

# DESIGNING & REMEDIATING CIP PROCESSES FOR SUSTAINABLE CLEANING

STRATEGIES, OPPORTUNITIES &  
REALISATION

VALIDEIRE, COPENHAGEN  
SEPT 11<sup>TH</sup>, 2024

CIP, SIP & EM Conference



**Hyde**  
ENGINEERING  
+CONSULTING



**PEOPLE**   
End poverty and hunger  
in all forms and ensure  
dignity and equality

**PLANET**   
Protect our planet's  
natural resources  
and climate for  
future generations

**Sustainable  
Development**

**PROSPERITY**   
Ensure prosperity  
and full employment  
for all

**PARTNERSHIPS**   
Improve  
the quality of  
institutions

# DECADE OF ACTION

## SUSTAINABLE DEVELOPMENT GOALS



 <b>13</b> CLIMATE ACTION	 <b>14</b> LIFE BELOW WATER	 <b>15</b> LIFE ON LAND	 <b>16</b> PEACE, JUSTICE AND STRONG INSTITUTIONS	 <b>17</b> PARTNERSHIPS FOR THE GOALS	 <b>4</b> QUALITY EDUCATION	 <b>5</b> GENDER EQUALITY	 <b>6</b> CLEAN WATER AND SANITATION
 <b>8</b> ECONOMIC GROWTH	 <b>9</b> INDUSTRY, INNOVATION AND INFRASTRUCTURE	 <b>10</b> REDUCED INEQUALITIES	 <b>11</b> SUSTAINABLE CITIES AND COMMUNITIES	 <b>12</b> RESPONSIBLE CONSUMPTION AND PRODUCTION			

**SUSTAINABLE DEVELOPMENT GOALS**



What has cleaning got to do with it?  
What can we do?





# Discussion Topics

**Impressions**

**Impact**

**Input**

**Identify**

**Invigorate**

**Implement**

**Instagram**

**Re-iterate**







Discussion  
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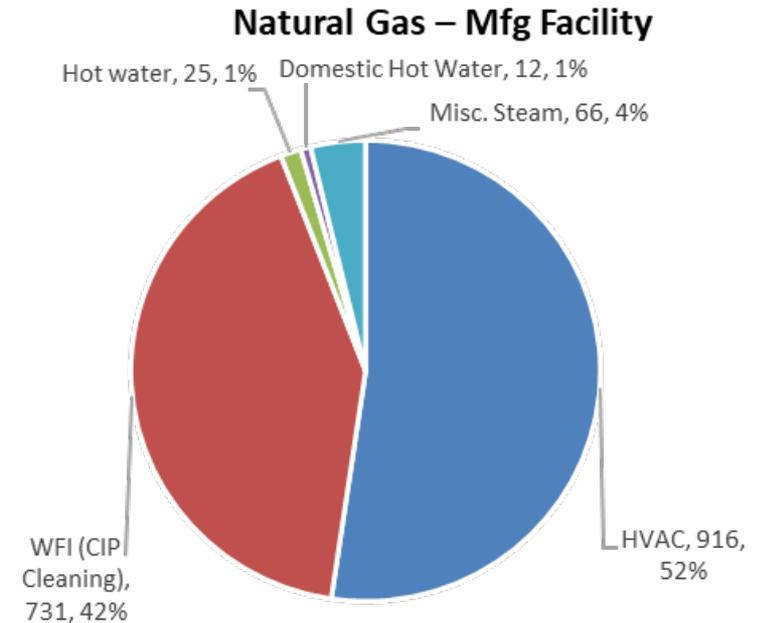
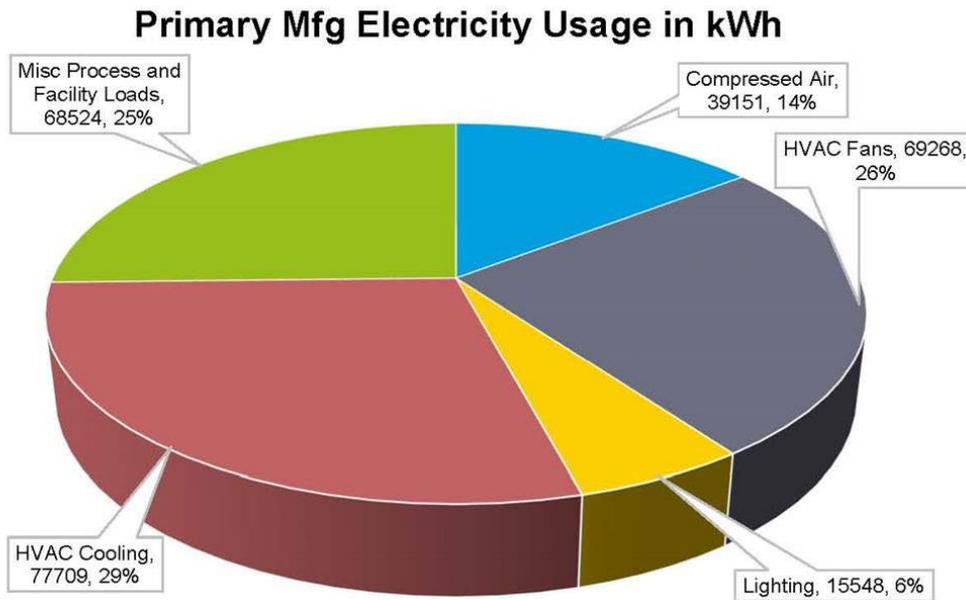
**Re-Iterate**

