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# **Implementation Case Study**

## **Rapid Flexible Capacity Expansion Utilizing 6x2000L SUBs**

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CMC Biologics

# Single-Use Systems at CMC Biologics

## Overview:

- **Brief overview of available single use technologies**
- **What are the advantages vs. Stainless Steel for CMC as a business and for our customers?**
- **Case studies related to SU implementation at CMC. Is the scale a real limitation for SUS?**

# Global cGMP Manufacturing

*Manufacturing facilities designed to optimize capacity and technological flexibility, fully compliant with global regulatory standards*

## Copenhagen, Denmark



- Mammalian and microbial
- 3 cell culture lines – 100L to 2000L
- 1500L x 2 L microbial line
- QC, AD, CLD and process development
- Danish (EMA) commercial facility authorization
- FDA PAI Mid-2015
- Centre of excellence for microbial development and manufacture

## Seattle, WA



- Mammalian facility
- Cell culture lines – 2x 3000L SS and 6 x 2000L SUB Line
- QC, AD, CLD, formulation and process development
- Certified for commercial production; PAI by FDA in 2014, EMA 2012
- Centre of excellence for Analytical and Formulation Development

## Berkeley, CA



- Early stage mammalian facility
- 3000 m<sup>2</sup> in one plant
- 1 cell culture line –100L to 3000L
- Expansion capacity of additional 2x3000L lines or various Single-Use Bioreactors



# Single Use Technologies

# Application of Single-Use/Disposable Systems

## Upstream

- Media Prep / Storage
- Shake Flasks
- Rocker Bag systems
- SUB's
- SU ATF and Acoustic cell retention for perfusion
- Clarification
  - Depth Filters
  - Centrifuges
  - Quattroflow pumps



**QUATTROFLOW™**  
Fluid Systems  
Part of Fluid Solutions Group  
SANGUINET



# Application of Single-Use/Disposable Systems

## Downstream

- Buffer prep and storage (with SU conductivity and pressure sensors)
- Pre-pack columns
- Viral filtration
- TFF
- Storage and Shipping (Process intermediates)



# Single Use/Disposable vs SS – Pros and Cons

## Pros

- Reduced CAPEX and installation timelines
- More flexibility / less facility downtime
- Less Cleaning
  - Water / Energy usage, CIP, SIP
  - Validation
  - Labor
  - Reduced risk of cross contamination



## Cons

- Leachables / Extractables
- Durability / Integrity
- Single Source considerations and non- standard connections
- Plastic waste – mostly has to be incinerated
- Scale limitations...so far...

VS





# Case Studies



# 2000L SUB Installation at Copenhagen

- Increase SU capacity to match launch/commercial production (mAb): 2000L
- Integrate into existing facility without affecting current clinical manufacturing
- Minimize limited company resources
  - Project used 1 Engineer and two validation resources
- Meet cGMP requirements – EMA, FDA
- Thermofisher selected as vendor for 2000L SUB with Applikon EZ control



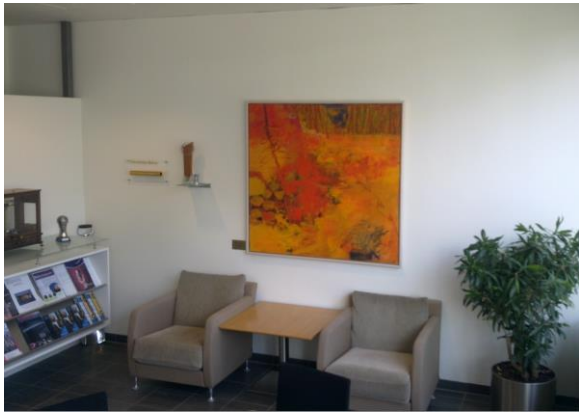
**Thermo**  
SCIENTIFIC

**applikon**<sup>®</sup>  
BIOTECHNOLOGY



# 2,000L SUB Installation Q3 2011

Reception Area Before



7 months from start to finish

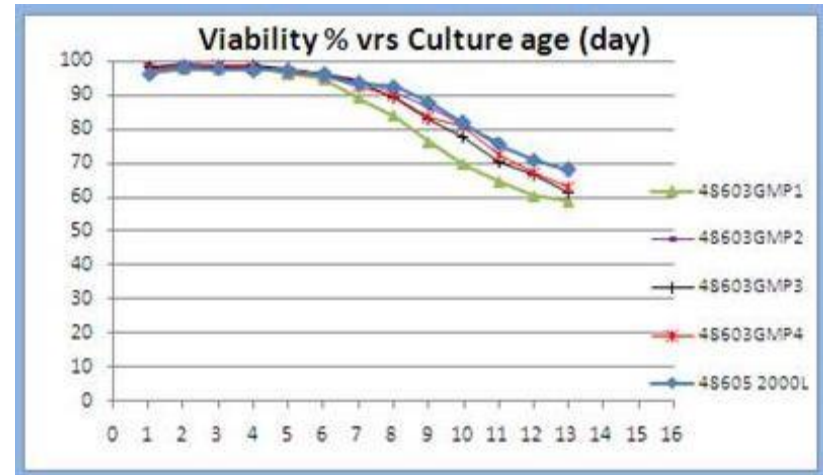
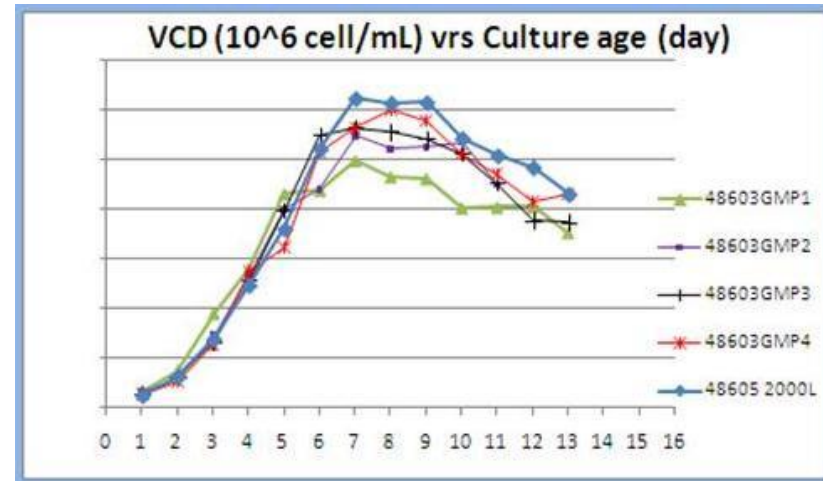
**Project Scheduling + Milestone plan**

