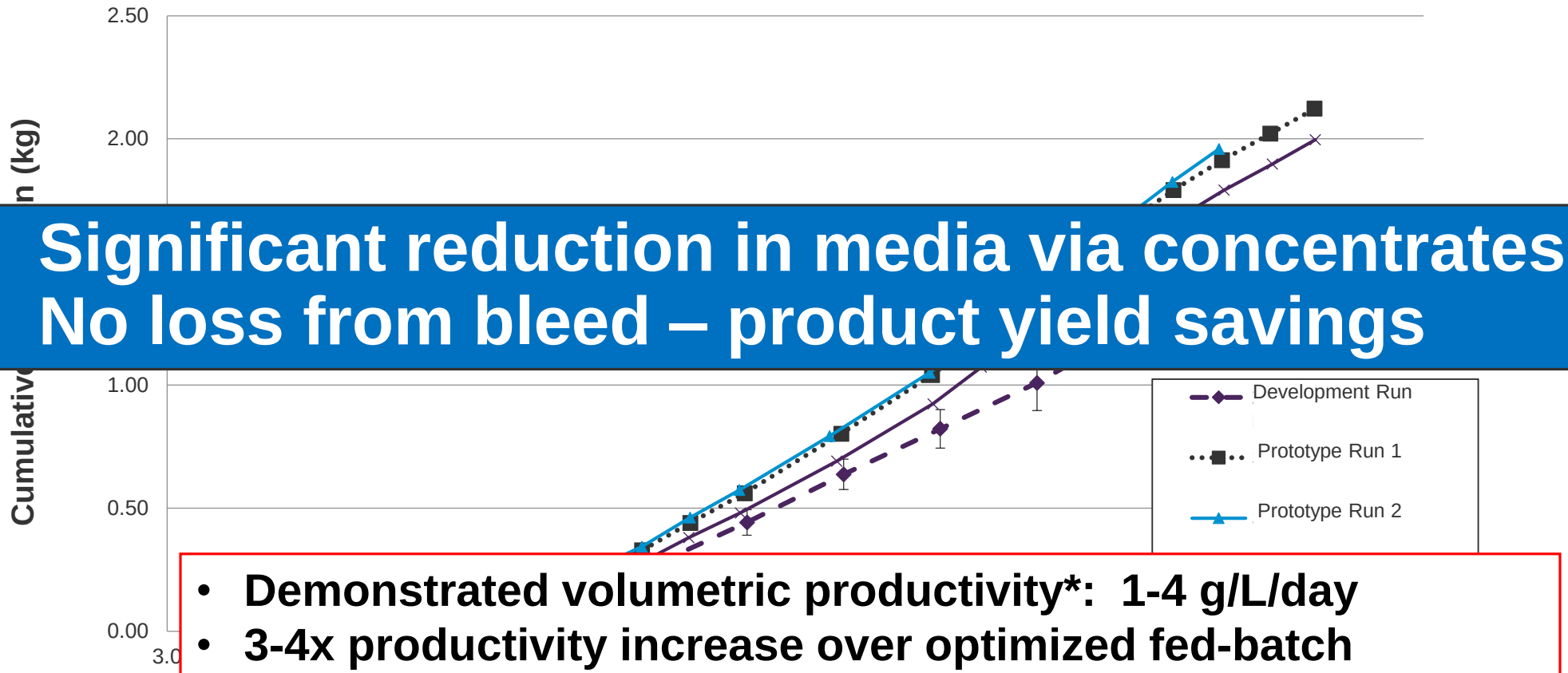


Future State: iSKID



Cumulative 100L SUB Production:
Output Can Exceed 2 kg of mAb in Permeate

Development and Prototype Runs Average Cumulative Production in Perfusion Permeate

