2000L Single-Use Bioreactor Evaluation and Implementation

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hargrove life sciences

ISPE® | Delaware Valley Chapter

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2000L SUB Technology Platform Selection

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Retrofit Challenges with Ongoing GMP Operations

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Lessons Learned for Future SUB Renovations

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do more
feel better
live longer

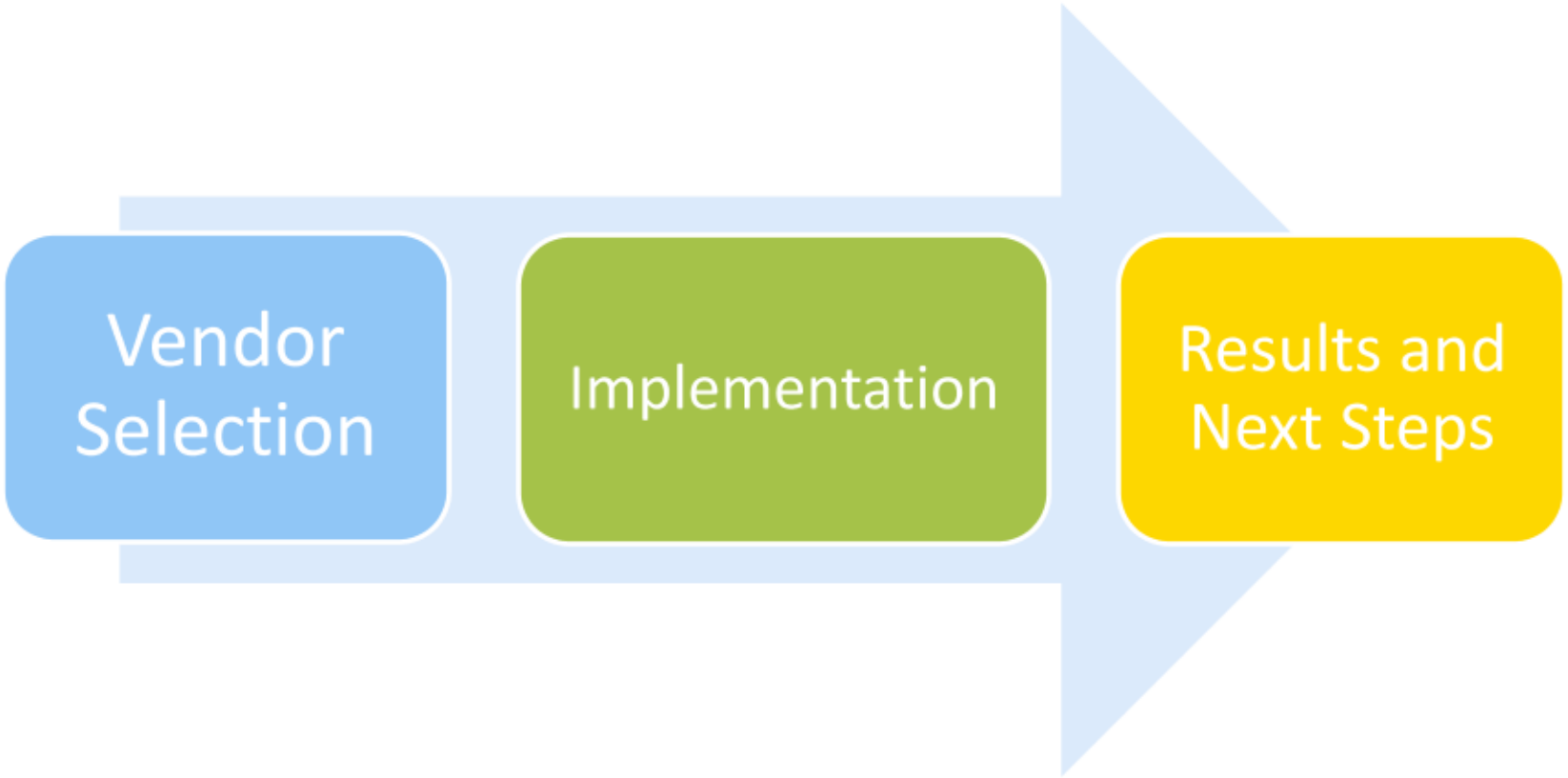
Upper Merion, PA
Building 38

Multi-product GMP Biopharmaceutical Facility

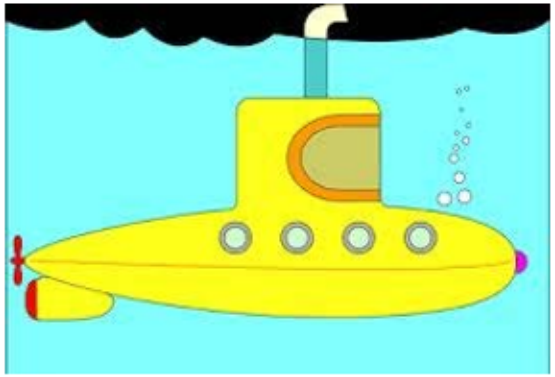
Manufacturing of purified drug substances to support all phases of clinical trials worldwide

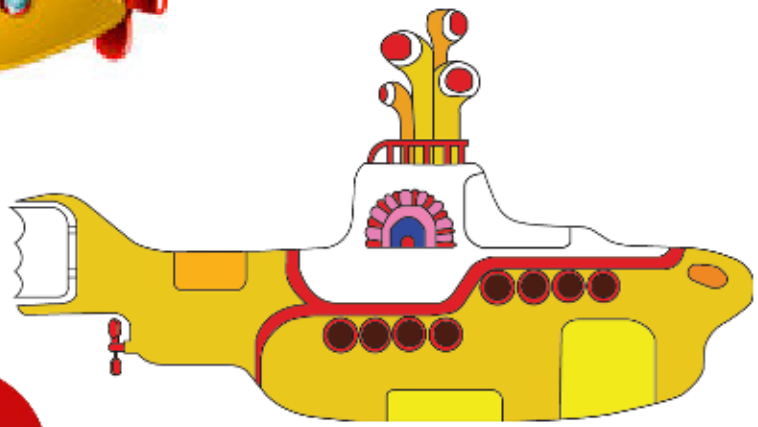
Establish a Global Manufacturing Platform Strategy for scale-out with 2000L Single-Use Bioreactors

AGENDA



SUB Platform Selection Process





SUB Technology Selection

- Qualitative and quantitative assessment from three vendors where 2000L SUBs were commercially available.
- Used existing 1200L SS Bioreactor as control.
- Obtained reactors and installed in a non-GMP lab for all wet-work testing.
- Objectively evaluate results.

SUB Evaluation - Qualitative

- Industry and commercial experience of each vendor, including third party experiences and references
- Scale down representation
- Vendor supply chain robustness, including bag lead times
- Vendor support
- Ergonomics and ease of operation, including bag installation
- Flexibility and options in bag design, including agitation and sparge options

SUB Evaluation - Quantitative

- Mix times at full and partial volumes
- kLa and CO_2 stripping capabilities
- Computational fluid dynamics
- Cell growth comparison to stainless steel reactors using platform cell line, evaluating performance and product quality data vs. historical data

Mass Transfer

- $k_L a$
  - Determined by monitoring the increase in dO_2 of the vessel contents while sparging gas (air).
  - Tests were conducted over a range of operating conditions (agitator power input; gas sparge rate) to develop performance correlations.
  - Measurements were made both at the lower tangent line and just below the liquid surface to assess spatial variation, if any.
- CO_2
  - Experiments were conducted over the range of gas rates (superficial gas velocity) and agitator speed (energy dissipation rate).
  - pH was monitored and its change versus time analyzed as a CO_2-saturated solution was stripped via air sparging.
  - Measurements were made both at the lower tangent line and just below the liquid surface.