	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER																														
	Week5	Week6	Week7	Week8	Week9	Week10	Week11	Week12	Week13	Week14	Week15	Week16	Week17	Week18	Week19	Week20	Week21	Week22	Week23	Week24	Week25	Week26	Week27	Week28	Week29	Week30	Week31	Week32	Week33	Week34	Week35	Week36	Week37	Week38	Week39	Week40	Week41	Week42	Week43
Kick Off																																							
URS writing and QA approval																																							
Specification of long lead items																																							
Inquiry, quotation evaluation, negotiation																																							
10% approval (steering committee meeting)																																							
Order long lead time item 2K SUB																																							
Design, engineering, purchasing, pre-validation (URS, FAT, IQ/OQ protocols etc.)																																							
2 K SUB shipment from THERMO-FISHER, Holland																																							
2 K SUB arrival at Applikon, Holland																																							
2K SUB control unit/SCADA integration at Applikon, Holland																																							
2K SUB FAT at Applikon, Holland																																							
2 K SUB arrival at CMC, CPH																																							
Construction kick off																																							
Equipment install - Except 2 K SUB																																							
Construction complete - Except 2 K SUB																																							
Facility Commissioning and qualification until complete																																							
Equipment Commissioning and qualification complete																																							
Ready for first engineering run																																							

First in Europe!

# 2000 L SUB Implementation in Copenhagen

- Experience with the 500 L SUB installation leveraged to guide installation and operation
- 2000 L SUB performance closely matches performance at bench and 500 L scale



## Process Data

- 2000 L SUB (light blue)
- 500 L SUB (the others)

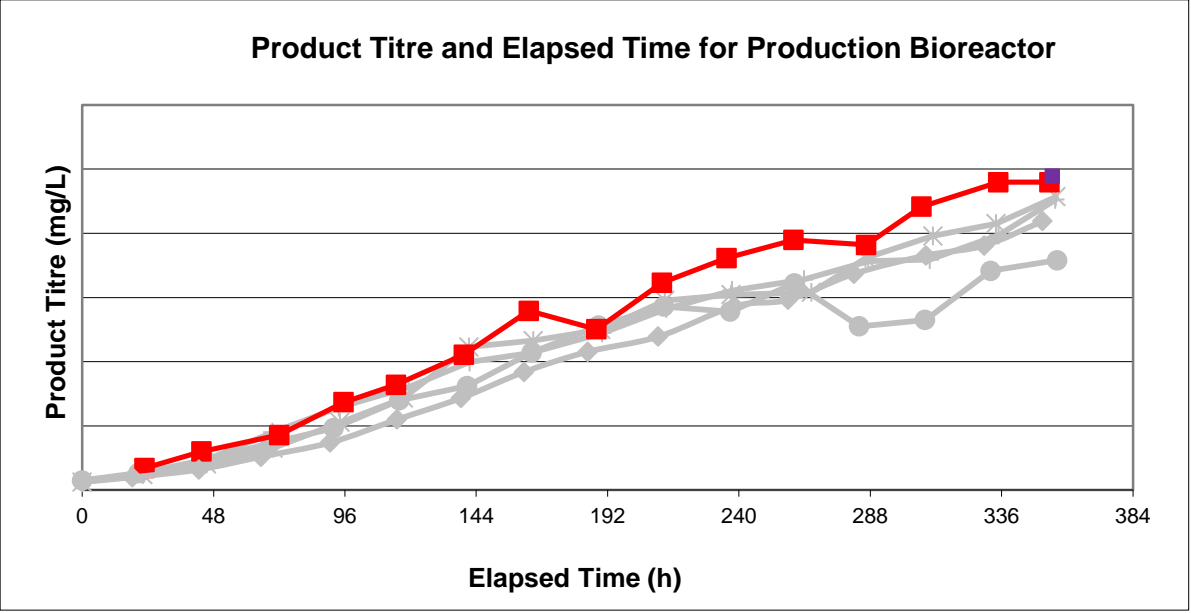
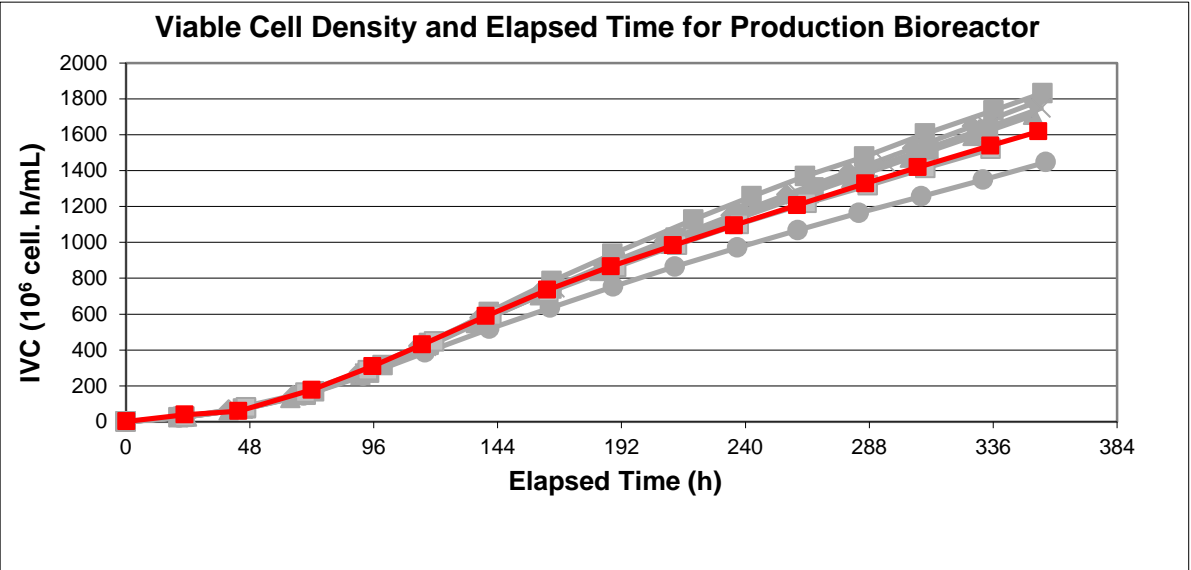