# Sustainability in BioPharma



GSK Baseline Info – ISPE Annual 2023

Biotech Facility



## Summary Biopharma sustainability

- Carbon footprint predominantly by electrical and natural gas consumption
- ~40% of electricity used for process (25%) and compressed air (14%)
- ~As much as 40% of natural gas used for Purified Water generation

# CIP Cycle Environmental Impact



## Operational Data for large scale MAB facilities :

- **Water consumption per gram of drug substance**
  - As much as 20L water / 15L of Purified Water per gram of bulk drug substance
  - Up to 80% of the purified water can be used for cleaning
- **Natural gas/CO2**
  - Up to 40% of natural gas usage for purified water
  - Reduction of CIP water = Reduction in natural gas of facility
- **Electricity**
  - Substantial portion of the 40% process and compressed air electricity used for CIP
    - CIP Supply and Return Pumps (~7.5-15 KW) running ~80% of time during each CIP cycle
    - Several air blows during CIP cycles
- **Waste Streams of drug substance**
  - Process wastewater will require neutralization and cooling prior to disposal
  - Bio-inactivation will require additional energy for thermal inactivation

# CIP Impact on Manufacturing Capacity



- Utilization efficiency issues resulting in manufacturing bottlenecks:

- **Cleaning**

- Extensive down time of process equipment
- Delays due to CIP skids overutilization
- Delays due to overlapping CIP circuits

- **Purified Water**

- Delays due to insufficient purified water
- Up to 80% of purified water used for CIP
- Larger volumes than anticipated during design

Cost of Goods impacted by inefficient CIP cycles

Reduced manufacturing capacity

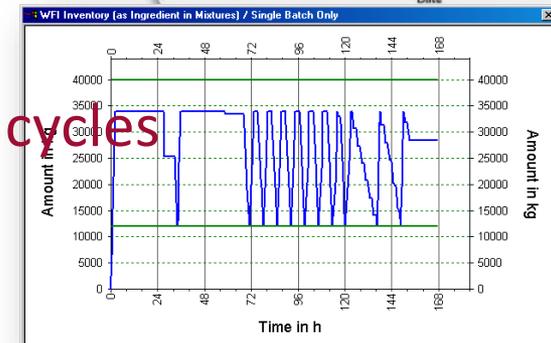
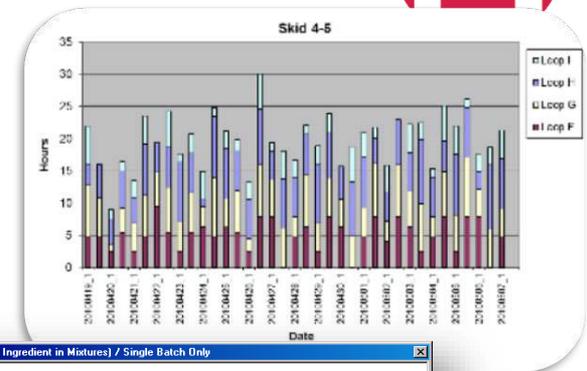
Typical response: Higher utilities consumption

- Additional CIP systems and Purified Water Generation

- Expensive
- May not solve facility capacity issues
- Does not improve sustainability

- **Single Use**

- Sustainability: shifting from CIP system waste to SU waste
- May not be feasible for large scale or existing processes