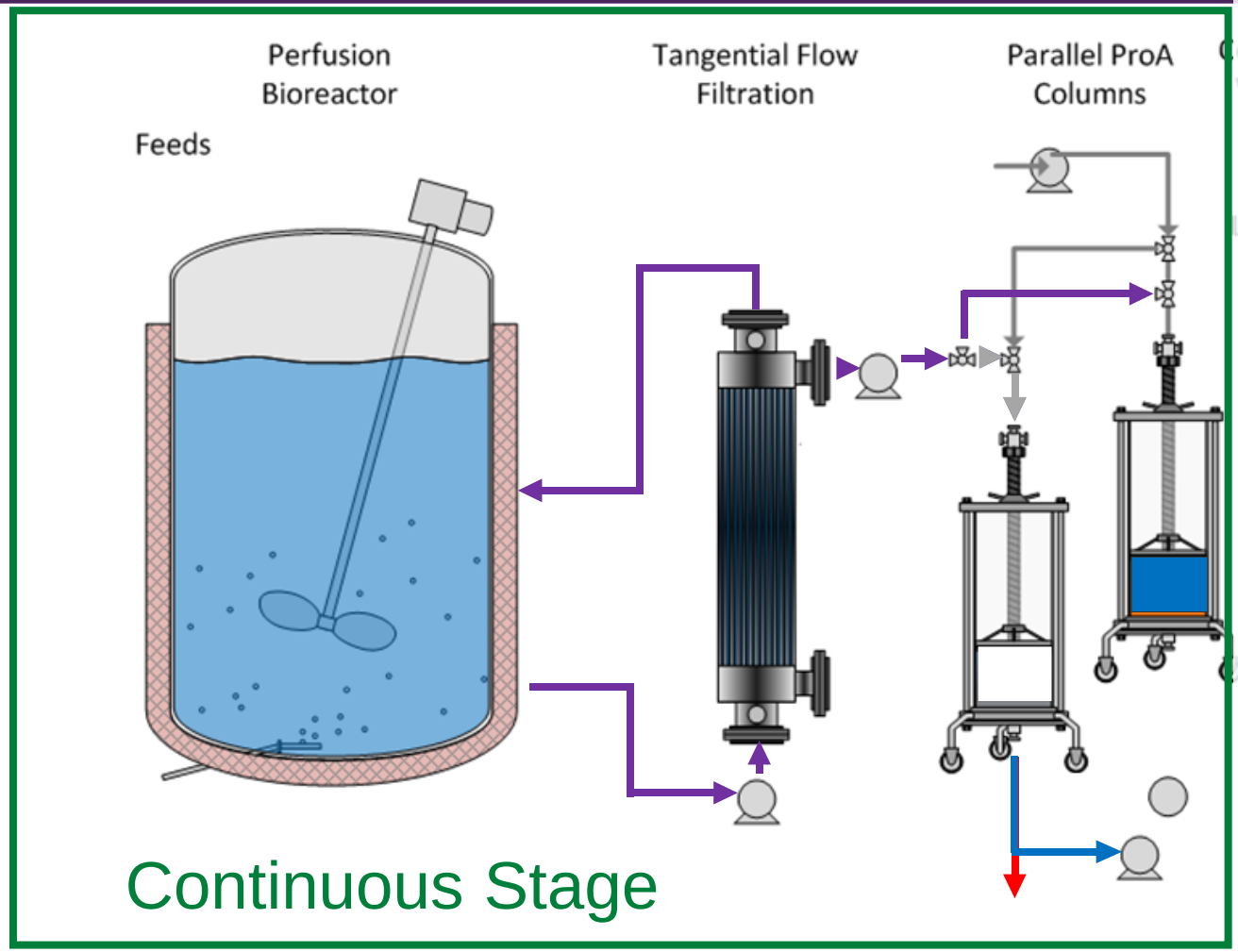


- **Significant reduction in media via concentrates**
- **No loss from bleed – product yield savings**

- **Demonstrated volumetric productivity*: 1-4 g/L/day**
- **3-4x productivity increase over optimized fed-batch processes**