k_La and CO_2 results

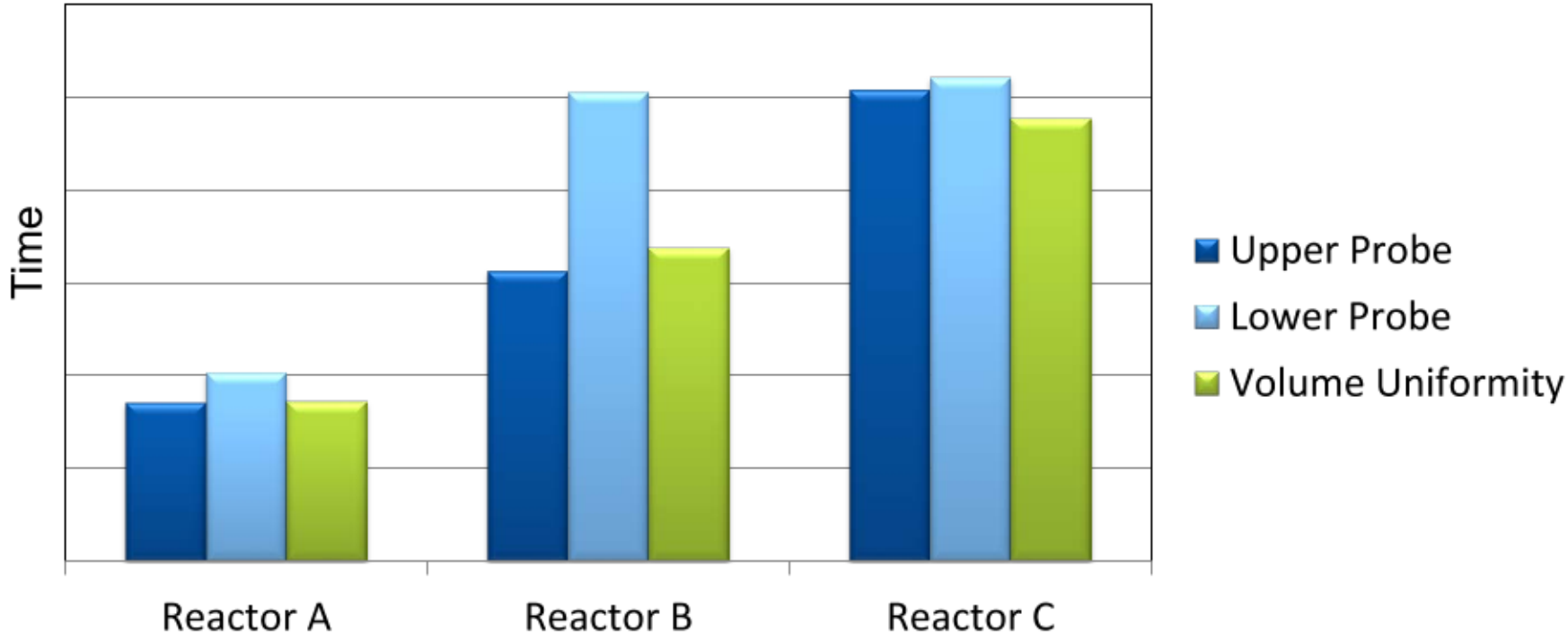
- Results were correlated for tested volume.
- Correlations were used to extrapolate to 2000L scale.
- Significant differences were observed.
  - *Greater differences for oxygen transfer, less for CO_2 stripping.*
  - *The sparger design was a contributing factor.*
- One system tested outperformed the stainless steel control system.

Bioreactor Blend Time

- Determined by measuring the time required for a bolus of acid to be dispersed throughout the vessel.
- Replicate tests were conducted over the range of operating speeds examined in the mass transfer tests.
- Measurements were made both at the lower tangent line and just below the liquid surface.

Blend Time Results

- Reactor A shows the best performance
- Reactor B has greatest variability
- Reactor C had the longest blend time

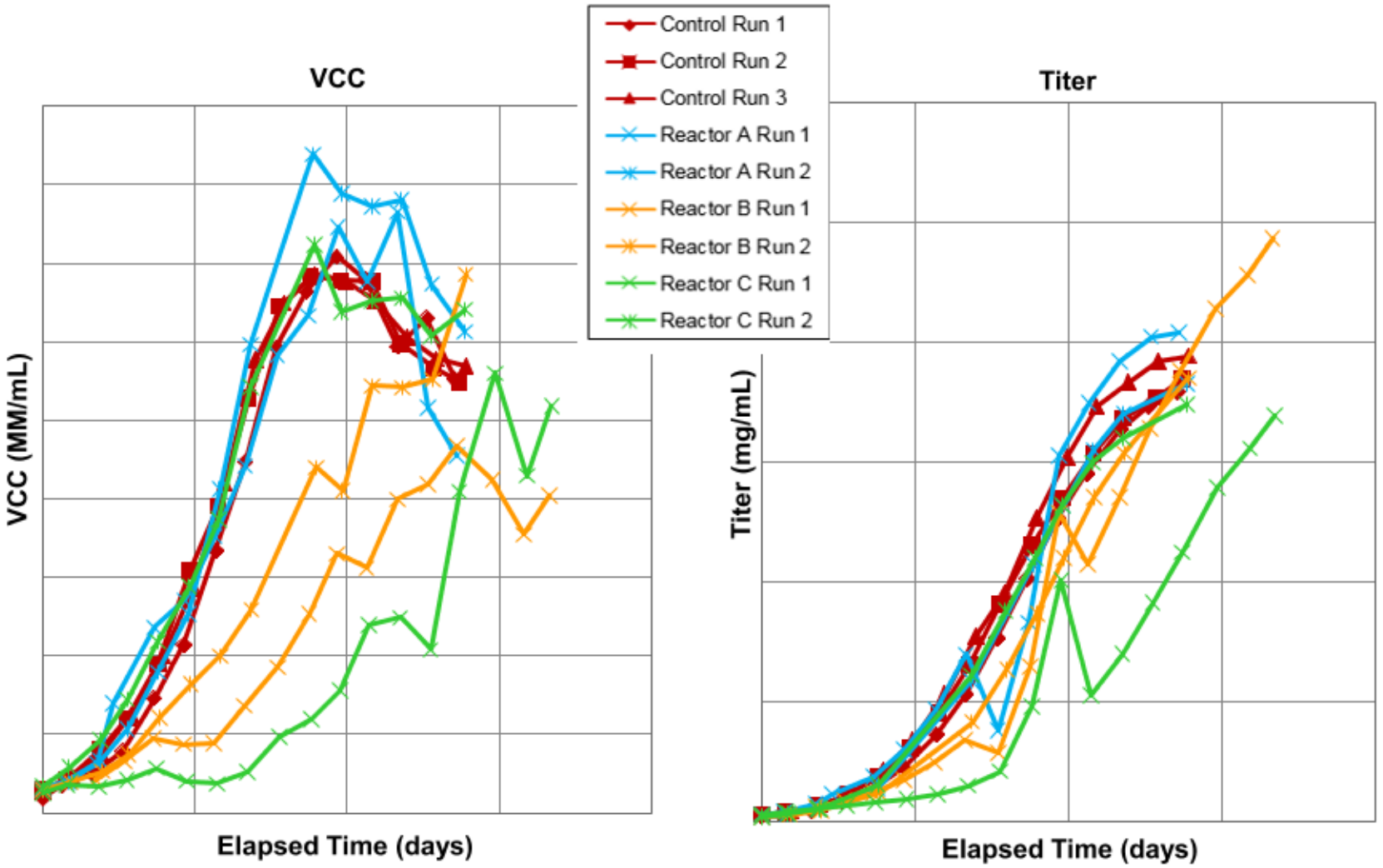


Computational Fluid Dynamics

- Predict the performance of the three mixing vessel designs at 2000L.
- Each SUB was broken into 3-5 million units, with a mesh size of 1-2 cm diameter and modeled.
- Testing was performed by a third party and used 24-32 processors and required 15-20 days of processing time.
  - *Solve for the time-accurate mixing behavior of the vessel.*
  - *A virtual tracer is introduced into the mesh at a location comparable with the experiment.*
  - *Compare tracer concentrations and mixing times with experimental data.*

