



Single-Use Systems for Pharmaceutical Applications

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CSL's Large Scale Cell Culture Facility

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Objective

How CSL maximised the opportunity to build a state-of-the-art facility while minimising risks.

- Large scale facility scope
- Facility design needs
- Facility features
- Process features
- Project schedule

CSL's New Facility Drivers

CSL current in-house capacity

- *500L OK for preclinical and early clinical-phase materials*

Large volume/ Late-phase supplies - CMO.

- *Working with CMO presents issues such as access and control*

Due to the expense and length of clinical trials, there is a strong business case for in-house capability.

- *Business case is strengthened by a strong product portfolio*

During clinical phases, it is advantageous to have the ability to respond rapidly to changes in material demands, technology and process changes

Cautions: New Facility Risks

Long build- and delivery timelines often mean that decisions to build are made too early

- *Delaying the build decision may delay speed-to-market and increase cost to build*

Risk of owning a redundant facility due to:

- *Molecules failing to reach late-stage clinical study or market*
- *Technology becoming obsolete*

A redundant facility may have little resale- or reuse value due to geographic location, installations of major equipment and design philosophy

Design Brief for CLS's New Facility

Deliver a large scale facility based on cell culture

- *'Footloose' location -multiple options*

Provide required capacity to cater for Phase III clinical trials and early market entry.

Accommodate a range of process technologies including recombinant proteins and mAbs.

- Comply with FDA, EU and TGA requirements.
- Leverage CSL worldwide group technical capabilities

Facility Scope Limits

Cell Culture based on 2,000L bioreactor train

- 1x train initially, expansion space for 3x

Clarification by filtration

- Space for centrifuge

Downstream purification to post-VI Bulk Drug Intermediate

- BDI: frozen intermediate shipped to CSLB Germany

Expansion space for processing to Bulk Drug Substance

- BDS: frozen bulk shipped to CSLB Germany

Facility Key Features

Must cater for multiple products and technologies at unknown scales and utilisation rates

- *Adaptable facility design*
- *Flexibility of use and easy process change-over for campaigns and new technologies*

Control highest risks

- *Do not compromise product quality*
- *Reduce the risk of a redundant facility*
- *Limit capital exposure*
- *Delay decision to build as late as possible*

Control cost of goods

- *Low COGS even at low capacity*

Decision: Choice between Conventional and Single-Use facility design

Facility Location Factors:

- Develop and retain large scale recombinant protein technology expertise on-shore in Australia.
 - Leverage CSL's recombinant protein- & bulk protein handling expertise within its world-wide network.
- Commonwealth- and State of Victoria governments grants linked to investment and job creation.
 - CSL's Behring network in Germany has highly developed protein purification and drug product finishing capabilities.

CSL's New Facility Location

(ref: NewMap.com)



New Facility Location

Existing: Main Stores, QA/QC, Primary Utilities, Engineering Services, Admin, HR, HS&E, etc.



CSL Broadmeadows site chosen because of the proximity to CSL large-scale cell culture expertise at Parkville, large-scale protein purification expertise at Broadmeadows and CSL research capability at Bio21 Institute, Melbourne.

Risks of Single-Use

COSTS

- Higher batch operating expenses
- Rising cost due to hydrocarbon-source raw material
- Environmental cost and disposal costs

TECHNOLOGY

Technology is immature, changing, unstandardised

Supply chain concerns

- *Viability of suppliers; single source; quality and reliability is untested*
- *Film changes, film variability*

OPERATIONS

More manual operations

- *Ergonomics/ handling risks; Intensive operator training*

PROCESSES

Process scalability questions

- *Mixing, aeration, flow rates etc. are different to conventional systems*
- *Production scale limited at ~2,000L*

VALIDATION/ REGULATORY

Validation is more complex

- *Extractables and leachables questions*
- *Chemical resistance; surface adsorption studies*

Nevertheless, in spite of the risks, facilities based on single-use are viable and approvable

Technology & Process Challenges of S-U

Process Modifications Due To:

Volume & flow restrictions

- *Small diameter tubing; low pressure systems*

Technology limits

- *Limited agitation = different mixing characteristics, new aeration strategies*
- *Incompatibility between different vendor components and fittings*
- *Dimensions, configurations, availability of components*
- *Robustness, durability of s-u components*
- *Customization of vendor “standard” configurations*

Validation Challenges

Increased (& new) process validation

Film characteristics

- *Surface adsorption, potential gas penetration, higher extractables and leachables*

Due Diligence for Single-Use Facility and Process Design

Approved Therapeutics:

- Visited several companies with FDA-approved products in single-use manufacturing systems

Facility/ Process Design:

- Consulted thought-leaders in facility design and process engineering

Validation Issues:

- Engaged thought-leader consultants on E/L and validation issues

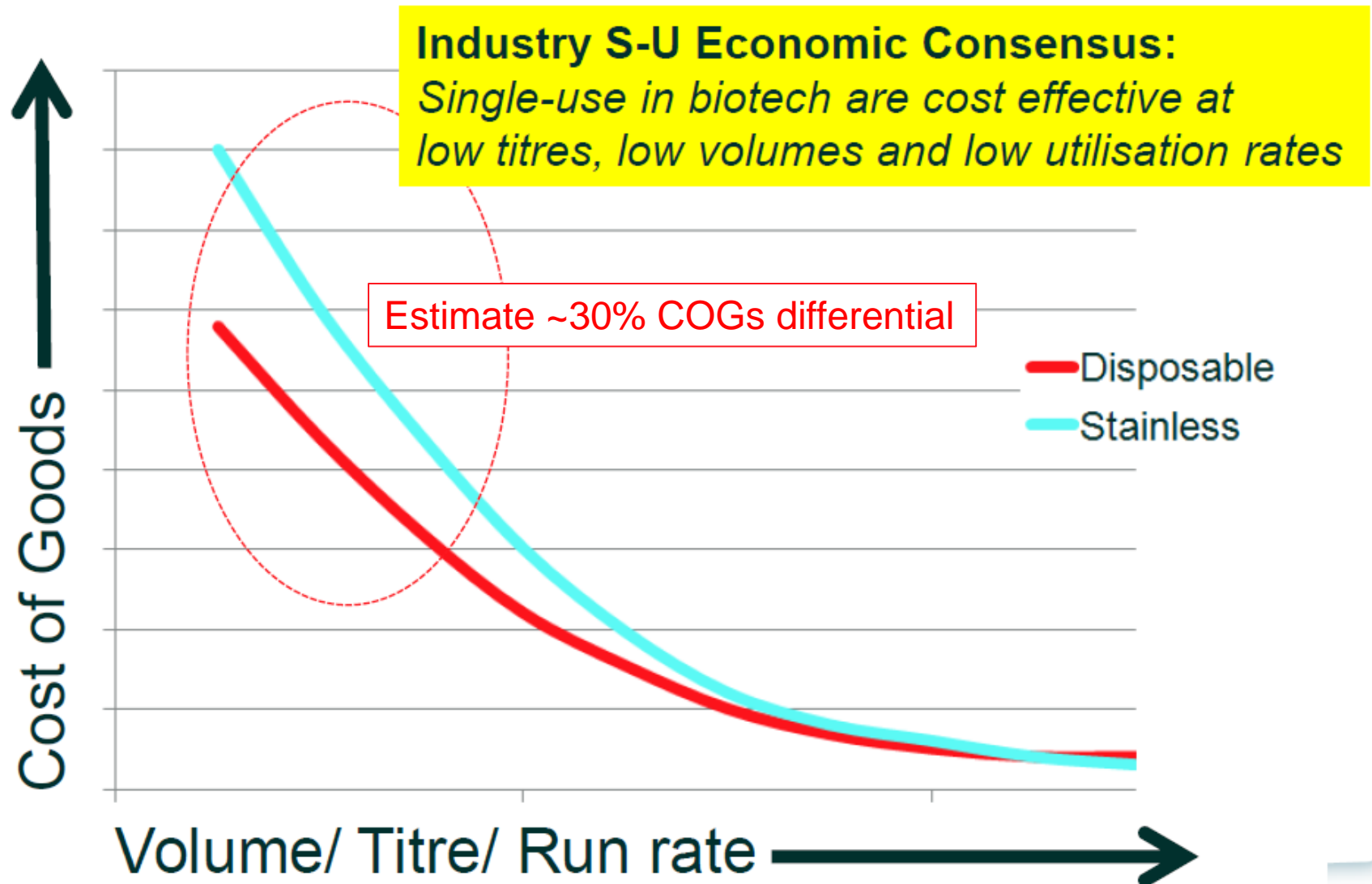
S-U Vendors:

- Visited and audited vendors and their suppliers/ fabricators

Process Integrators:

- Compared capability to provide integration of the entire process stream

Cost of Goods Expectations: Single-Use vs. Conventional



Conventional/ Single-Use Comparisons

Ref: Article Series: BioProcess International and BioPharm Services

Conclusions: Single-Use vs. Conventional stainless steel:

Hybrid Option: As you increase the use of disposables, you move fixed up-front costs to activity-based costs

- *You only spend the money when you need to manufacture*

“Monoclonal Antibody Manufacturing Cost Benefits of Hybrid Disposable Systems” by Andrew Sinclair and Miriam Monge

BioProcess International, Vol. 9, No. 9, October 2011, pp. 12–17

CSL Facility Design Outcomes

Opportunity to simplify conventional facility design model

Facility:

- Adopted “ballroom” concept for processing areas, separated by process needs
- Facility environment matches increased containment of single-use items
 - *Sterile process containers, closures and aseptic connectors to improve process integrity*
 - *Open processing manipulations in HEPA hoods*

Process:

- Chose single-use where beneficial, and stainless steel where sensible in the process
- Mobile modular Upstream and Downstream process skid, with off-the-shelf & upgradeable components

Utilities:

- Utility services have 75% turndown capability to cope with capacity changes

Automation:

- Skids have local controllers with standardised interfaces and upload capability
- Initially no automated batch functionality or electronic batch records

Validation:

- Increased validation at vendors’ sites to decrease on-site validation load

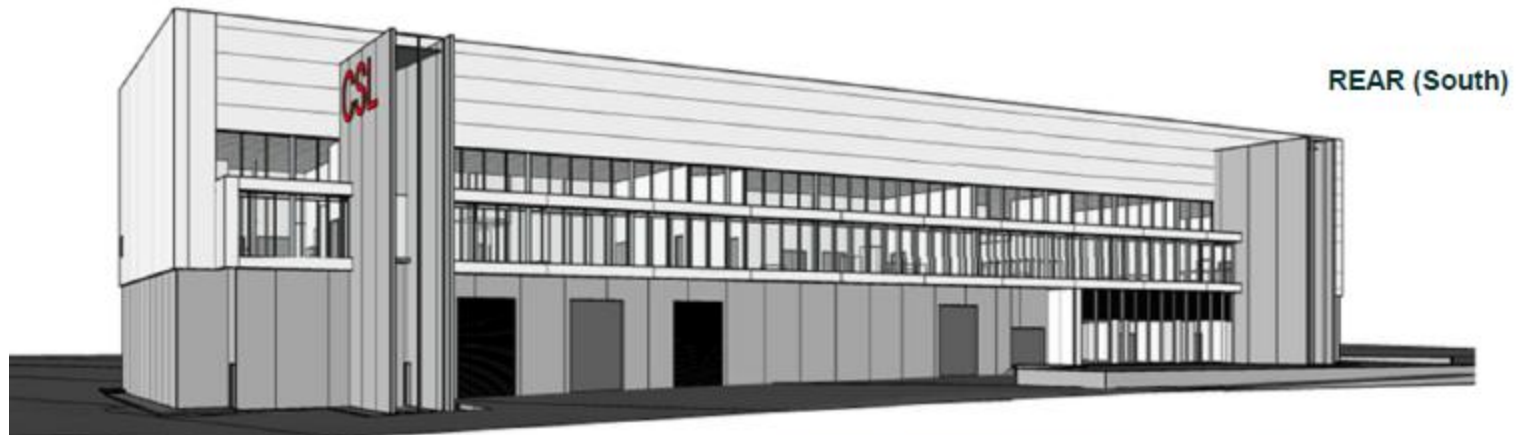
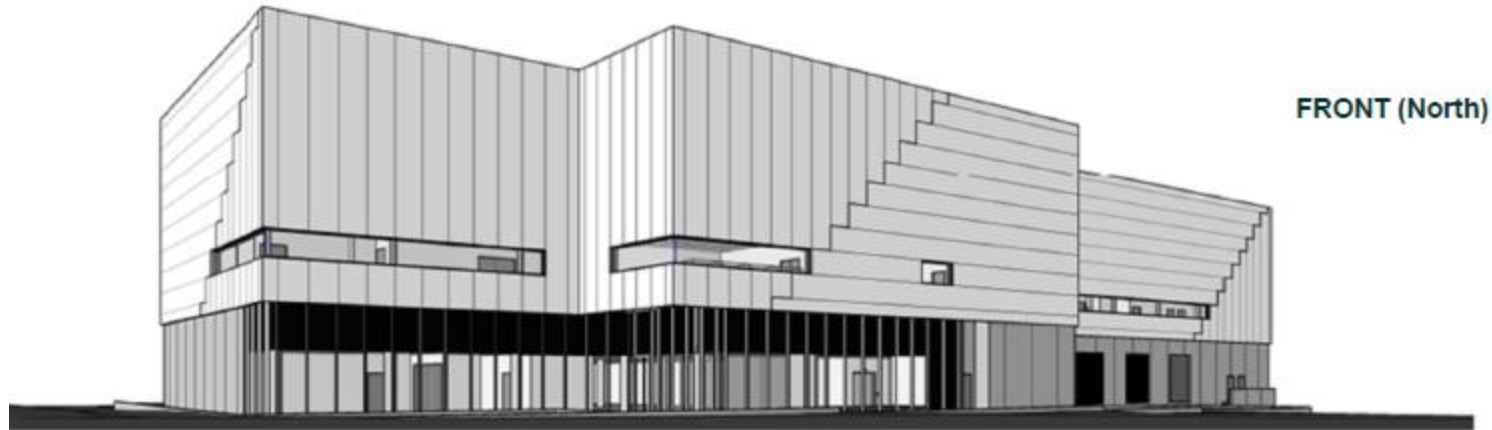
GMO Containment:

- CHO cells: PC1. Design and certify facility at PC2-LS for future use

Project Schedule (Targets)

- Design phases 1 & 2 started July 2009
- Commenced construction Nov 2010
- Complete mechanical/ process installation ~July 2012
- Eng runs ~October 2012
- Complete validation ~January 2013
- Ready for GMP February 2013