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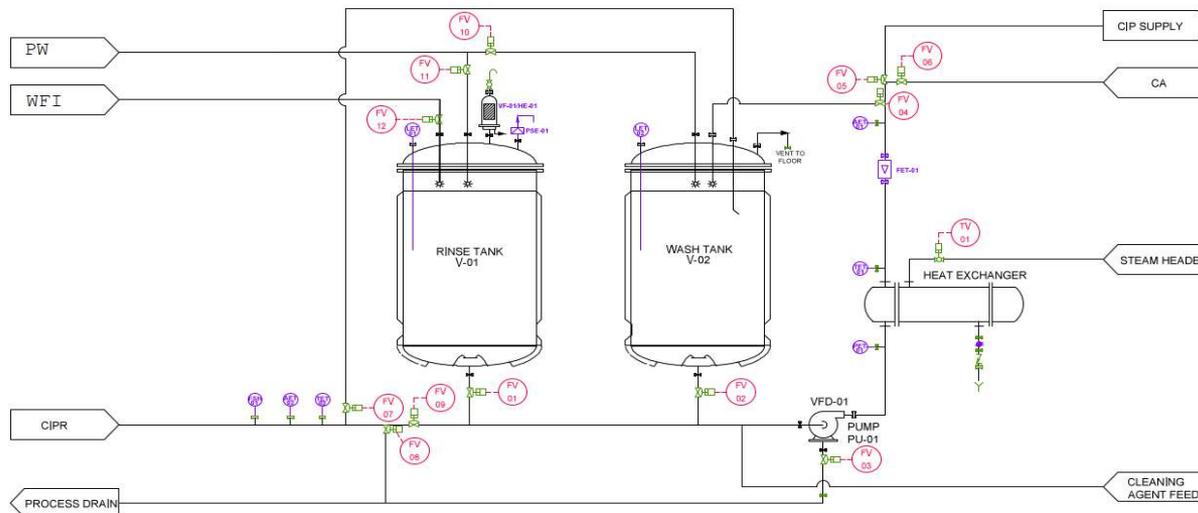
**Re-Iterate**

# Baseline: CIP Skid and CIP Cycle



- **Two Tank CIP Skid**

- 2 tank system, with CIPS pump, heat exchanger, chemical addition, valves and instruments



- **Typical CIP Cycle**

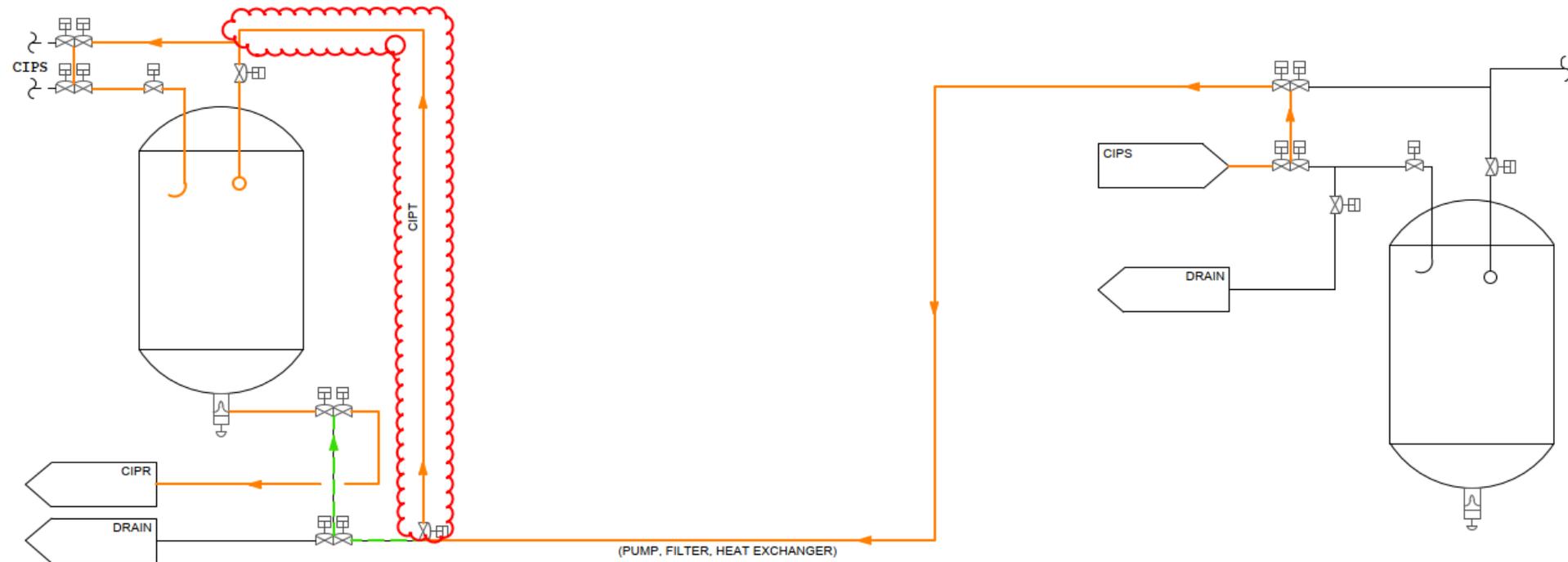
- Pre-rinse (once through)
- Alkaline Wash (recirculated 2-5% chemical wash at elevated temperature)
- Intermediate rinse (once through)
- Acidic wash (recirculated 1-2% chemical wash at elevated temperature)
- Final rinse (once through)