Tracer Volume Concentration Animation

Cell Performance Testing



Vendor Comparison Overview

SUB Rankings

	Weight	Reactor A	Reactor B	Reactor C
Cell Performance and Comparison	5	5	3	3
Mixing/kLa	5	5	5	2
Computational Fluid Dynamics (CFD)	3	5	3	2
CFD 2000L	3	5	2	2
Vendor Supply Chain	5	3	5	3
Ergonomics and ease of operation	3	5	3	3
Turn down ratio	3	5	1	5
Industry experience at 2000L	3	2	5	5
3rd party feedback	3	5	5	3
Scale down representation	3	5	3	5
Controls and source code access	3	3	1	5
Vendor Support	1	3	5	3
Weighted Score		173	139	133

Legend:

Advantage	5
Acceptable	3
Improvement Required	1

Weighting:

5 = Hi

3 = Medium

1 = Low

Retrofit Challenges

GlaxoSmithKline – Upper Merion Building 38

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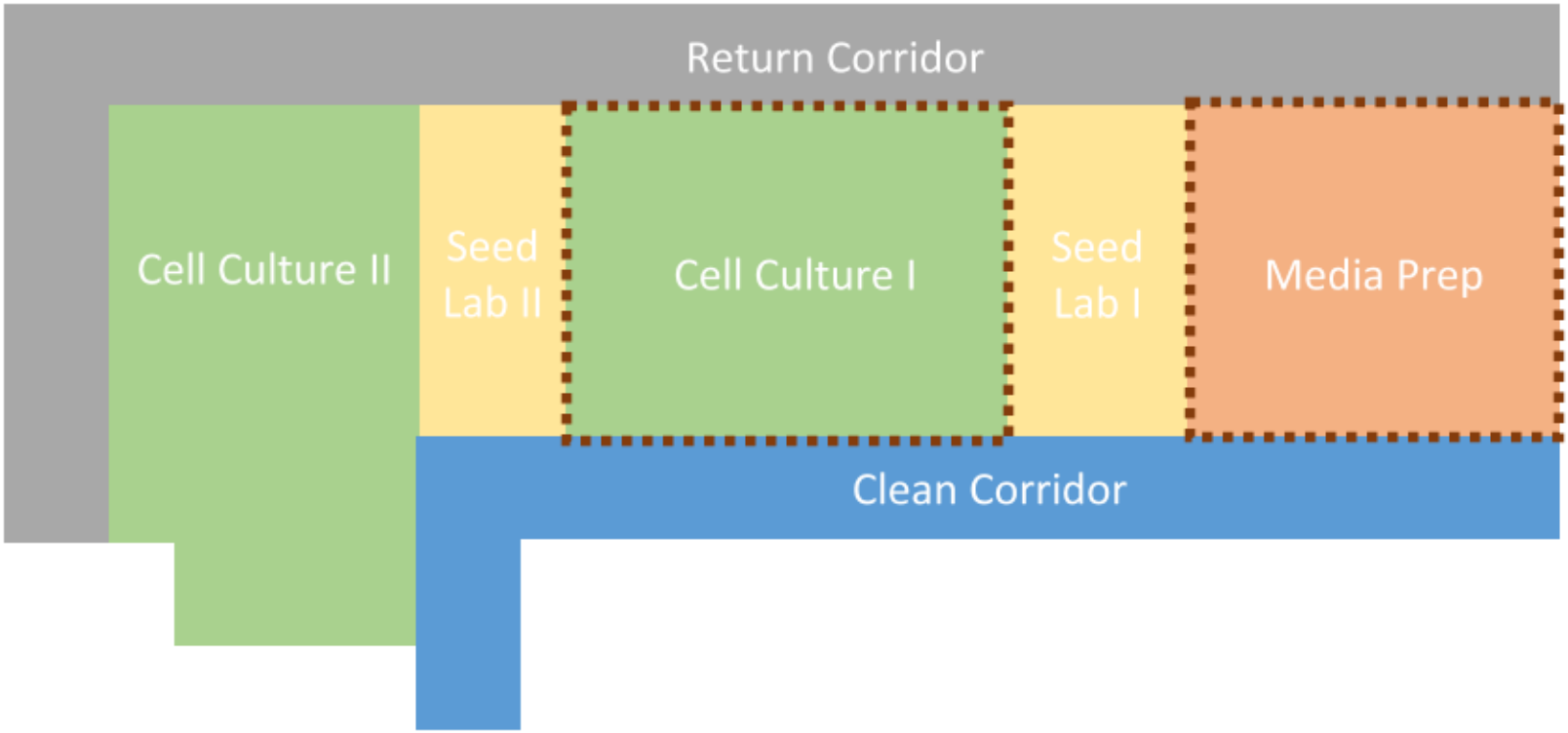
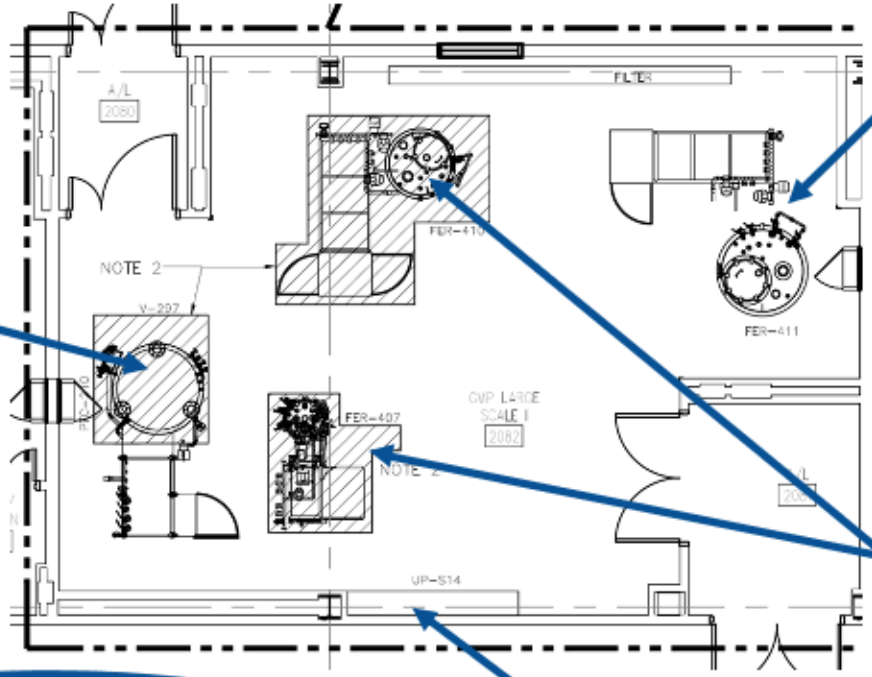
UM38 Second Floor
Single-Use Technology
Phase I Renovations