**2000L '6-Pack' Expansion at Seattle  
Project Overview**

# 2000L 'Six-Pack' - Project Brief History

- In May 2014 CMC Seattle was challenged by a customer to develop a plan for producing commercial supply of their product which was entering Phase 3 Clinical Trials:
  - The target capacity requirements as provided by the customer were based on 10,000L production scale.
  - CMCs production scale at Seattle facility was 2 x 3000L Stainless Steel and 2 x 500L SUB.
  - Timelines required Process Characterization and Process Validation to be completed by Q2 2015 to support BLA in Q4 2015.
- Process was transferred to CPH to test the “concept” in the 2000L SUB.

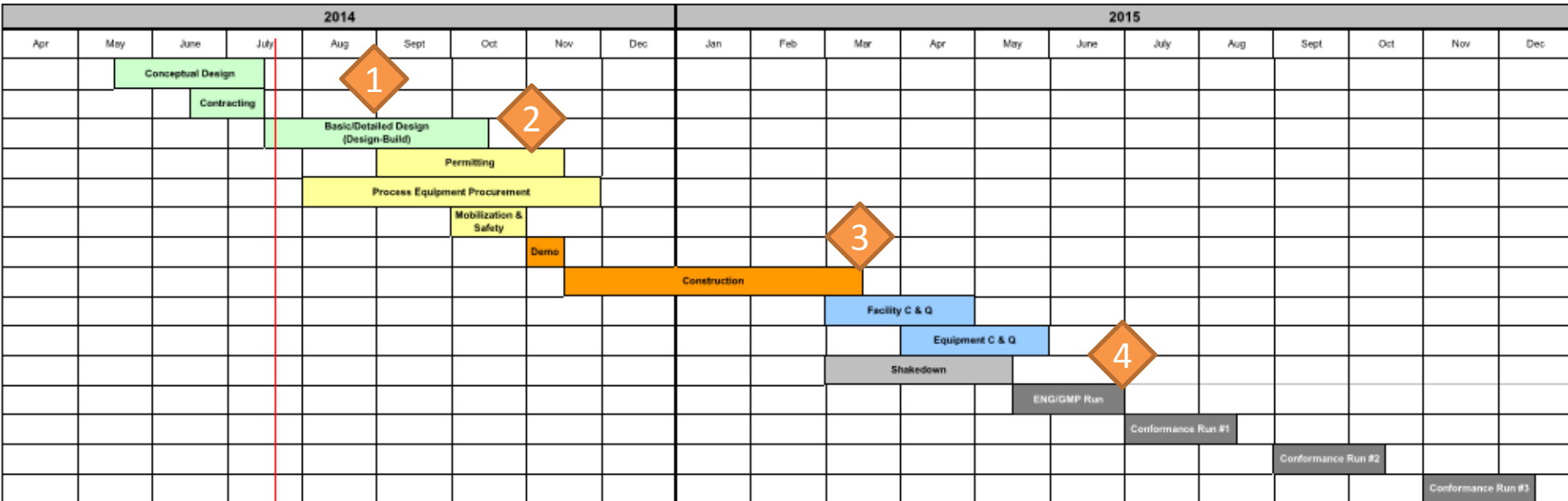
# Demo run 3000L SS vs 2000L SUB



# 2000L 'Six-Pack' - Timeline


**Timeline Overview (Level 0 Schedule)**  
**A86 Project - Bldg 2 Remodel**

Design Activities  
 Pre-Construction Activities  
 Construction Activities  
 Commissioning & Qualification  
 Shutdown  
 Manufacturing

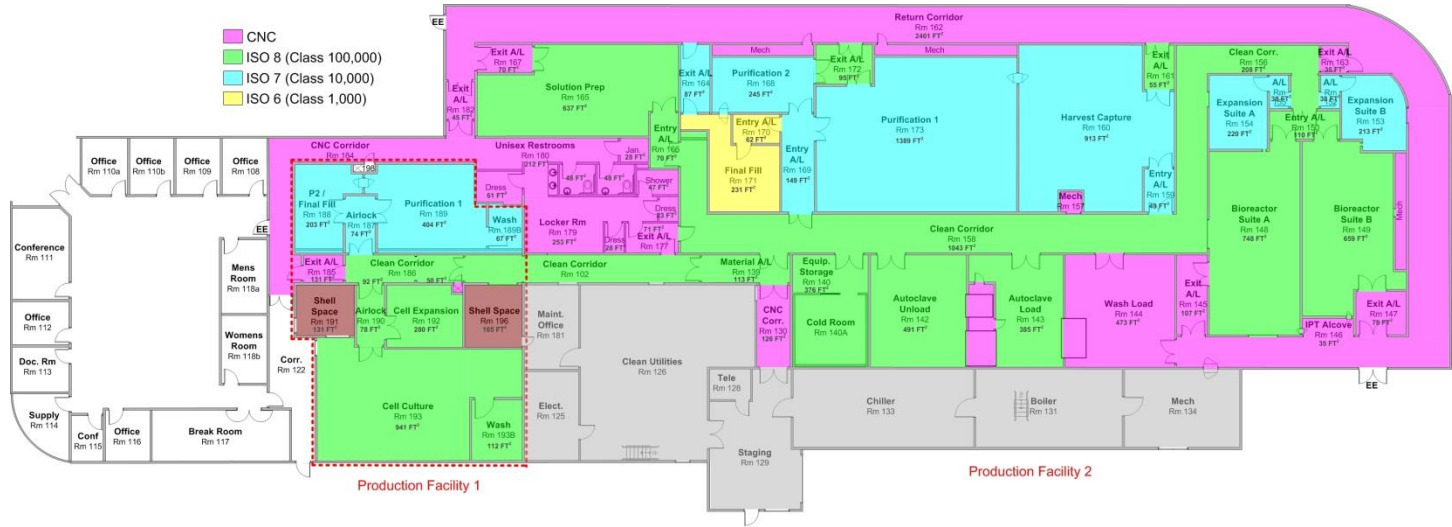


## Major Milestones:

- 1 – File for building permit (Sept 1, 2014)
- 2 – Begin Demo & Construction (Nov 1, 2014)
- 3 – Begin C&Q (Q2-2015)
- 4 – Begin Conformance Run #1 (Q3-2015)