# Improve CIP Efficiency: CIP Circuit Design



## Minimize CIP circuits/lot and integrate process and CIP piping

- CIP all equipment after process step (e.g., combine vessels with transfer lines, multiple vessels)



## • Significant Efficiency gains (4 x 10kL fermentation mAB facility)

- 40-60% increase manufacturing capacity
- Up to 60% fewer CIP cycles per lot
- 40-60% reduction water use and waste
- faster startup, reduction val/reval

# Improve CIP Efficiency: Distribution Piping Design



- CIP skid location close to process
  - Minimize CIPS and CIPR piping lengths
    - Every 15 metres of distance
    - → 30 metres of 2" CIP lines
    - → requires ~50L fill volume
    - → ~ 250 L/CIP cycle (5 phases)



- Sanitary equipment and piping design
  - Sanitary (CIP-able) components
  - Minimize piping branch length
  - Ensure turbulence during CIP Cycle
- Unsanitary design and operation can lead to excessive final rinse volume and time:
  - 2x final rinse volume, can mean ~20% extra water per CIP cycle



# Reduce Purified Water CIP Cycles: Use Softened or RO Water



## Use Purified Water (WFI) for complete cycle

- Final Rinse ~20% of typical CIP cycle
- Other CIP phases ~80% of typical CIP cycle

## Use Softened or RO water for all steps except final rinse can provide ~80% reduction of purified water in CIP

- Replace purified water with water that has some level of treatment
- Reduces purified water generation cost (energy and wastewater)
- 10% water loss in PW
- Additional 10% loss in WFI

# Improve CIP Efficiency: Heat Recovery



## Waste streams at elevated temperature

- Alkaline wash: 65 – 80 °C
- Acidic Wash: 20 – 55 °C
- Final Rinse: 20 – 80 °C

## Waste streams may need to be cooled prior to disposal

- Limitations municipal wastewater and wastewater piping material

## Heat recovery of CIP Waste could be used

- Reuse some energy and avoid cooling load
- Boiler feedwater preheat
- Preheating CIP alkaline wash (would require large wash storage vessel)

Challenging option with complex operations that may only work in certain situations

# Improve CIP Efficiency: Acidic Wash



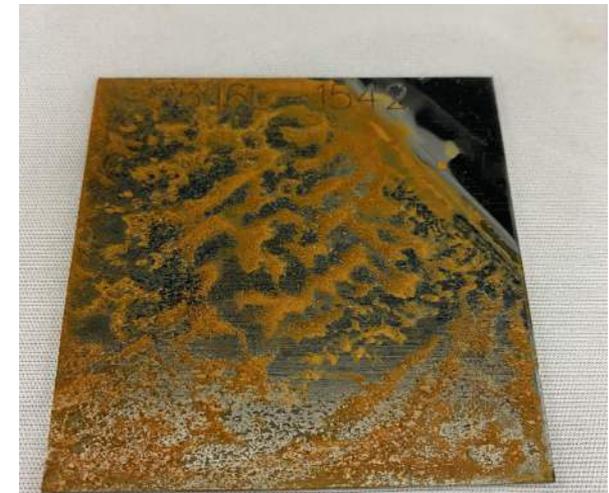
## Purpose of Acid Wash?

- Primary Purpose is Neutralization and demineralization
  - May not be required with certain alkaline wash cleaning agents
- Derouging
  - Can also be handled with periodic maintenance cycle



## Eliminating/Reducing Frequency of Acid wash benefits:

- Water savings (~30% of total CIP cycle)
- ~30% average CIP cycle time reduction
- Add periodic derouging cycles (maintenance)



# CIP Design: Conclusions and Recommendations



CIP cycles have significant impact to sustainability and manufacturing capacity

## Options to improve CIP efficiency:

- Minimize number of CIP cycles per lot
- Utilize softened/RO water for all CIP phases except final rinse
- Reduce acid wash frequency based on performance monitoring
- Evaluate heat recovery of wash and final rinse solution

## Efficiency improvements in CIP:

- Improve sustainability of manufacturing facilities
  - 50-80% reduction in CIP water, purified water, heating load, chemicals, waste
  - Results in 40-60% reduction water consumption for facility
  - Results in reduction in carbon footprint for facility
- Eliminate manufacturing bottlenecks and increase capacity production by 40-60%