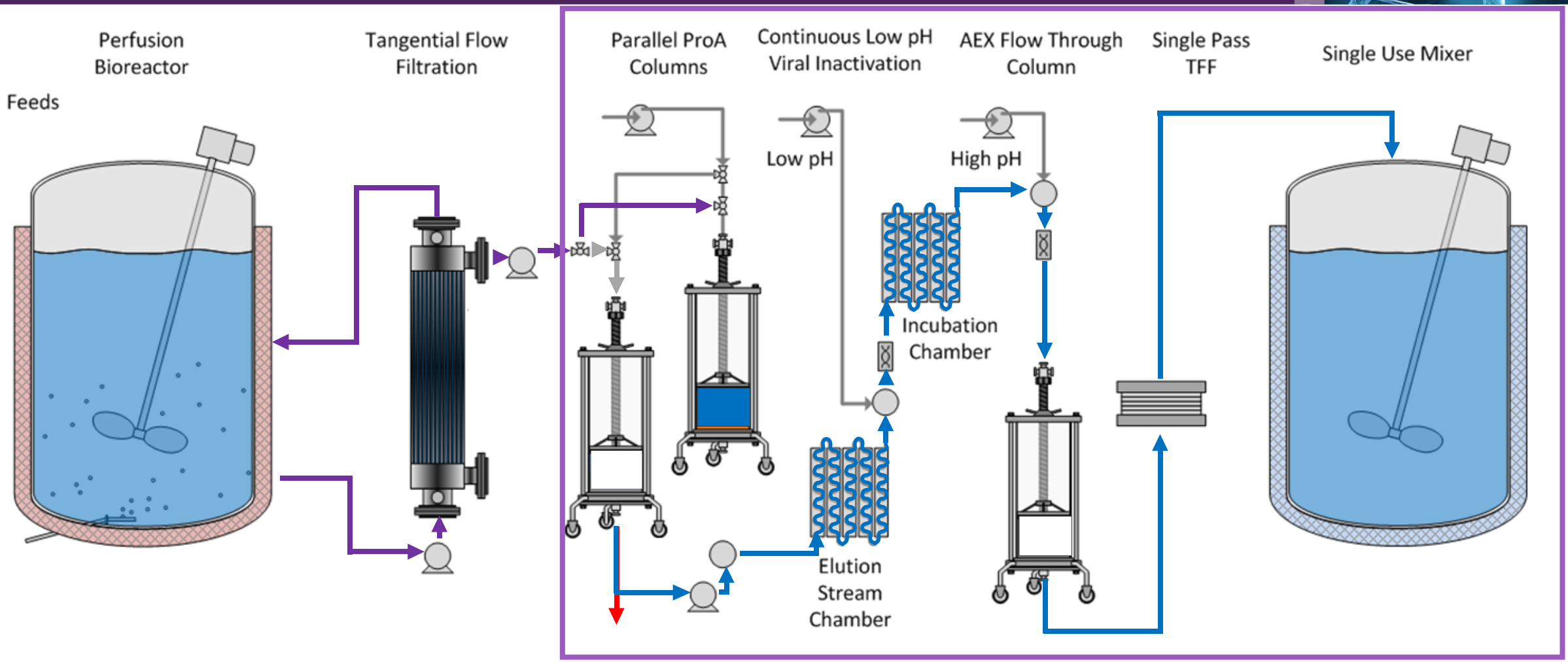
calculated from day 0

Short duration perfusion integrated with simple, two column continuous capture



- Removed product from the bioreactor faster
- Better downstream utilization
- Accommodates variability and wide range of upstream conditions
- Fully automated continuous two column harvest: simple operation, easy development, better Protein A utilization

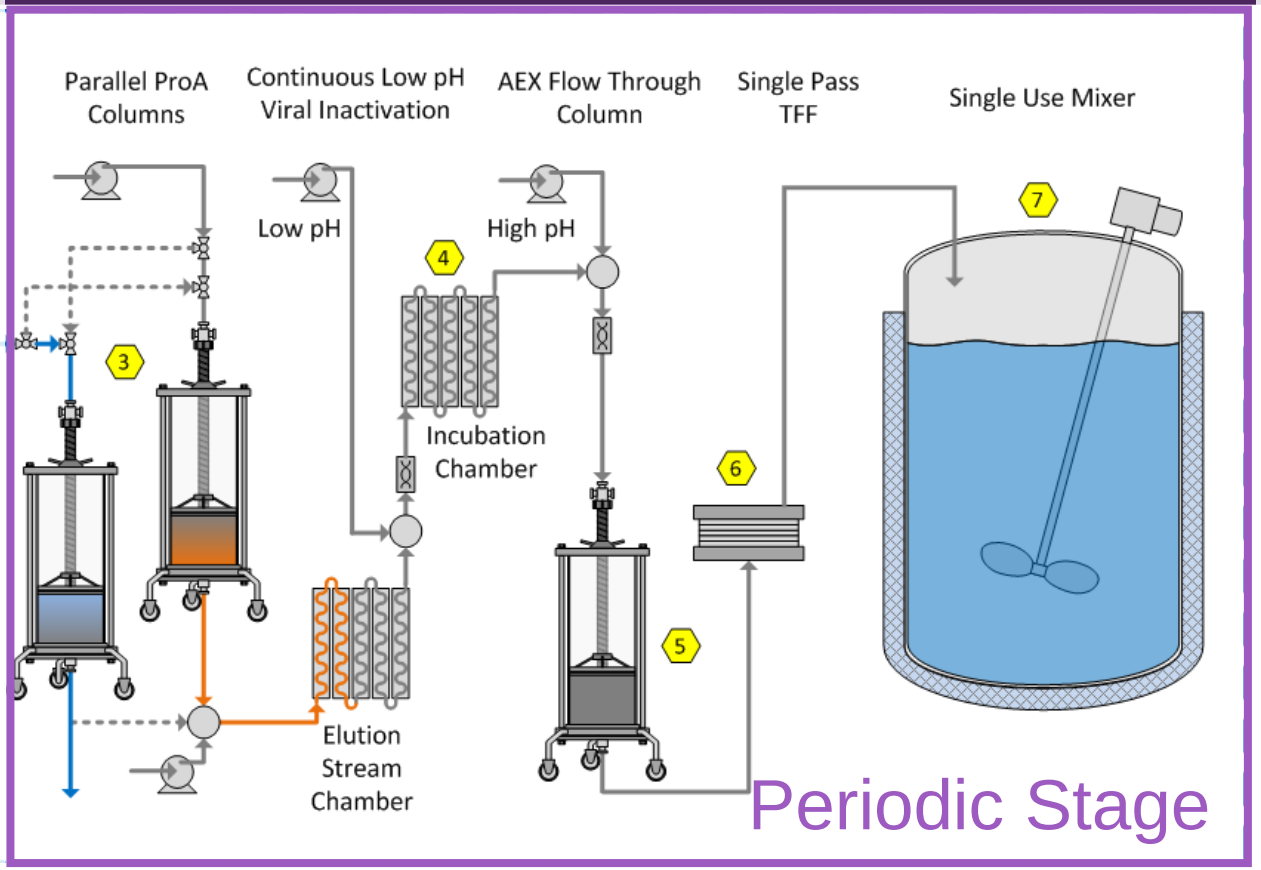
Periodic stage intensifies polishing operations by relying on robust development history