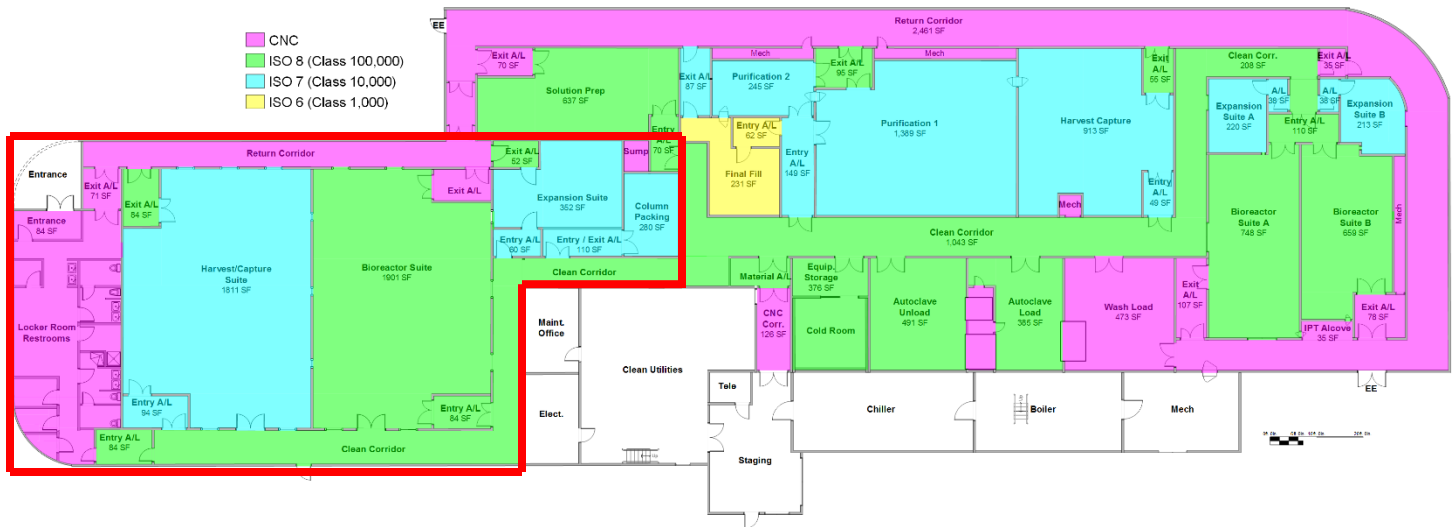
# 2000L 'Six-Pack' - Facility Layout

Old Layout



Scope of Work

Current Layout

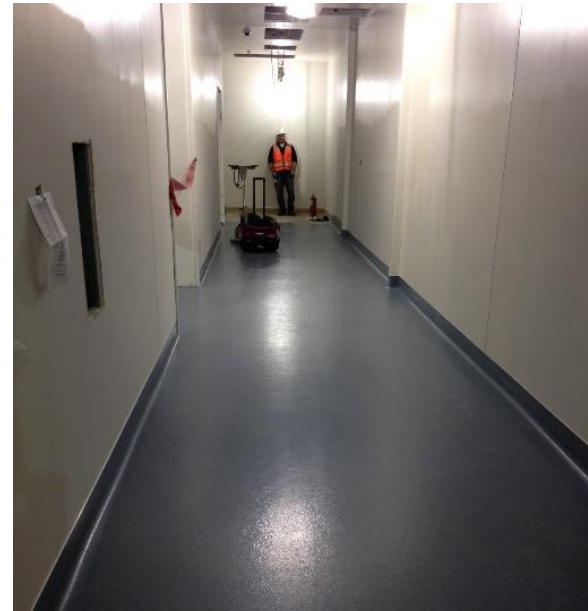
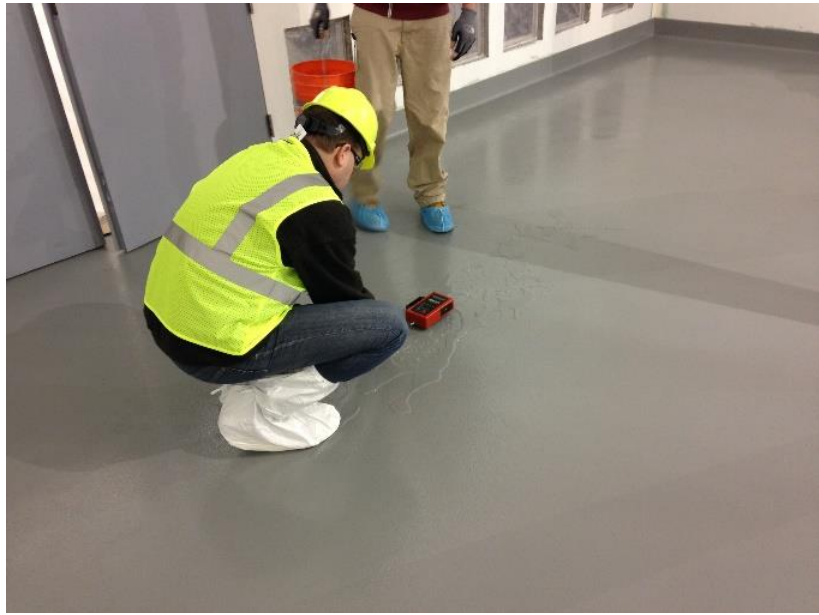