Cell Culture – Pre-Renovation

Replace 1500 L Harvest Tank with 2500 L and adapt skid



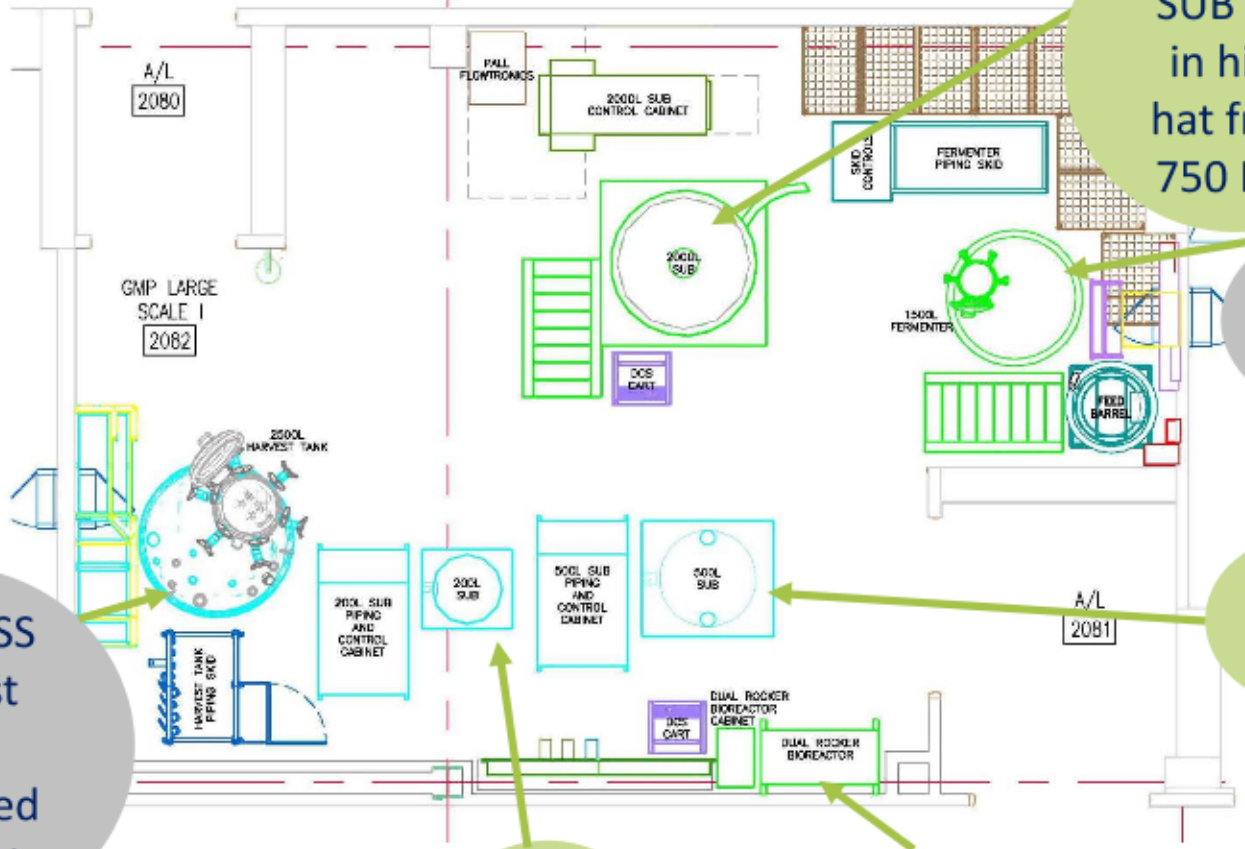
Stainless Steel 1200 L Bioreactor stays

Remove 100 L & 750 L Bioreactors

Re-use existing piping for media and harvest transfers, GMP utilities & building utilities