Periodic Stage

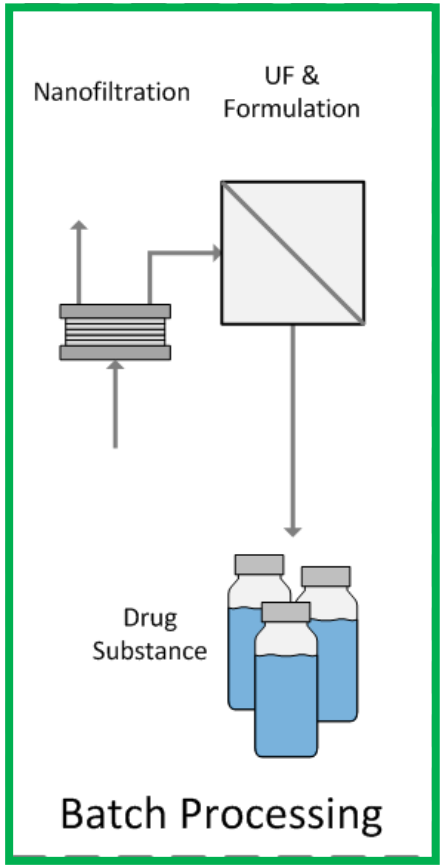
Periodic stage intensifies polishing operations by relying on robust development history

- Eliminates in-process holds
- Process development can leverage rich batch experience



Batch Stage reduces regulatory risks and provides flexibility

- Enables straight forward implementation of additional polishing steps
- Simple regulatory strategy for virus filtration and room segregation
- Allows flexibility for drug substance formulation
- Final filtered drug substance defines a batch



Batch Stage

What Does it Look Like?