# Construction



# Construction



# Trim & Upfit



# Trim & Upfit



# Finished facility (1)



## Finished facility (2)



# Finished facility (3)

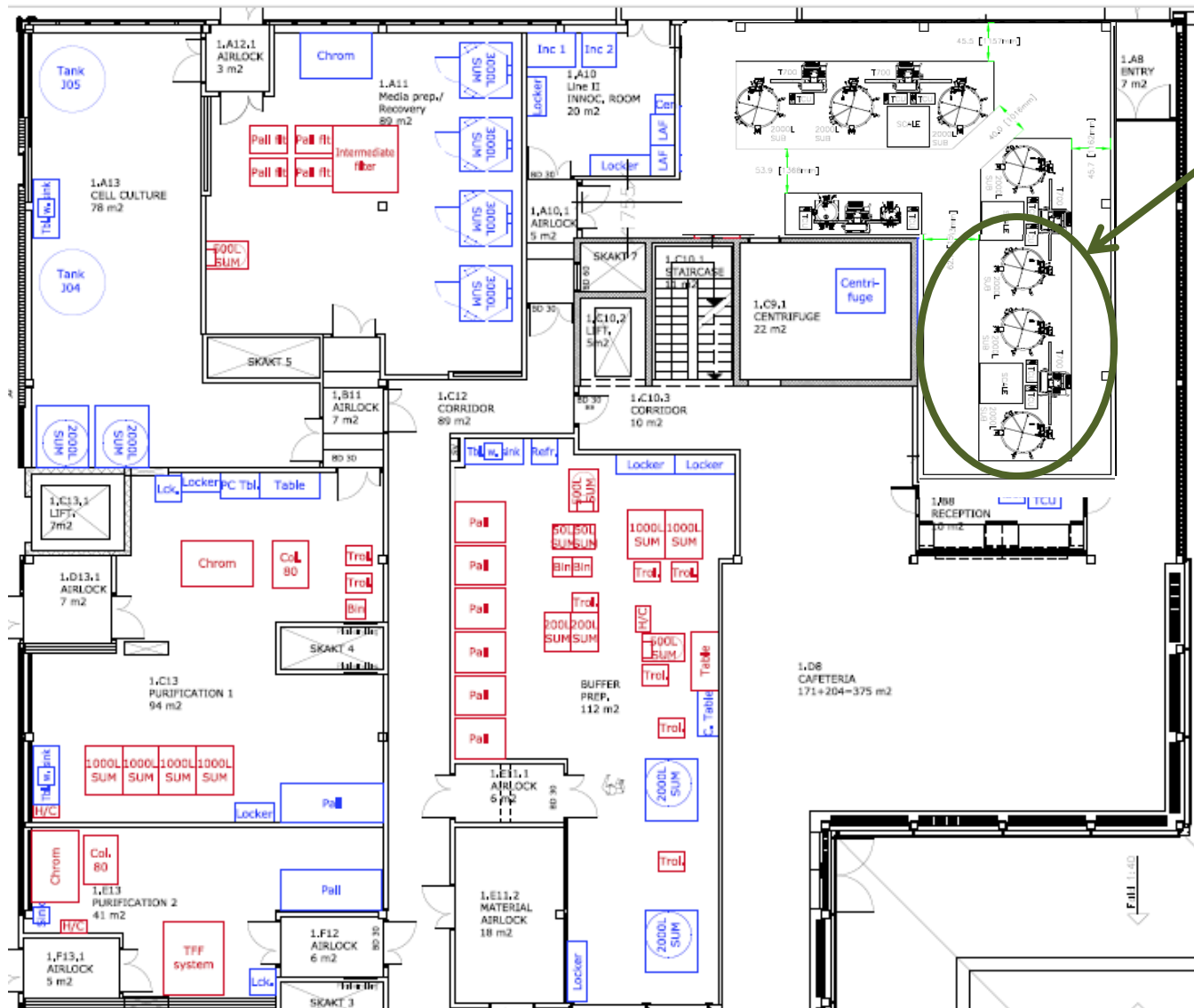




## 2000L '6-Pack' Expansion for CPH



# CPH 6 x 2000L Conceptual Design



Stage 1  
implementation  
3x 2000L SUB's  
Q4 2015

Stage 2  
implementation  
6x 2000L SUB's  
2016

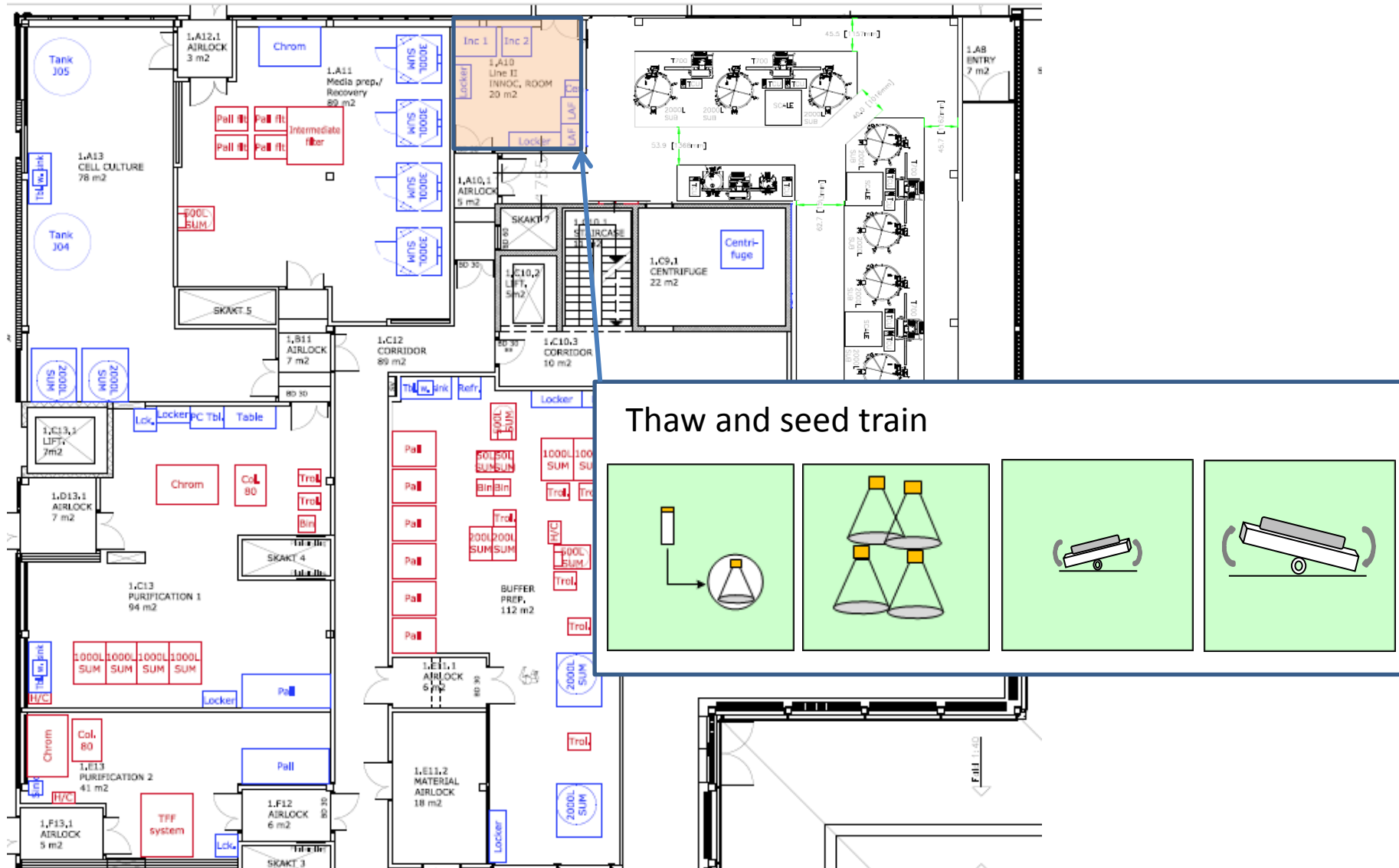