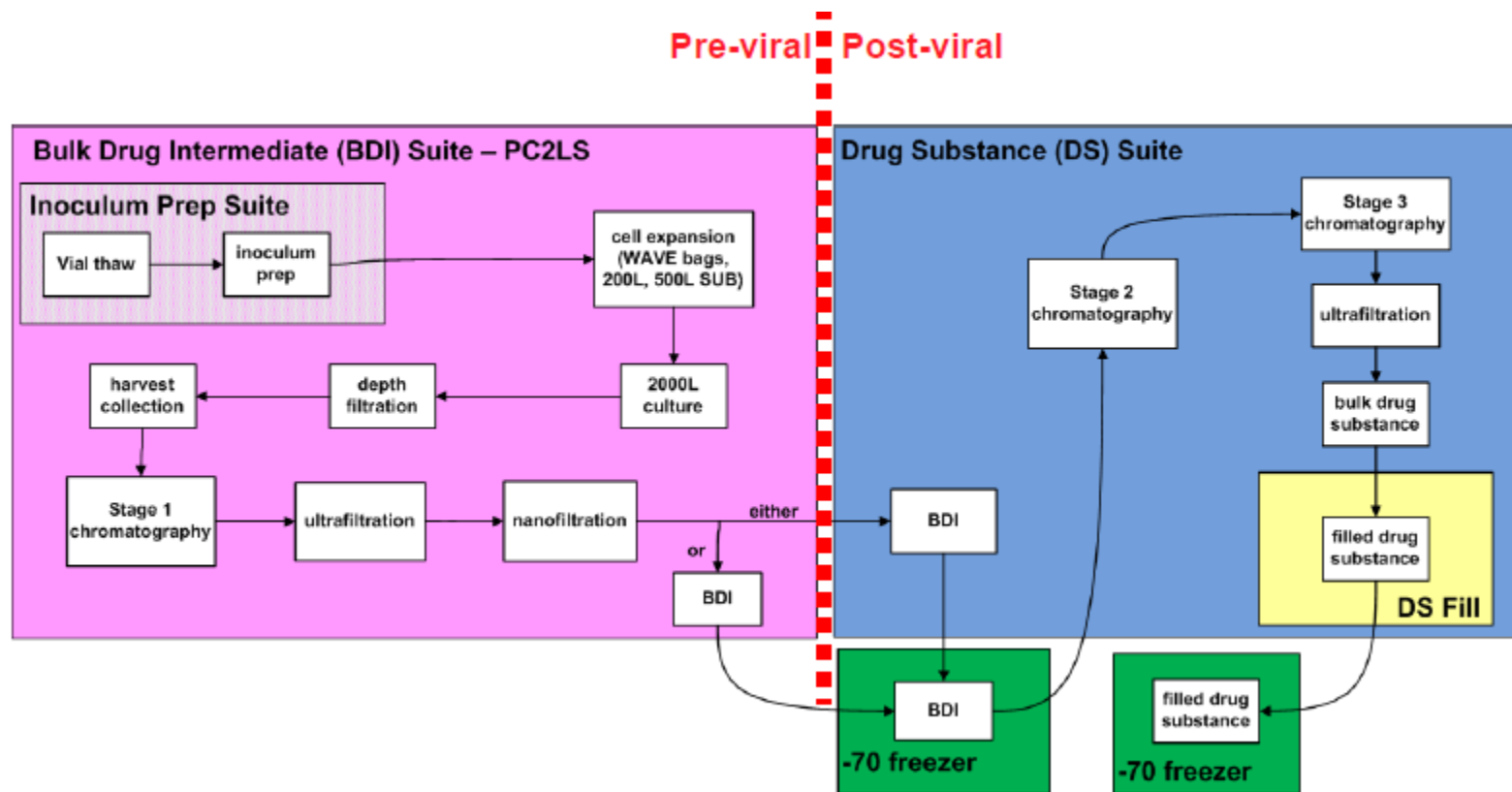
Elevations



Construction status- exterior



Process Schematic



Air Quality – Area Classifications

- Upstream processing areas
 - Grade D/ ISO-9
- Buffer preparation & BDI to DS processing
 - Grade C/ ISO-7
- Open manipulations:
 - Inoculum preparation (Grade C + Biosafety LAFU)
 - Other open operations in BDI and DS, use sterile connectors