Leave utility panel as is

Cell Culture – 2000L SUB



2000 L SUB Fits in high hat from 750 L SS

1200 L SS Bioreactor

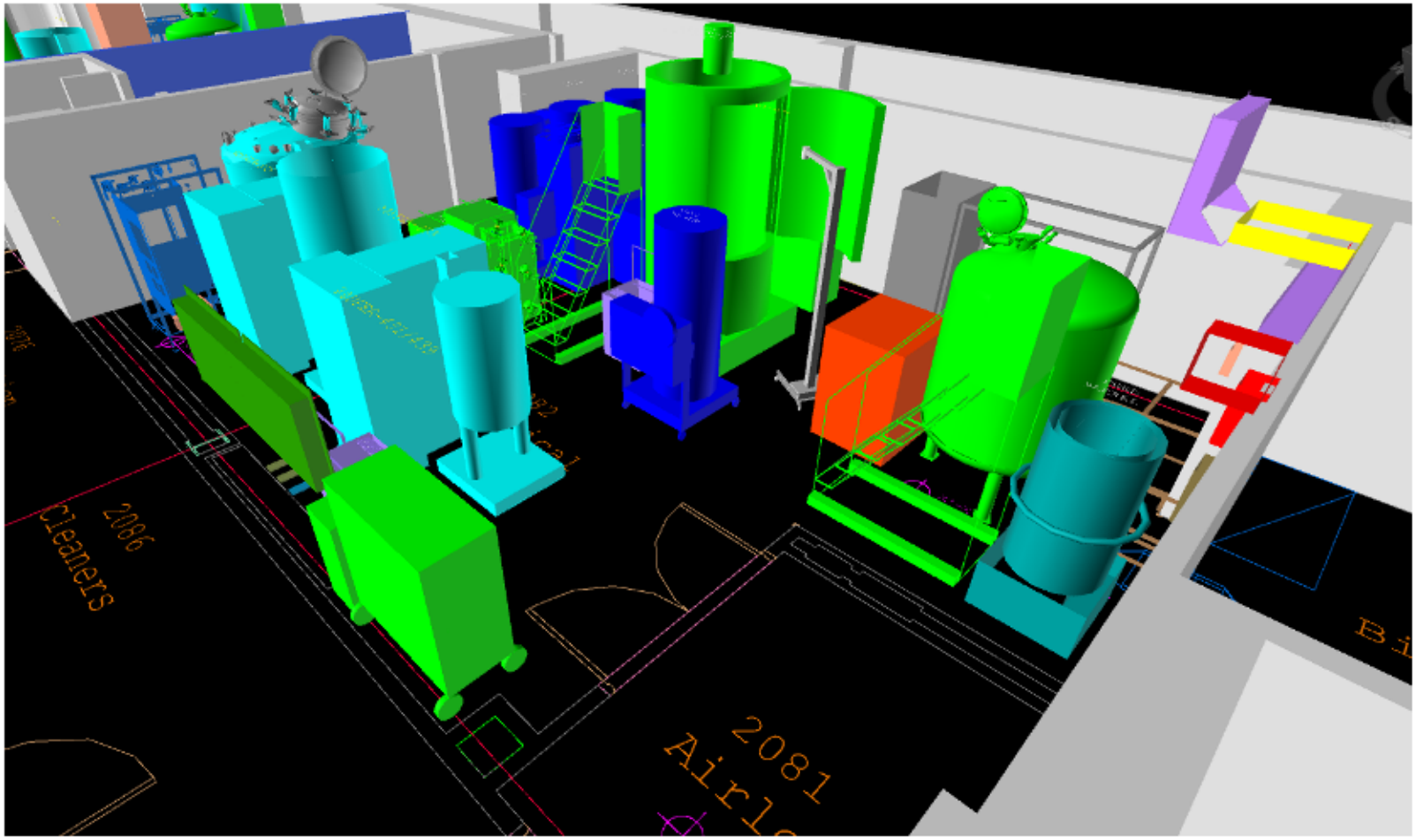
500 L SUB

2500 L SS Harvest with expanded high hat

200 L SUB

Dual Rocker SUBs

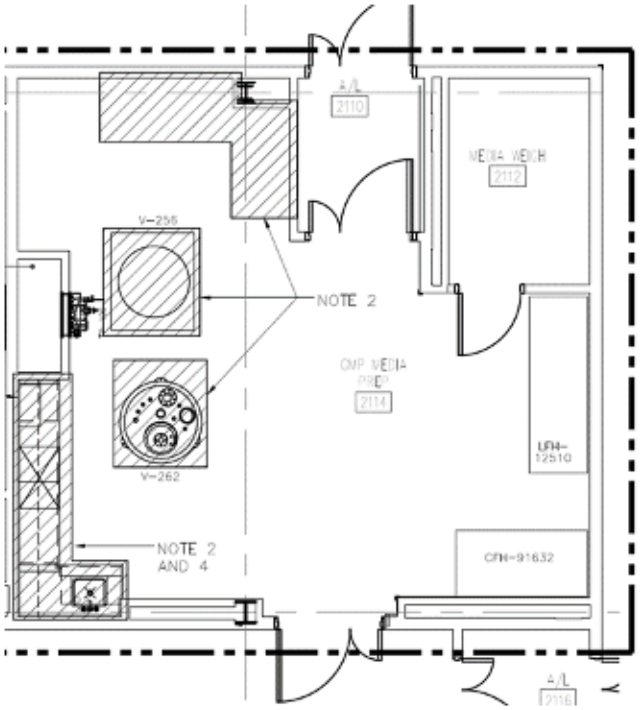
Cell Culture Renovation



Phase I Renovation – Media Prep

THEN

- 640L SS Media Prep
- 1100L SS Media Prep

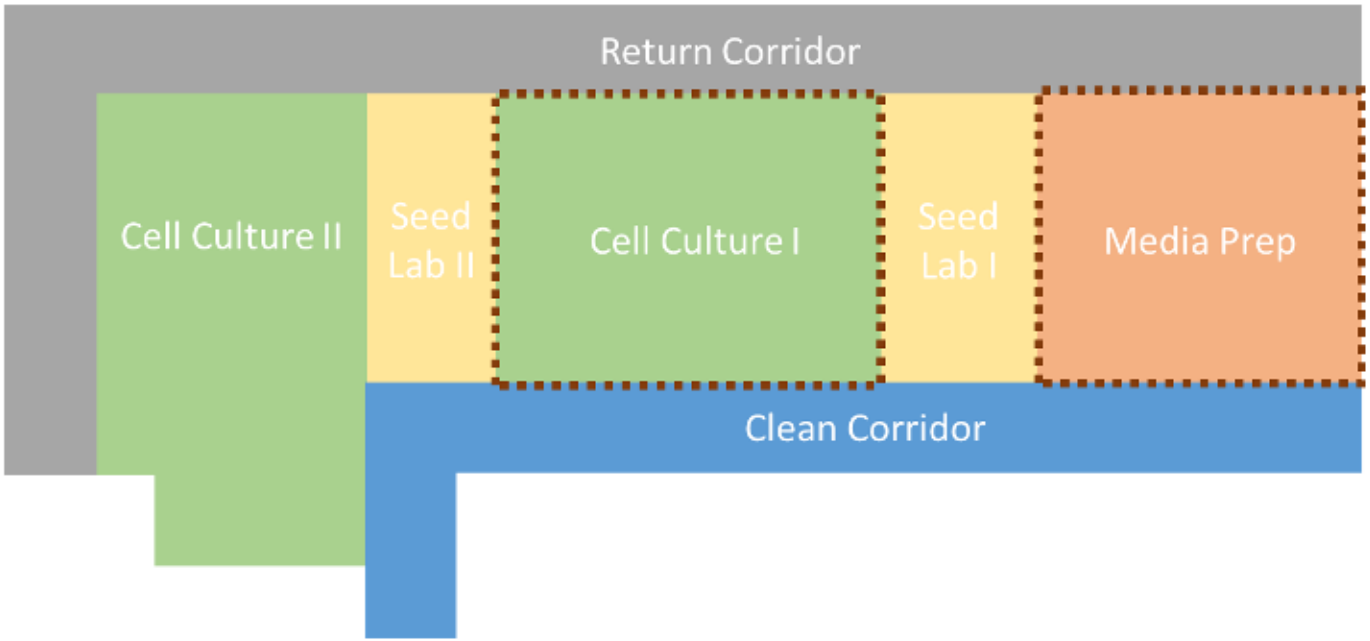


NOW

- 50L single-use Media Prep
- 200L single-use Media Prep
- 650L single-use Media Prep
- 1500L single-use Media Prep
- SS Inline Powder-Liquid Mixer
- Portable Jacketed Bag Holders
- Media Cooling Stations

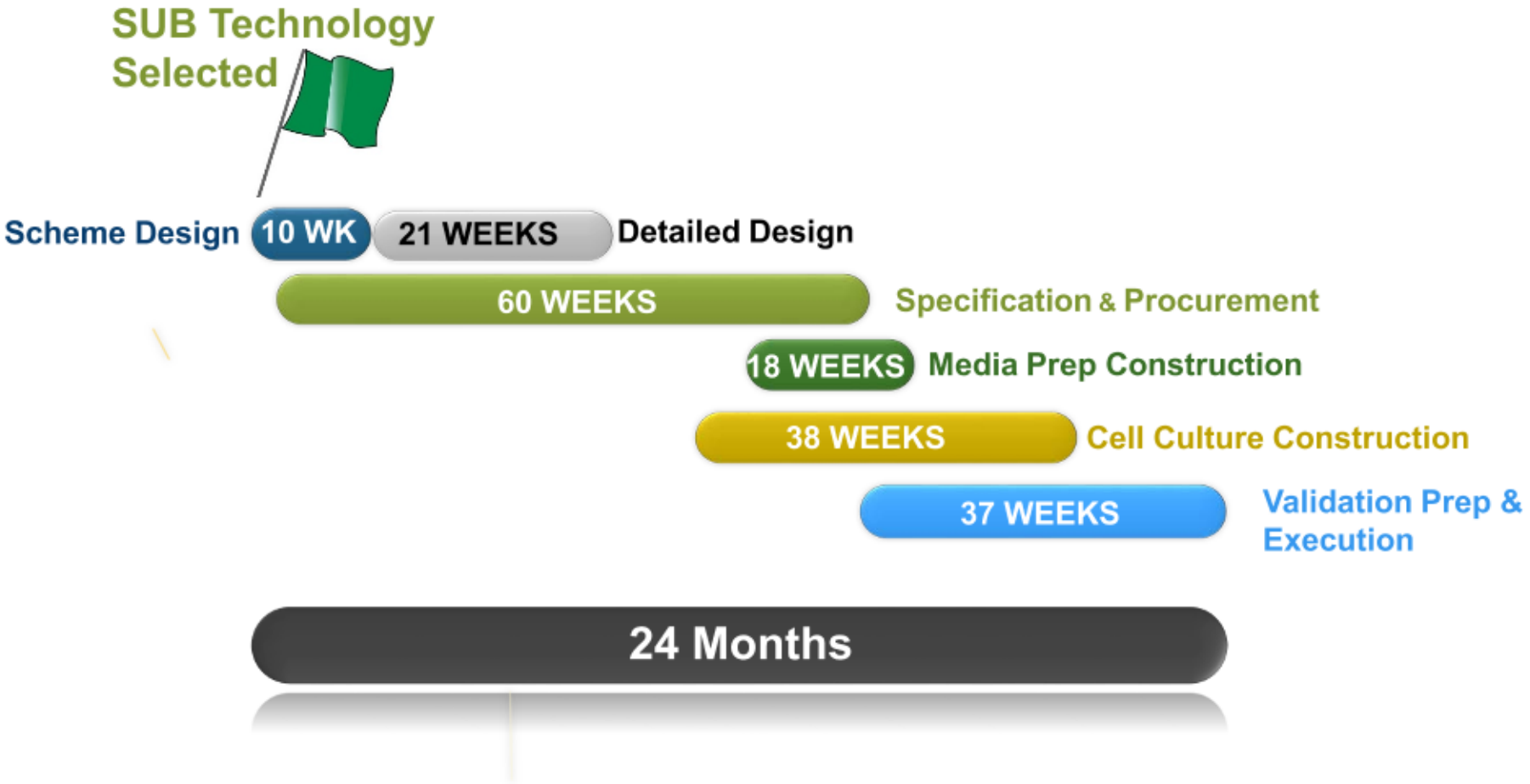
Why Hybrid?