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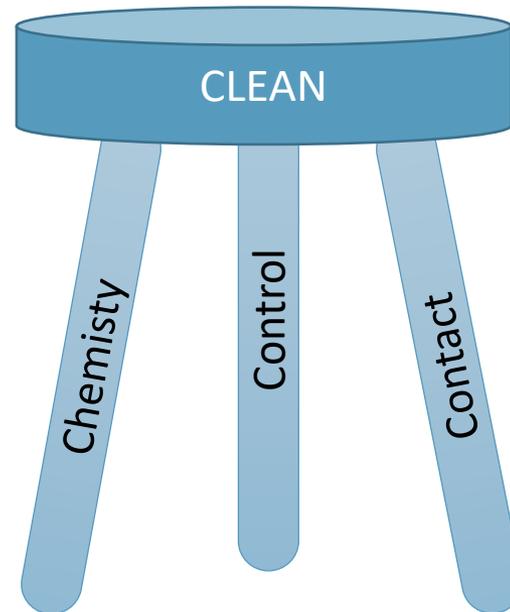
**Investigate**

**Identify**

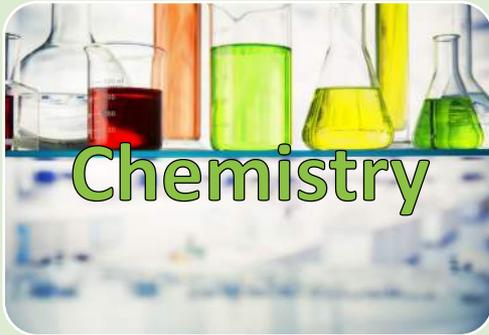
**Instagram**

**Re-Iterate**

Inputs to  
Cleaning?



# 'Raw Material' Inputs to Cleaning



Time  
Temperature  
Cleaning Agent  
Concentration  
Rinse Solution

System Qualification  
CIP Skid  
Manual/COP  
Alarms/Setpoints  
Automation  
Documented  
Processes/SOPs

Sprayballs  
Flowrate  
Pressure  
Loop Design  
Solution/Media



# Improve CIP Efficiency: Cycle Optimization



## Laboratory Studies

- Cleaning agent selection
- Cleaning Design Space Development (TACT)
- **2-3x** reduction in chemicals
- Reduced wash time

## Pre-population CIP recipe parameters

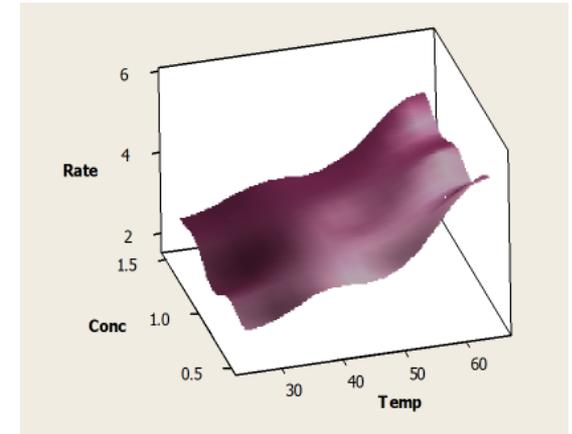
- Utilize Lab studies and hydraulic calcs to pre-populate CIP setpoints
- This can significantly reduce the cycle development time in the field, reducing overall start up timeline
- Faster facility startup

## Cycle development in field

- Confirm pre-populated recipe parameter and adjust to make efficient and robust

## Significant saving can be achieved with this route

- **Large** reduction in water, cycle time and chemicals





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# Site Assessment: Targeted or Open-Ended