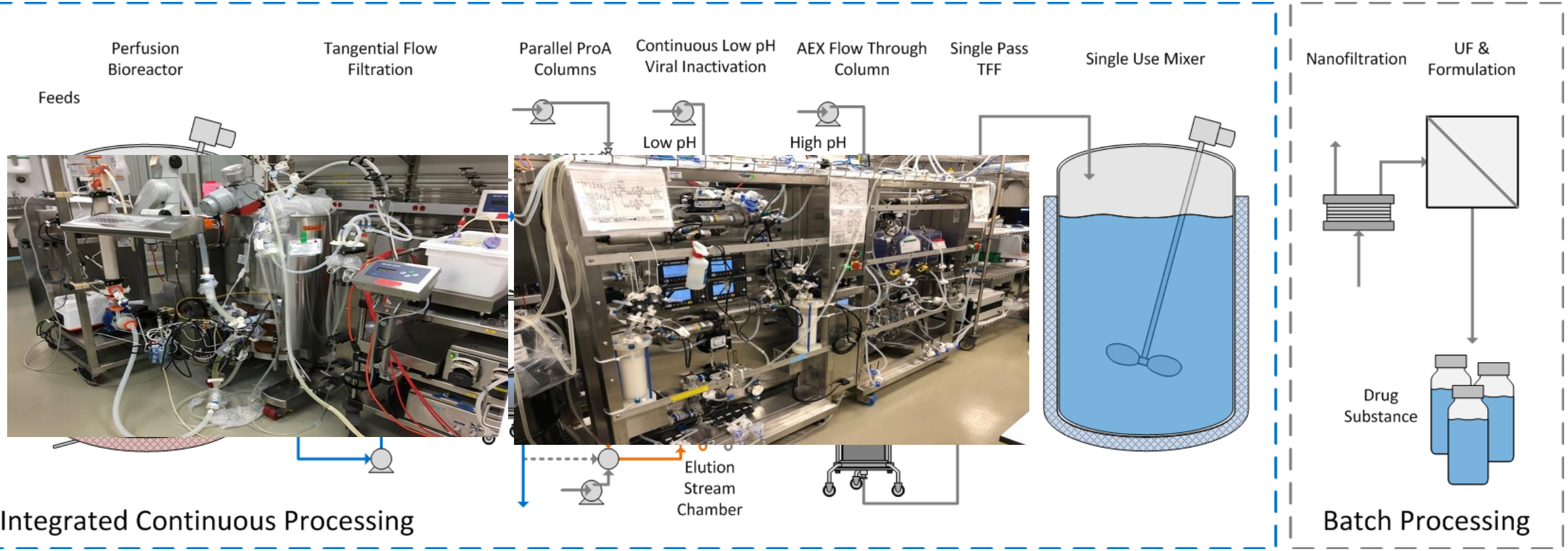


Figure courtesy of Mike O'Connor

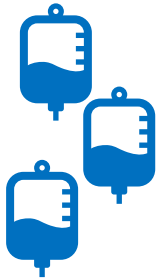
Current Development Paradigm

Process development

Facility fit Tech transfer

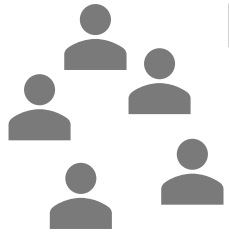
Early-phase Manufacturing Facility

DS Manufacture



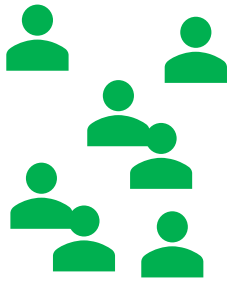
Current State

Initial manufacture supports early clinical studies

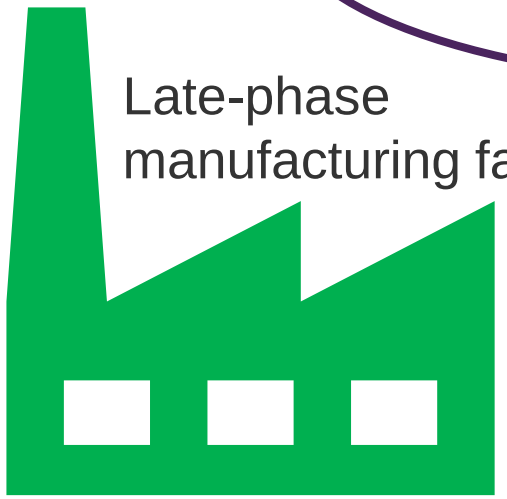


Phase 3 Process Development

Late stage manufacture at commercial scale

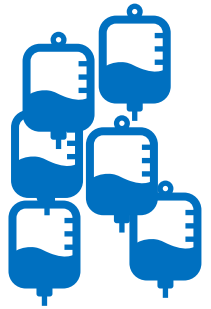


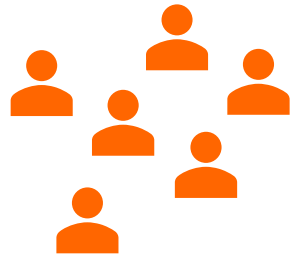
Facility fit Tech transfer



Late-phase manufacturing facility

DS Manufacture



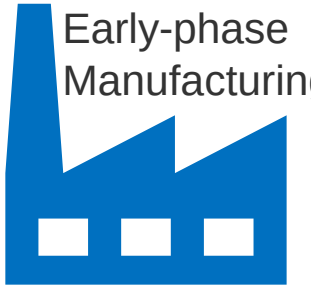


Comparability

iSKID™ Development Paradigm

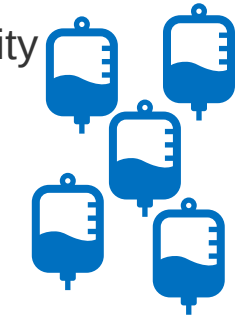
Process development

Facility fit Tech transfer



Early-phase Manufacturing Facility

DS Manufacture



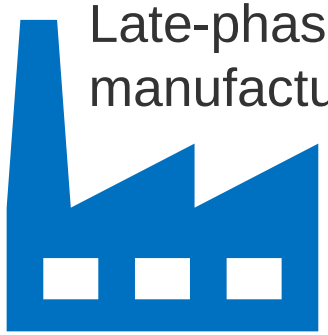
Future State

Initial manufacture supports Initial clinical studies

Phase 3 Process Development

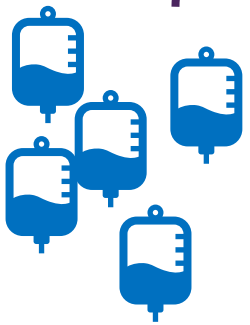
Late stage manufacture at commercial scale