- Existing Stainless Steel lines with CIP/SIP available
- Transfer large amounts of materials
- Room adjacencies
- Single-use option not available



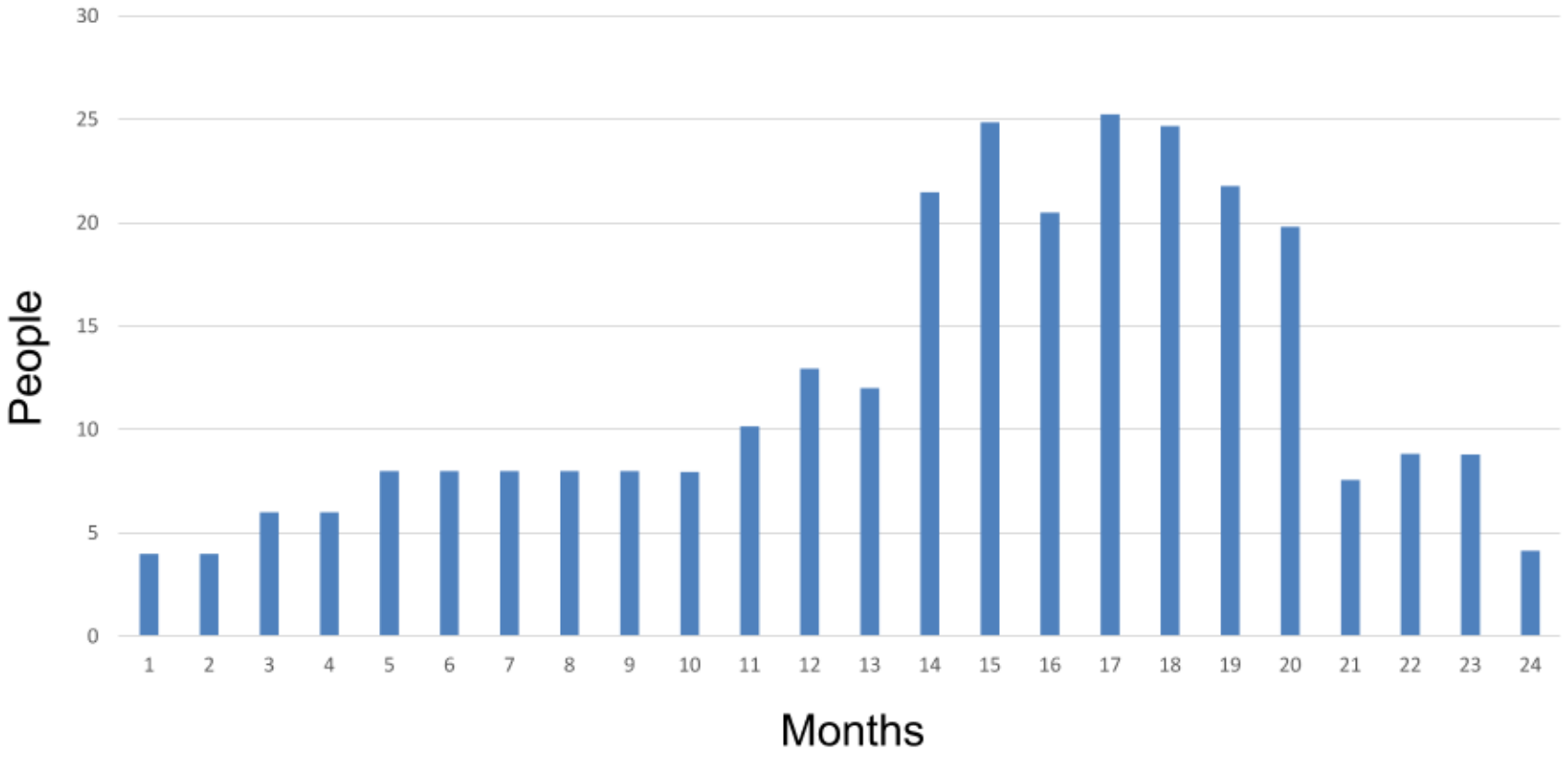
Project Risks – New Technology

- Change from stainless to disposable
  - Risk of leaks or other types of failures
  - Training of personnel
- Establish a long term relationship with single-use supplier
  - Vendor supply chain robustness
  - Create inventory of disposables plus storage space

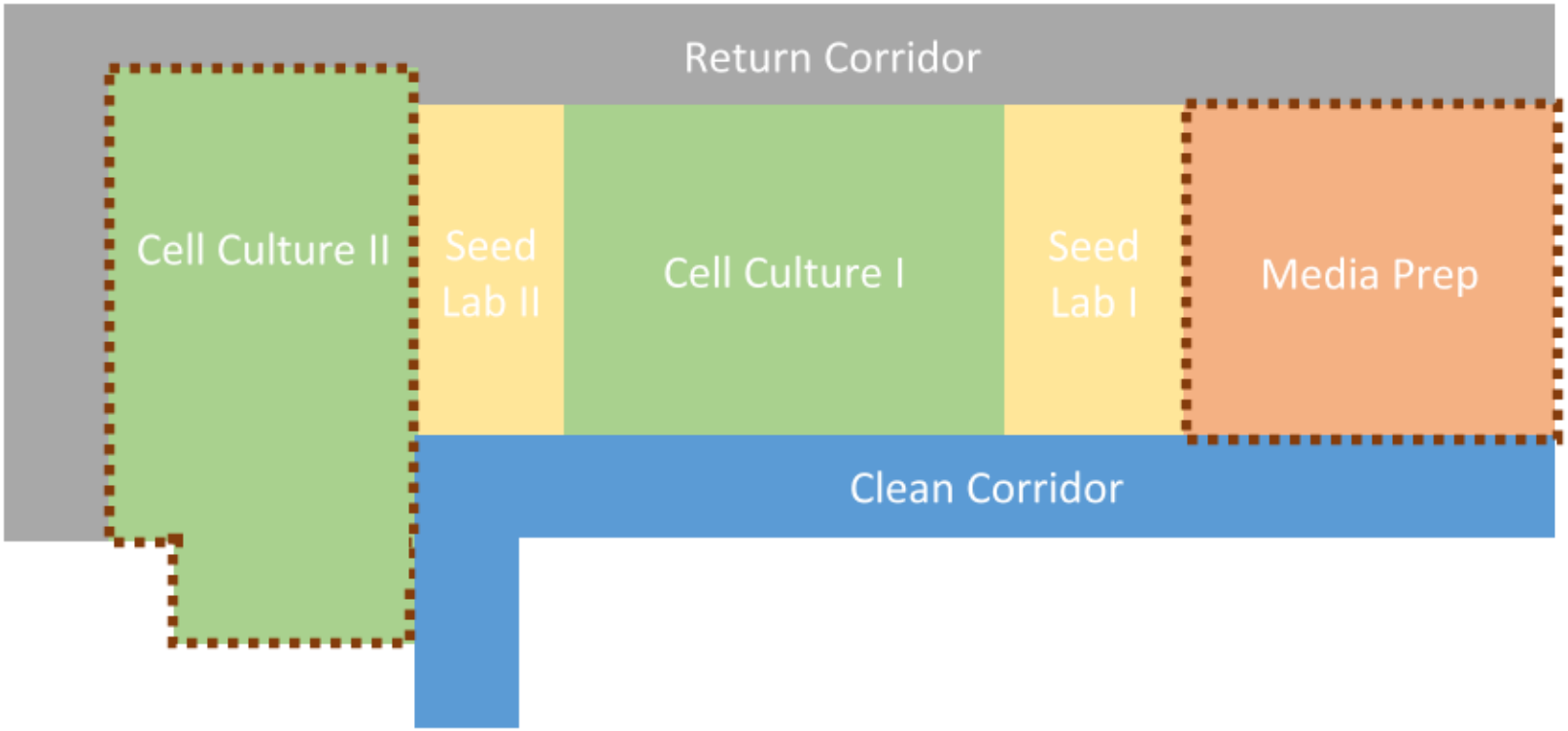

SUB Technology Selected
Scheme Design
10 WK
21 WEEKS
Detailed Design
60 WEEKS
Specification & Procurement
18 WEEKS
Media Prep Construction
38 WEEKS
Cell Culture Construction
37 WEEKS
Validation Prep & Execution
24 Months