**Can we take advantage of the 2000L '6-Pack'  
to manufacture a mAb Project?**

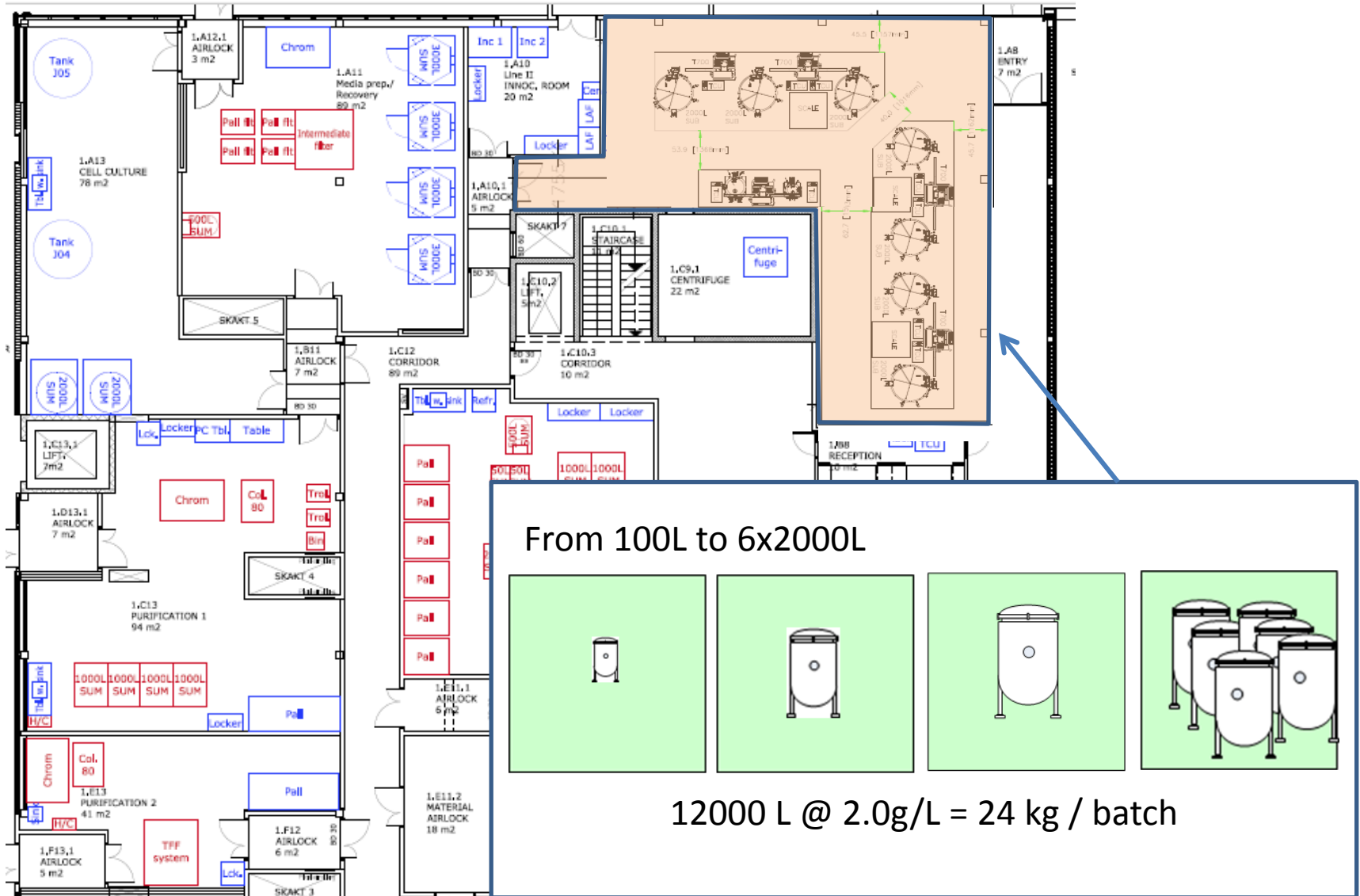
# Assumptions for mAb process

- Upstream:
  - Fed-batch
  - Titer: 2g/L
  - Main vessels 6x2000L SUB
  - Clarification: centrifugation
- Downstream:
  - Protein A (ø:80cm column)
  - Viral inactivation
  - IEX (ø:80cm column)
  - IEX (FT) (ø:80cm column)
  - Viral filtration
  - TFF