Reload



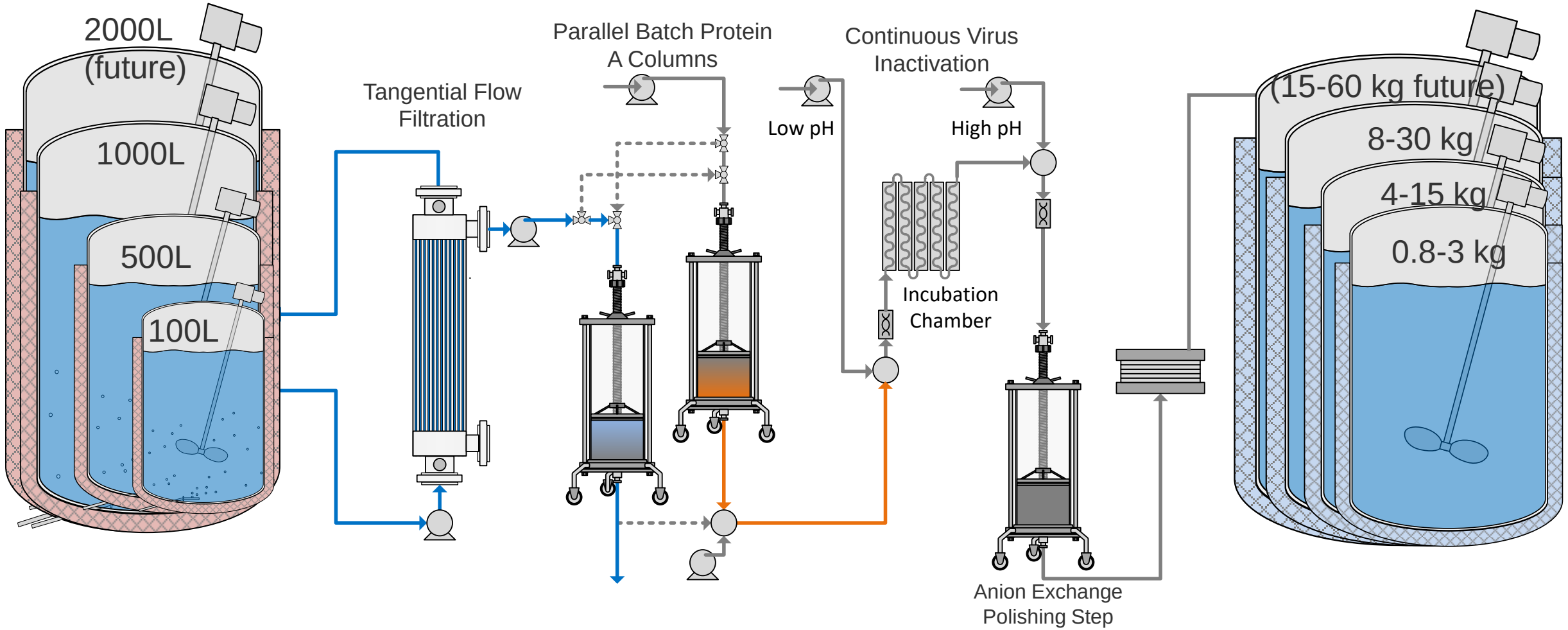
Late-phase manufacturing facility

DS Manufacture



Comparability

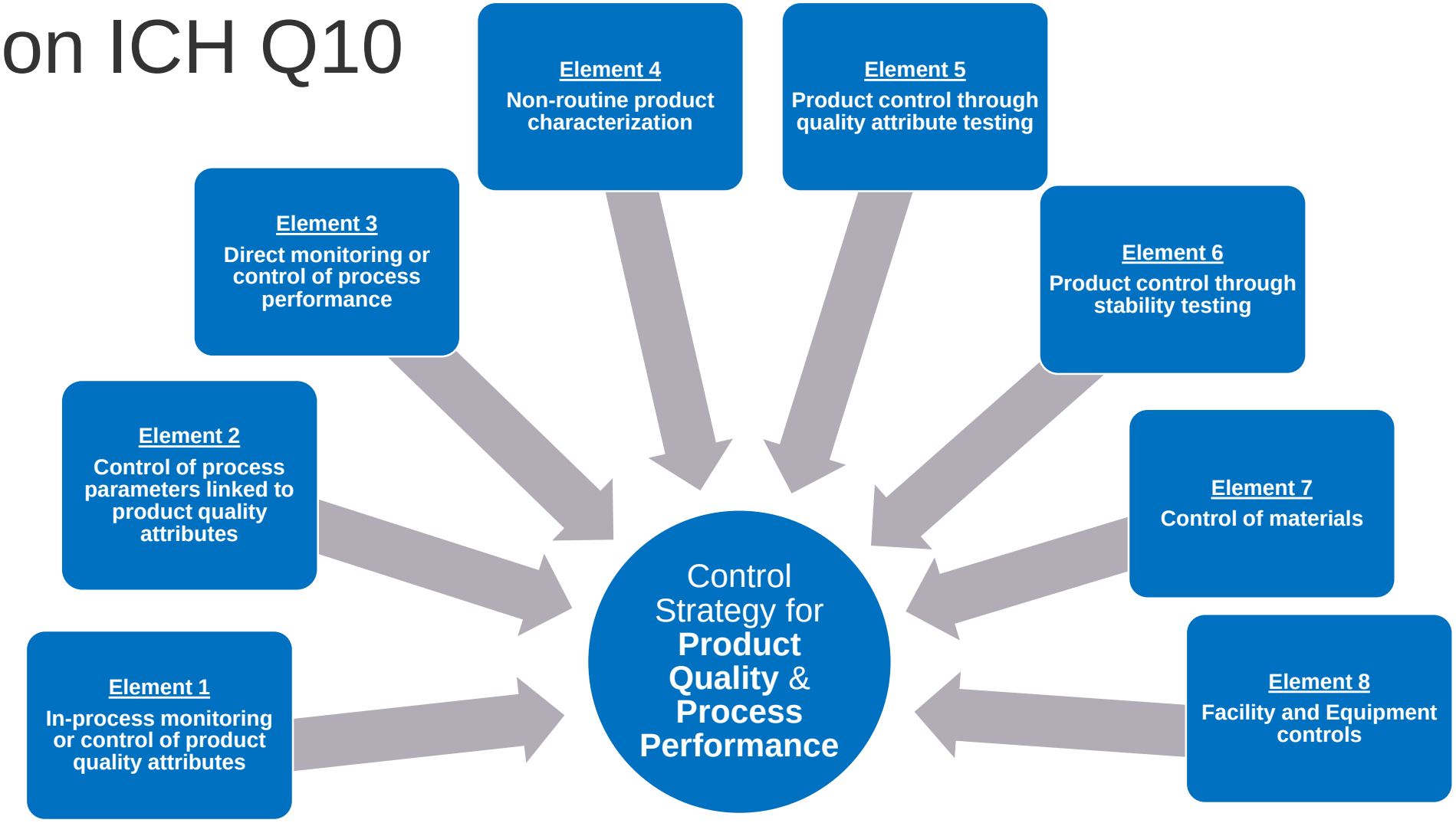
Current hardware design supports multiple scales