GSK Internal Project Support

Engineering, Technology, Manufacturing Operations, QA, QC, Validation, Calibration



UM38 Second Floor Single-Use Technology Phase II Renovations



Phase 2 Renovation – Cell Culture

THEN

- 1 x 25L Single-Use Rocker Type Bioreactor
- 100L SS Bioreactor
- 750L SS Bioreactor
- 1200L SS Bioreactor

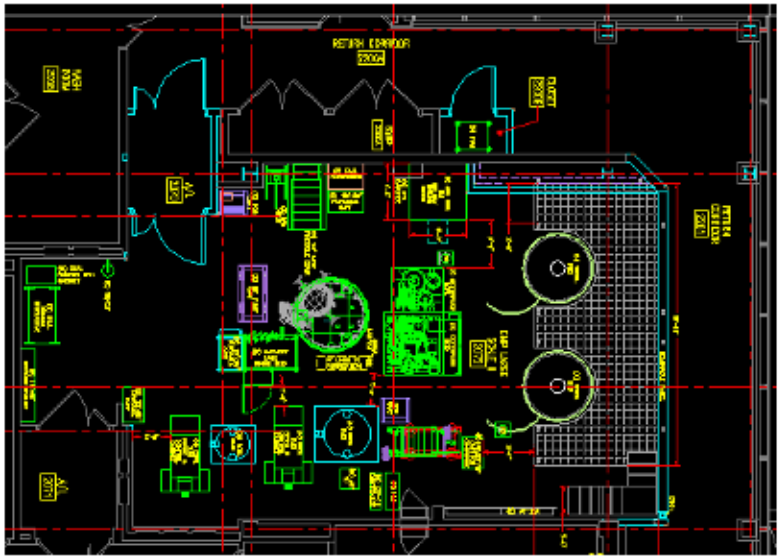
- 1500L SS Harvest Tank
- SS Clarification Skid

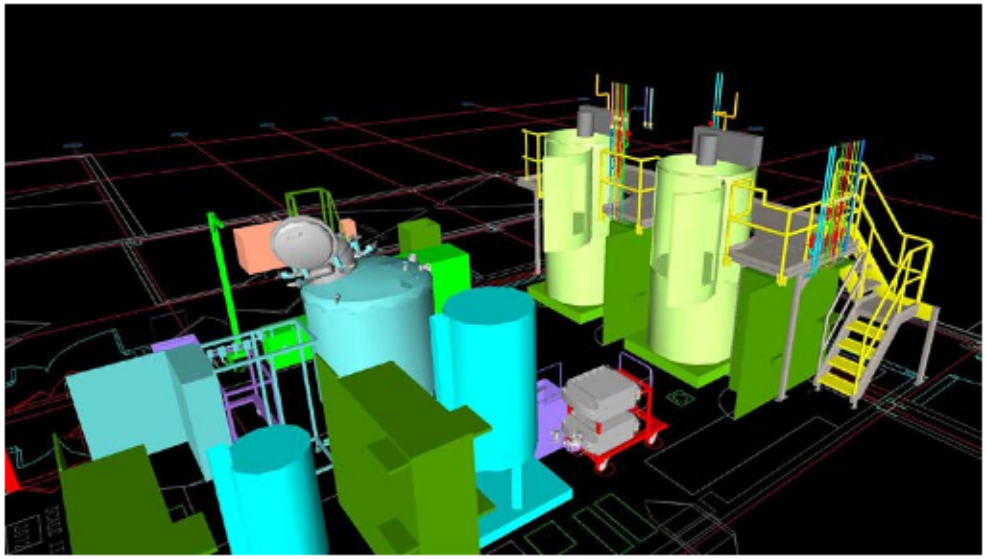
NOW

- 2 x 25L Single-Use Rocker Type Bioreactor
- 200L-250L SUB
- 500L SUB
- 2 x 2000L SUB

- 3500L SS Harvest Tank
- Single-Use Clarification Skid
- DCS Upgrade

Phase II Renovation
Two 2000L SUB's





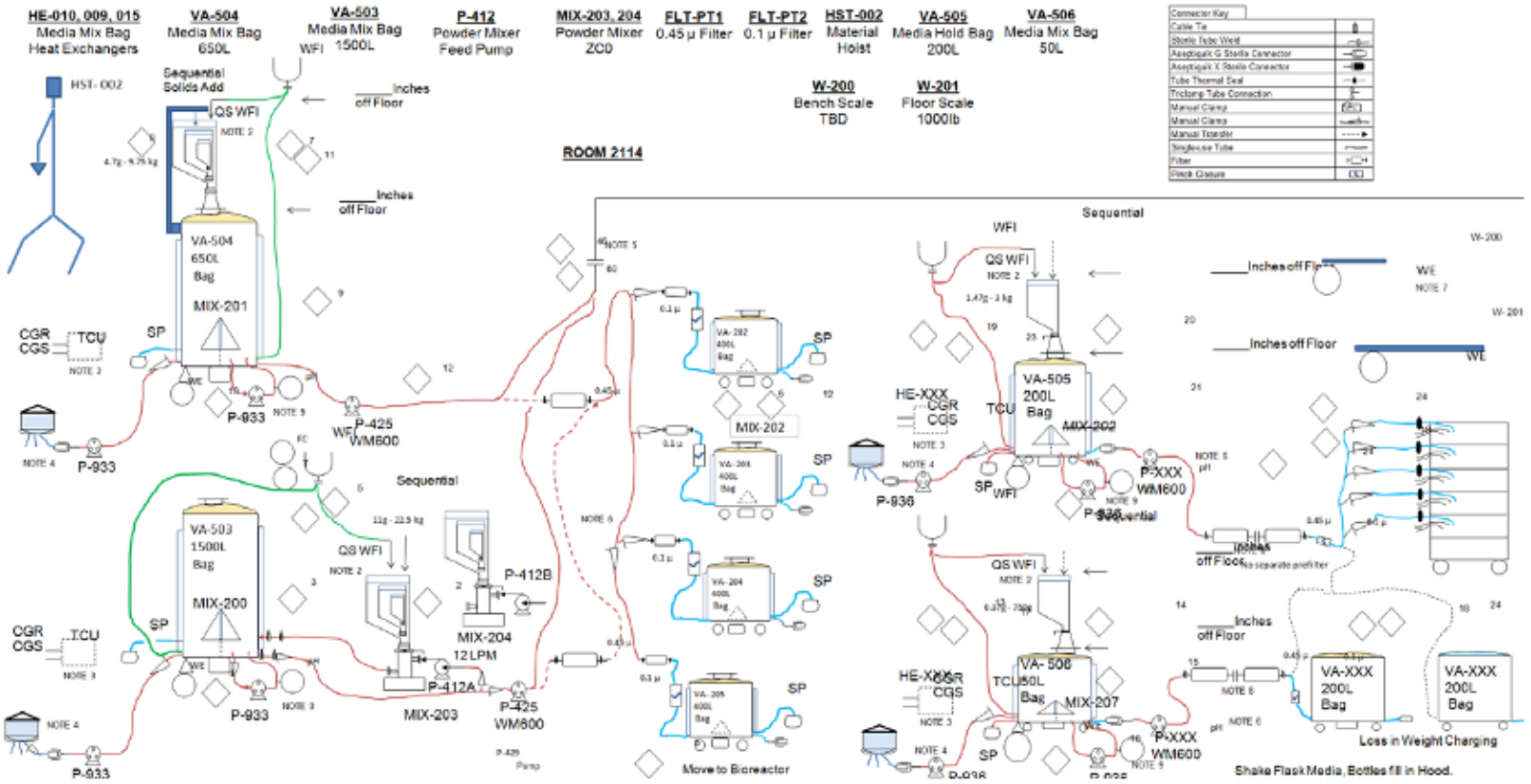
Risk Mitigation, Results & Lessons Learned