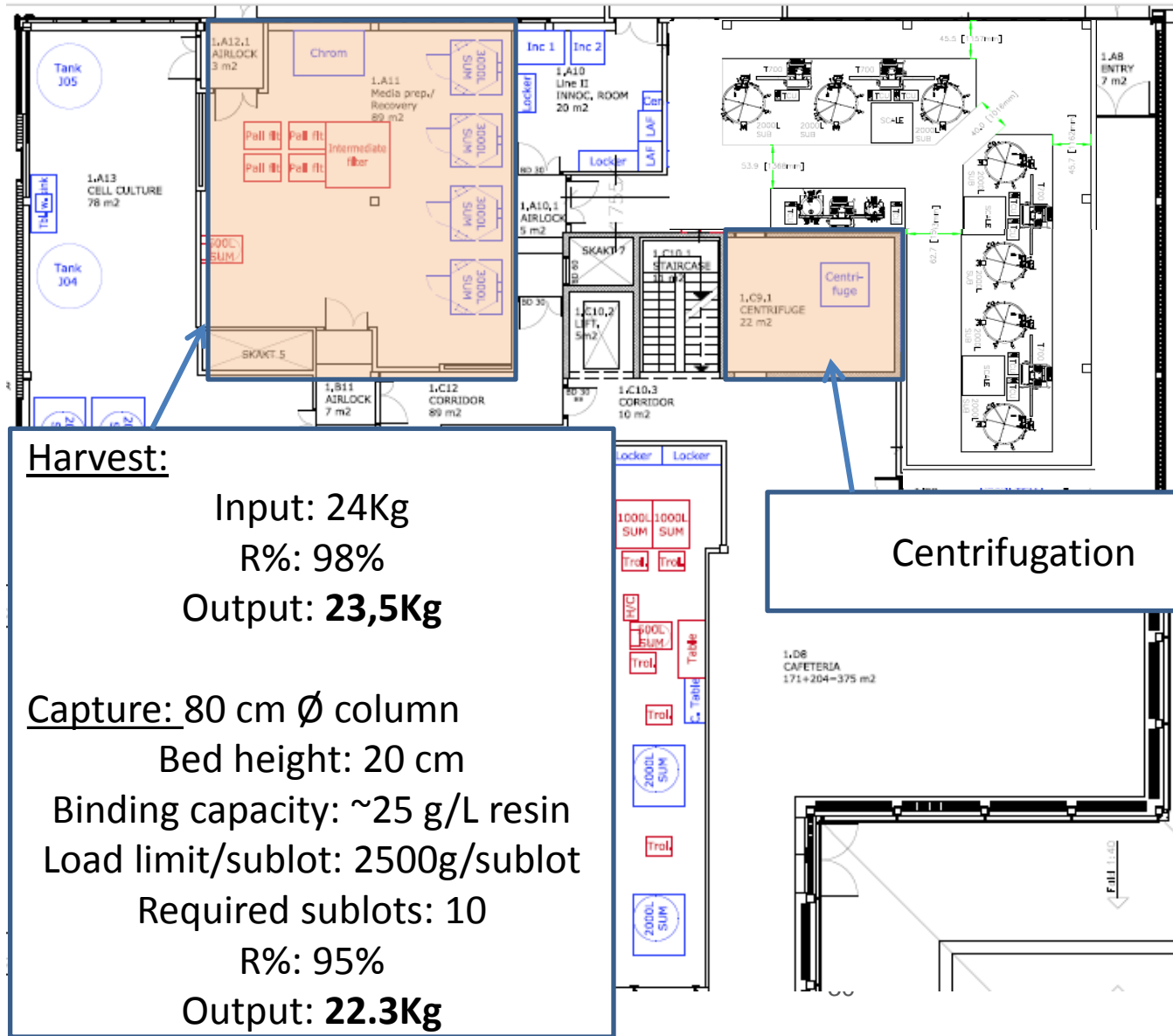
# CPH 6 x 2000L Conceptual Design



# CPH 6 x 2000L Conceptual Design



# CPH 6 x 2000L Conceptual Design



## Harvest:

Input: 24Kg

R%: 98%

Output: **23,5Kg**

Capture: 80 cm Ø column

Bed height: 20 cm

Binding capacity: ~25 g/L resin

Load limit/sublot: 2500g/sublot

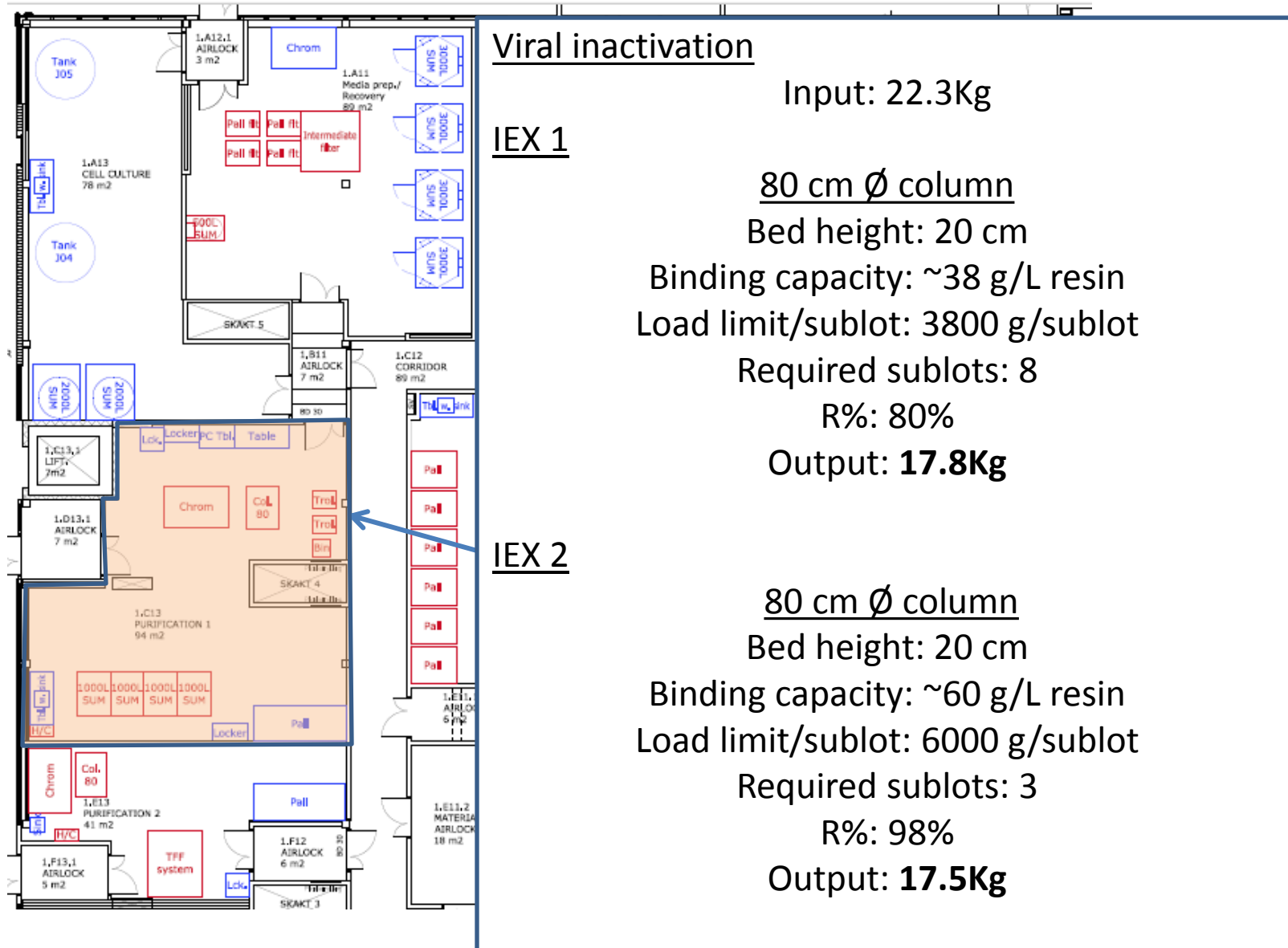
Required sublots: 10

R%: 95%

Output: **22.3Kg**

Centrifugation

# CPH 6 x 2000L Conceptual Design



## Viral inactivation

### IEX 1

Input: 22.3Kg

80 cm Ø column

Bed height: 20 cm

Binding capacity: ~38 g/L resin

Load limit/sublot: 3800 g/sublot

Required sublots: 8

R%: 80%

Output: **17.8Kg**