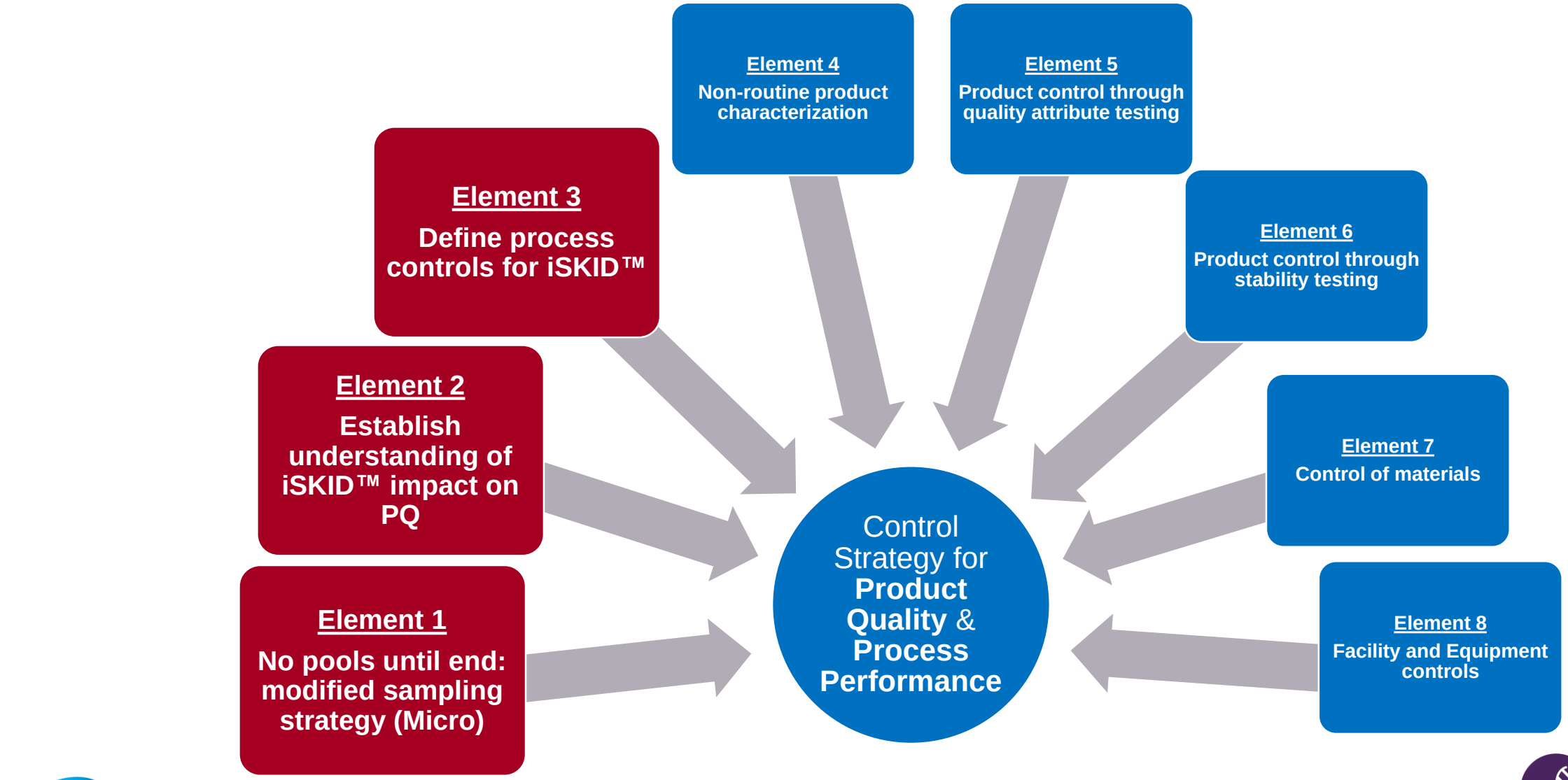
- Scale columns and disposable flow paths

How Does iSkid Design Impact Control Strategy?