Application of Lessons Learned for Future Single-Use Renovations

Risk Mitigation

- Conducted FMEA type impact assessments to identify risks and generate mitigation plans, covering:
  - Media prep
  - SUB Operations
  - Harvest and Downstream
- Scheduled engineering batches to train area staff
- Created Process Flow Diagrams to map out equipment, tubing and connectors needed
- Harmonization and standardization of disposable components
- Safety assessment of area, equipment, ergonomics and flows

Media Process Flow Diagram

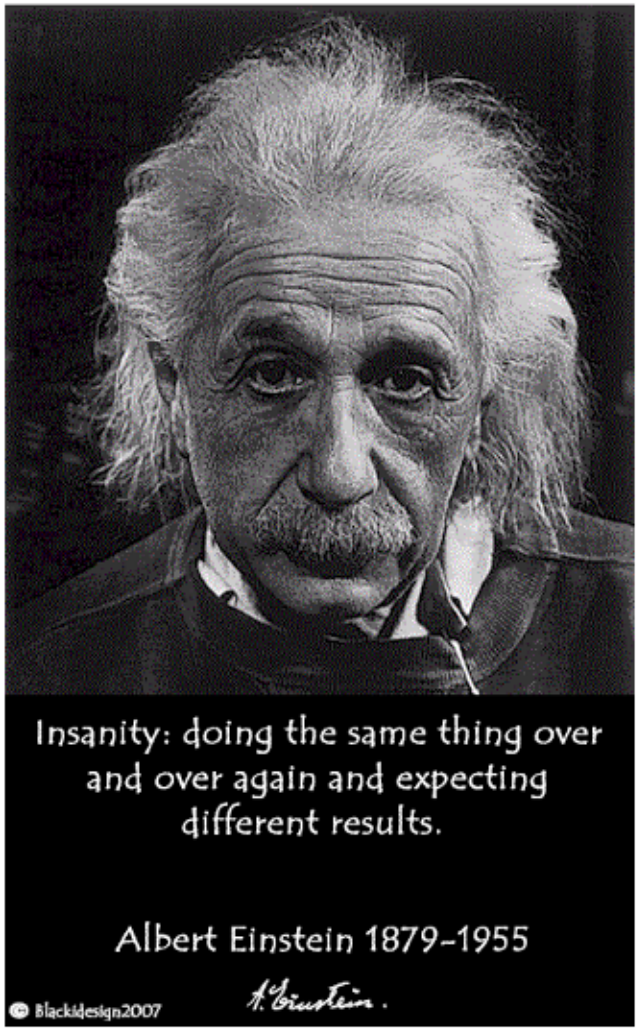


Results to Date

- So where are we today?
- We have successfully completed multiple engineering and clinical batches in both suites, using different cell culture processes.
- This included two parallel batches with a SS reactor to show comparability.

Lessons Learned

"Let's not have the same issue twice……"



Lessons Learned

- Opportunity to apply learning's from first phase of the project to the second phase
- Conducted After Action Review (AAR) with all groups involved: Operations, Engineering, Validation, Quality
- Also conducted an AAR with the SUB vendor
- Additional opportunity to apply learnings to a third phase……..

What Went Well

- Equipment successfully installed, commissioned and validated
- Automation upgrade successful
- Within budget
- Good collaboration with the equipment vendor
- Successfully completed GMP batches in other suites while installing SUB's

Lessons Learned From Both AAR's

- >250 observations (both likes and improvements) from AAR's:
  - Communication/coordination/schedule – internal and external (60%)
  - Documentation – specifications, validation, engineering, change controls and procedures – (30%)
  - Installation & Site Acceptance Testing execution (10%)
- Turned observations into actions for next phase of the project.
- Example - performed a vendor SAT without controls and then another internal SAT with controls, each with separate protocols – not efficient. Discussed with the vendor and performed a joint SAT with the same protocol for Phase 2

Specific AAR Highlights

- Wider input into schedule – get buy in from all parties
- Conduct regularly scheduled coordination "huddles" to look at current activities – one week look ahead
- Use engineering shake down or water runs to conduct safety walk-thrus
- Have clear roles and responsibilities, assign equipment leads, and a point person for contractor interfaces.
- Define roles of any third parties

Communication

- Communicate early and often, with wide distribution.
- Create simpler, more easily read project schedule with more frequent updates.
- Portal site for all project documents, accessible to project team, engineering company and vendor. Replaced e-mail for exchanging documents.
- Plan for a lot more disposables for start-up and validation and communicate usage to Materials Management group.
- Allow for unexpected events

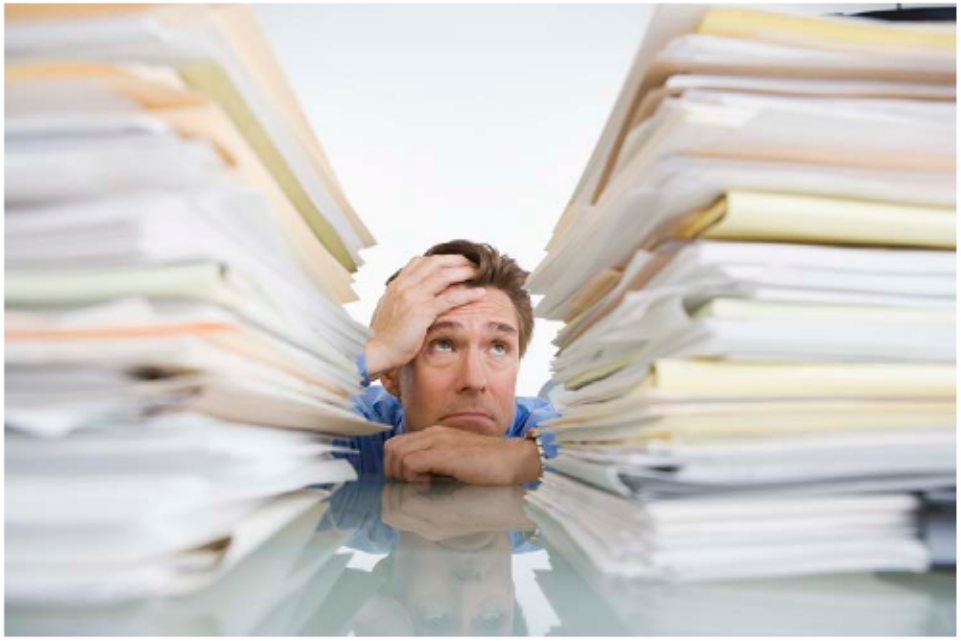
Communication

- You get what you ask for. Specify exactly what you want.
- Reviewed AAR items face to face with the vendor and made changes to our purchasing contract.
- Supply chain – worked with vendor to improve robustness and mitigate risks or single points of failure in the supply chain.
  - Film source
  - Bag components and connectors
  - Bag irradiations site
  - Shipping protocols

- Conducted a retrospective safety evaluation and review for first phase of the project, after the equipment was installed.
- Applied the learnings from this review prospectively for the second phase.
- Asked for modifications to the equipment P&ID's to address mostly ergonomic factors

Documentation

- Retrofit required revising, obsoleting or creating over a hundred documents – plan resources accordingly, particularly reviewers and approvers.
- Successfully leveraged documents from Phase 1 for Phase 2



Thank You

Acknowledgements

- GSK Team
  - SUB Selection Team
  - Operations
  - Process Development
  - Validation, Engineering
  - Quality
- Hargrove Team
  - Process and Facility Design
  - Project Management and Planning
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