### IEX 2

80 cm Ø column

Bed height: 20 cm

Binding capacity: ~60 g/L resin

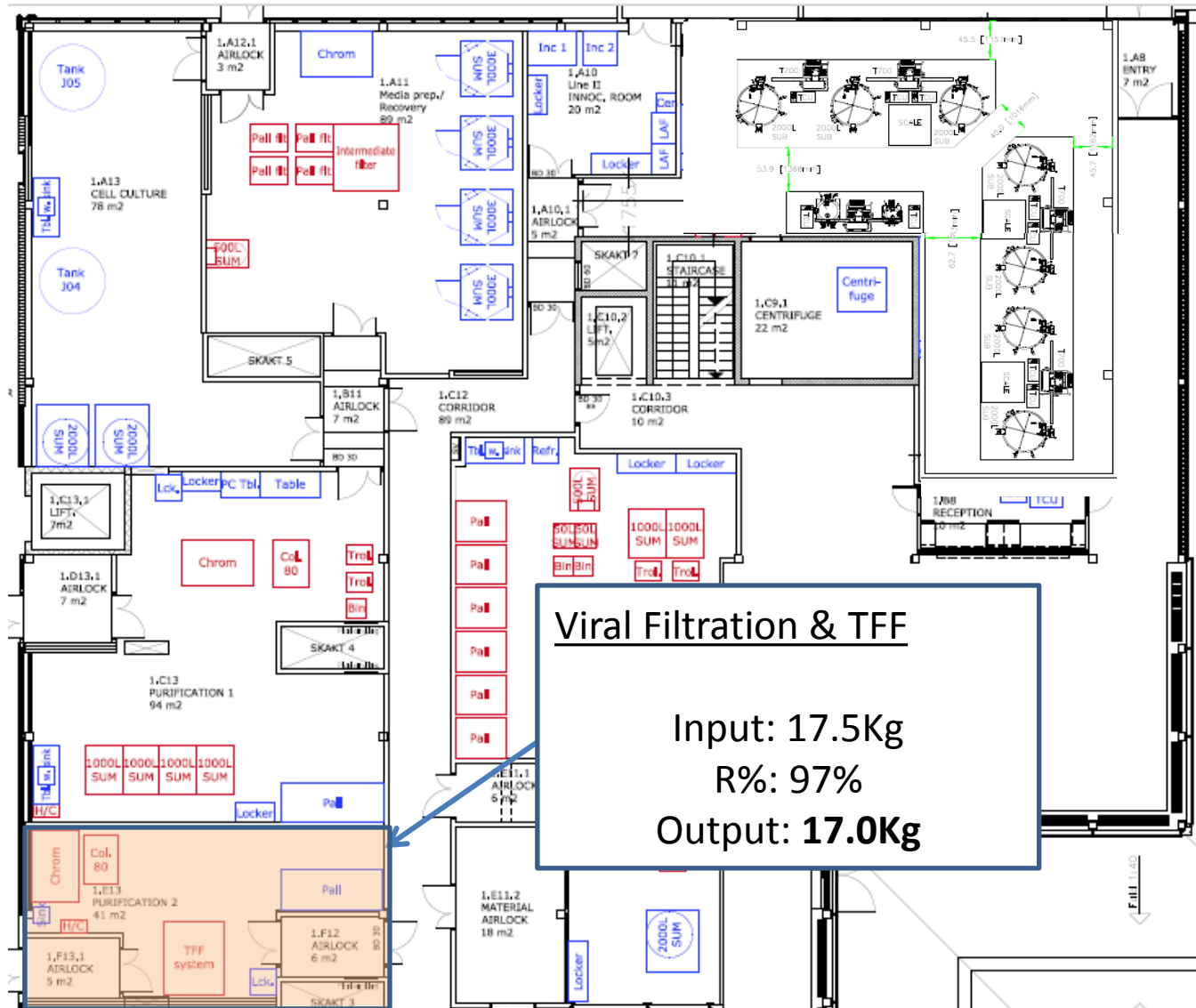
Load limit/sublot: 6000 g/sublot

Required sublots: 3

R%: 98%

Output: **17.5Kg**

# CPH 6 x 2000L Conceptual Design





# Conclusions

- SU technologies are an excellent option when flexibility is needed. (i.e. multipurpose facilities).
- Commercial processes are implementing this technology and the expectations are to see more products in the market using SU in the near future.
- Large scale manufacturing do not seem to be a real limitation for SU.

# Thank you



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