Level 2 Detail



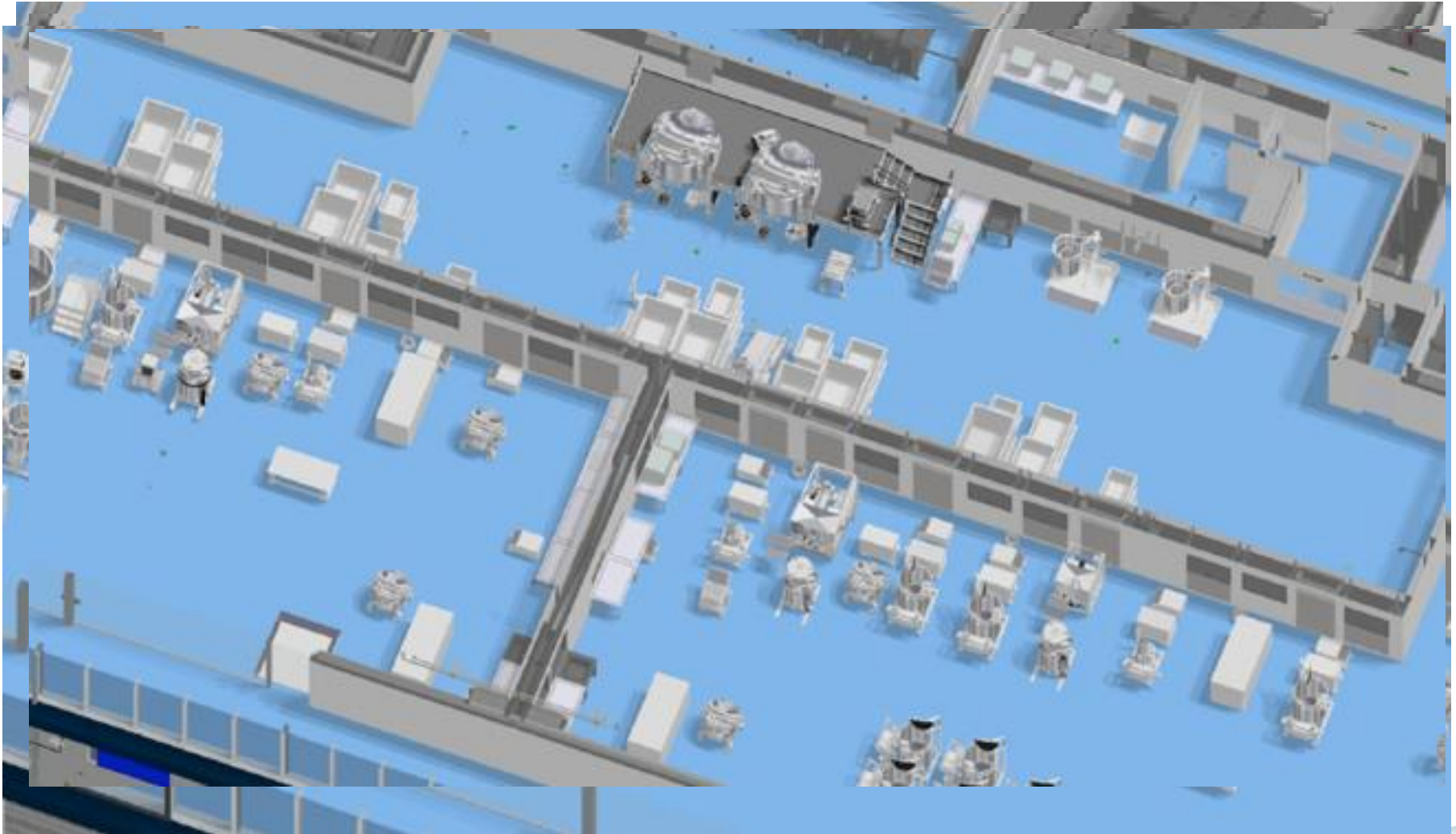
Upstream Detail

- Single-use media preparation adjacent to cell culture area
- Single-use inoculum train
 - *Shake flasks & Wave bags*
- Single-use bioreactors
 - *200L, 500L, 2000L, operable at 25% volume*
- Lenticular clarification filters (no centrifuge)
- Processing continues to nano filtration in this area

Downstream Train Detail

- Buffer prep: Stainless steel and single-use adjacent to USP and DSP areas
 - *In-line buffer dilution where possible*
- S/s Chromatography skids,
 - *Single-use flow path where feasible*
 - *Up to 60cm columns; dedicated resins*
 - *Multiple cycles*
- UF/DF – single-use flow path

Recombinant Protein Manufacturing Configurations



Processing

- Single-use mixing skids with sterile filtration
- Sterile bags inside totes for media, buffer and product hold
- Processing at ambient temperature
- Low temperature hold / storage:
 - $+4^{\circ}\text{C}$, -40°C & -70°C