## Purpose:

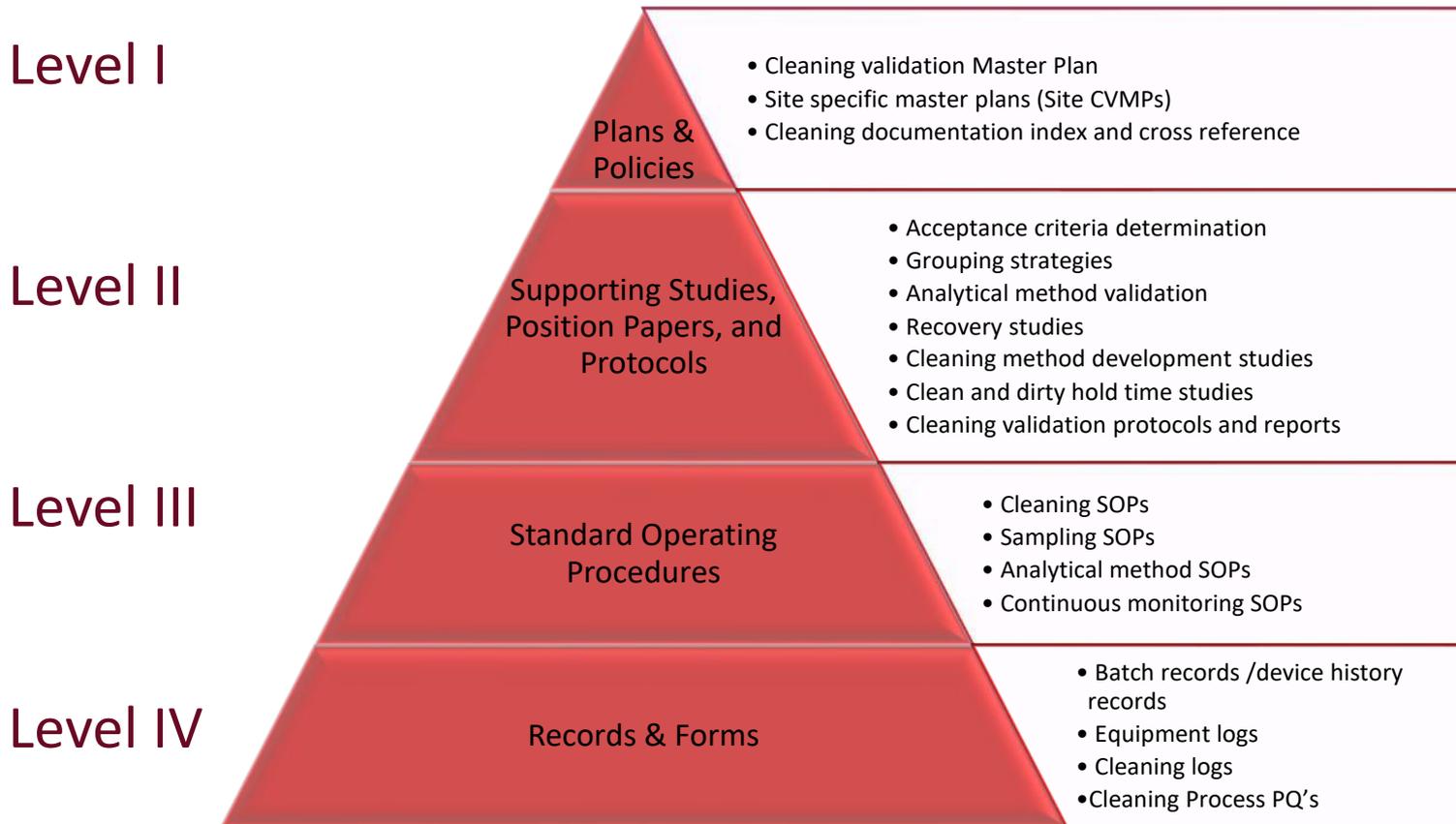
Develop complete understanding of site cleaning processes from daily forms up to global guidance documents, into the past for design and qualification and forward into maintenance, requalification and opportunities presented by incoming products/process changes