Based on ICH Q10



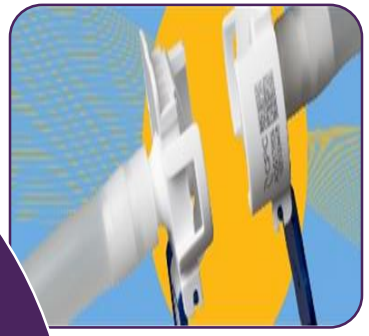
iSKID™ Will Require a Modified Control Strategy



Bioburden control- mitigation strategy

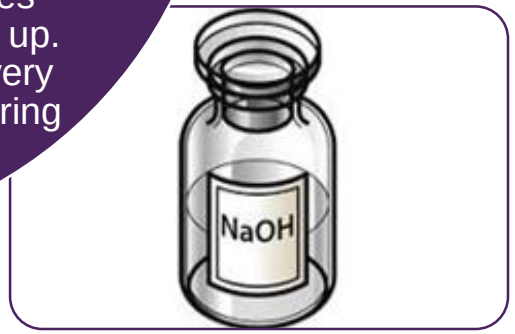
Gamma irradiated flow paths

Aseptic Closed Connections

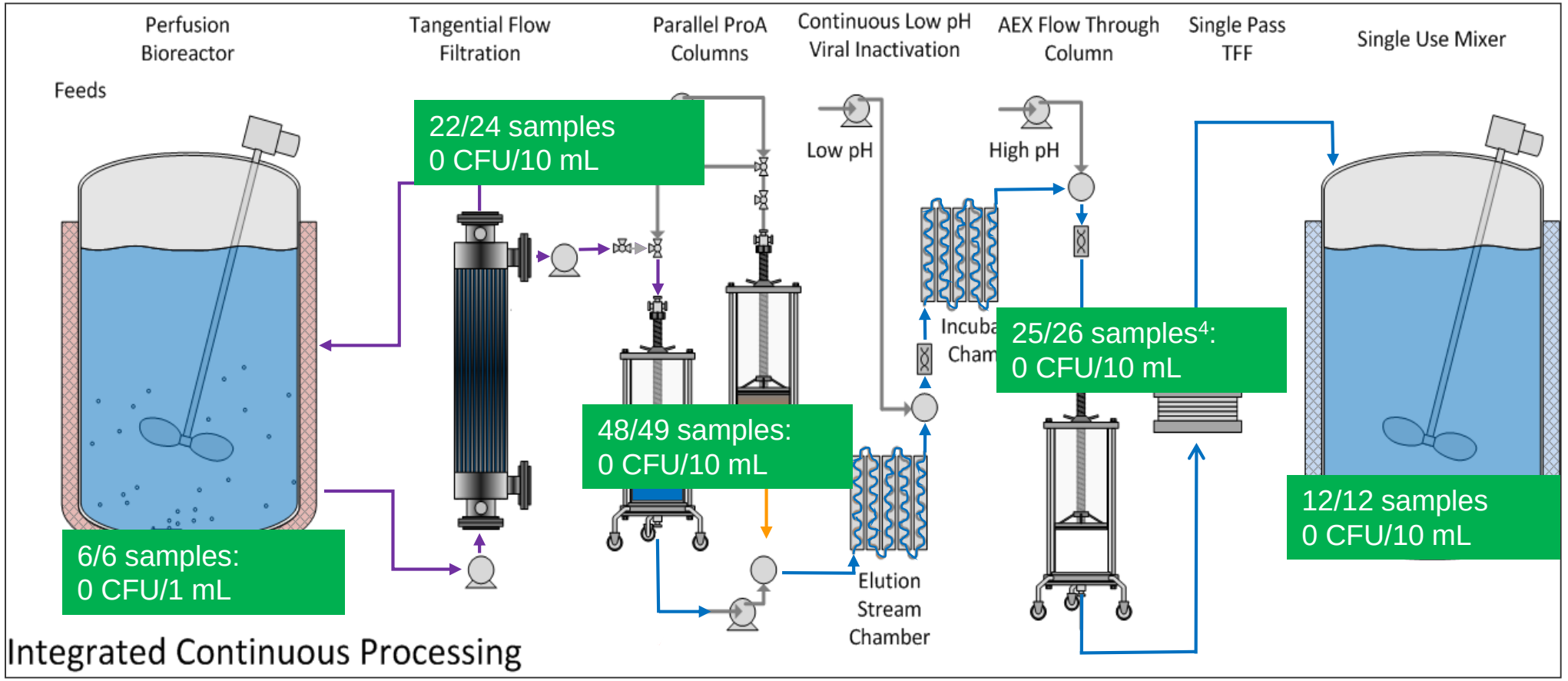


Aseptic sampling

Sanitize non-gamma irradiated disposables during start up. Sanitize every 4-12 hrs during ops.



Bioburden Data:
Prototype System Consistency Runs at STL & AND (6 total)



Drug Substance
All samples (6/6)
No growth

- **Samples with growth were all low level (≤3 CFU/10mL), well within non-GMP in-process expectations**

Note: All endotoxin data passed <=2 EU/mL

iSKID™ Summary

- Represents a successful collaborative initiative between Pfizer and BI
- iSKID™ expands development and manufacturing capacity
  - Short duration perfusion: highly productive and efficient
  - Simple downstream process: easy to develop and control
- Appropriate for low volume, high value products
- Scalable to accommodate increase in demand
- Enhanced Cost & Capacity Profile
  - Facility friendly
- Integration and automation facilitates improved operational excellence

Acknowledgements

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