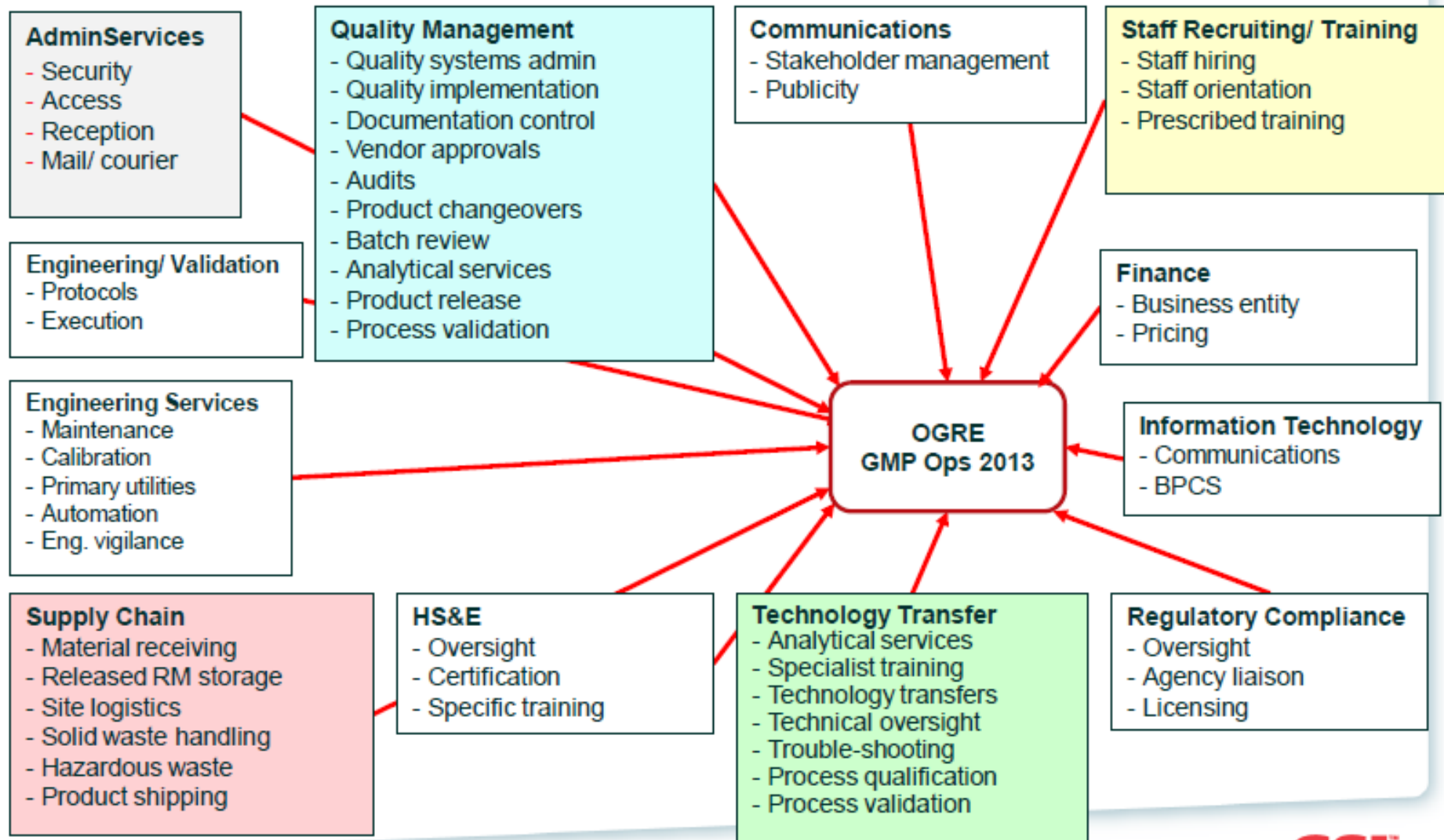
Process Services

- WFI throughout
 - *Less cost than a large PW system + small WFI system*
- Process gases
- Filtered compressed air
- Heat/cool packs
- Sterilisation autoclave
- Continuous heat decontamination unit

GMP Readiness

- Created **O**perational **G**M**P** **R**eadiness and **E**xecution team (**OGRE**).
 - *Prime objective: Ensure start-up of GMP processing on time*
- OGRE comprises 12 workgroups from all functional areas in CSL, each with unique deliverables
 - *Workgroups comprise sub-teams*
 - *Workgroups collaborate with other groups/ sub-teams*

OGRE Stakeholders & Deliverables



Questions?