## Scope:

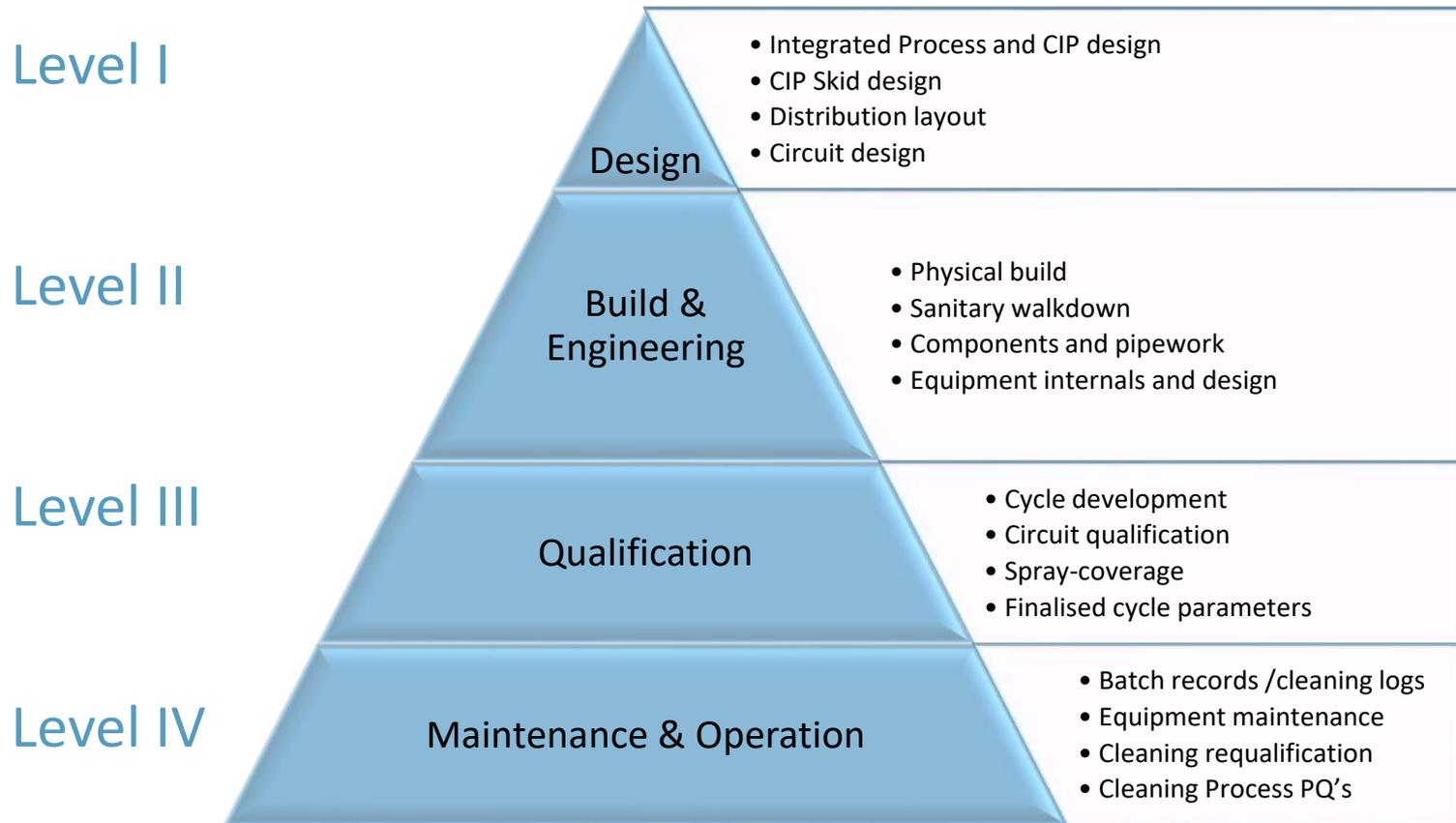
Targeted – reduce exploration depth in some areas/parameters to focus on a specific deliverable for a ‘win’

Open-Ended - find/uncover truths and options the site might have been unaware of, make business case for implementing change – compliance gaps, best practice updating, efficiency, cost, time

# Investigation Philosophy: Chemistry and Control



# Investigation Philosophy: Control and Contact



# Investigation Tools:

## GAP ID

### Physical Examination



Gap Indicator for Easy Sorting & Reporting of Departures from GAP

Critical Program Elements Tied to Regulations and Guidance

Standard Element	Regulatory Reference	Guidance Reference	Applicable	Comments	Document Number/Title	GAP Score
Is there a high level strategic policy or plan that addresses validation?	PIC/S Publication PI-006-3, 4.1.2					
If so, do the high level documents address cleaning or reference a separate document, such as a Cleaning Validation Masterplan that does?		PDA TR 29, Section 9.1 PDA TR 49, Section 9				
Is there a high level policy document that describes the approach to be taken for cleaning and cleaning validation activities within the organization?		PDA TR 29, Section 9.1 PDA TR 49, Section 9				
The following key elements of a cleaning validation program, typically defined and documented are addressed in a <i>Cleaning Validation Master Plan</i> or <i>Equivalent Document</i> .						
An overview of the site program and approach to perform cleaning validation for the equipment used for the manufacture of products intended for human consumption.		PDA TR 29, Section 9.1 PDA TR 49, Section 9				
The high level strategic documents provide a description of facilities, buildings, product classes, and references to plans for the same.		PDA TR 29 and 49				
The overarching strategic document defines a strategy for how Dirty Hold and Clean Hold Times are determined. The document also explains which specific documents or class of documents delineate and define practices surrounding DHT and CHT.		<b>Clean Hold:</b> PDA TR 29 Section 10.4, PDA TR 49, Section 11.10 <b>Dirty Hold:</b> PDA TR 29 Section 3.3.3.2, PDA TR 49, Section 3.5.2, and				

Sections of Questionnaire Echo ISO 9001 Documentation Hierarchy

List for Observations Outside of Structured Queries

Log for Documents Reviewed for Program Assessment



# Discussion Topics

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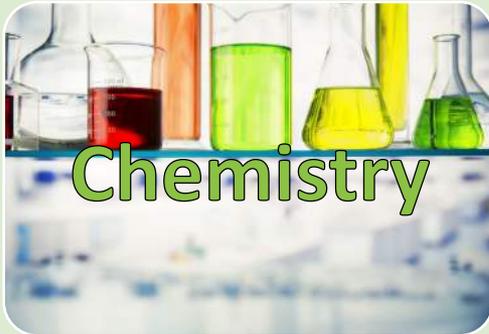
**Investigate**

**Identify**

**Instagram**

**Re-Iterate**

# Identify Areas for Improvement



## Reduce

- Temperature
- Cleaning Agent Concentration
- Cycle Time
- Water Usage



## Confirm & Optimize

- Sanitary Design
- Alarms/Set points accurate/optimized
- Documentation is optimized (remove duplication)



## Confirm & Optimize

- Correct cleaning solutions in place
- Sprayballs are correct design for use
- Turbulent flow is achieved
- CIP circuits are optimized





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# Invigorate - Stakeholders

Sponsor initiated exercise ✓

Investigations complete ✓

Opportunities identified ✓

Invigorate = 3 tasks

1. Quantify the potential gains - business and personal
  2. Design implementation programme
  3. Sell the business case to stakeholders



# Invigorate - Prioritisation

Procedural change

No validation required existing cycle change

Validation required existing cycle change

Engineering change

Capital investment in Infrastructure





# Discussion Topics

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# Implement – Stage Gates

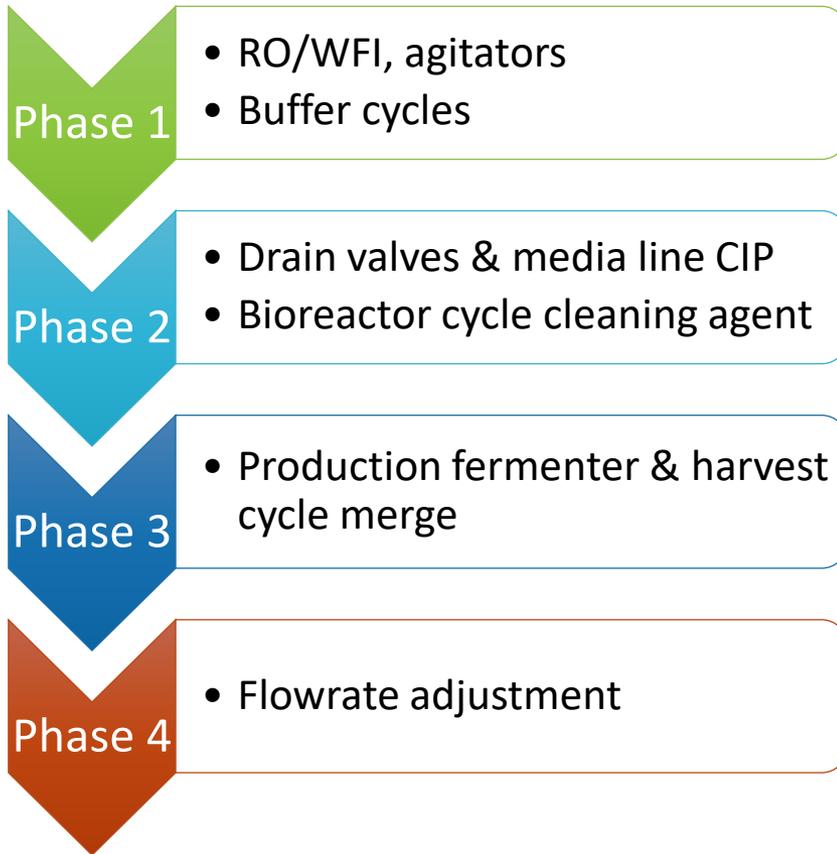
Primary issue will be cost and impact – buy-in

- Start small
- Easy and quick wins
- Demonstrate success
- Loosen budget and resistance to change
- Learn implementation ‘process’
- Think of long-game from the start – facilitate bigger wins



# Implement – Stage Gates

## CYCLE/EQUIPMENT WORKSTREAM



## PROGRAMME & DOCUMENT WORKSTREAM





Discussion  
Topics

**Celebrate**



**#thatwin!**

Own your success

Self-promote

*Why? So that you can do the next project*

Corporate Social Responsibility

Green Agenda

Public Perception



Discussion  
Topics

**RESULTS**

# Case Study 1

**Astellas, Ireland**

**Cleaning Cycle Turnaround?**



# Project & Site Introduction

2 products & equipment train is almost identical and shared

- 2 or 3 synthesis processes
- 2 or 3 crystallization steps
- Drying (intermediate and end)

Campaign manufacture

Continuous increase in market demand

Changeover plans were not meeting their desired planned time.

The cleaning and changeover of both products

- target of a 40 shifts and no repeat cleaning
- taking more than double this, several repeat cleans
- on only one occasion achieved the target





# Cleaning Process Adjustments

- Decoupling of the equipment trains for cleaning
- Equipment cleaned in parallel
- Re-Use of solvent from Step A in Step B pre-clean removed
- Most effective cleaning solvents selected
- Boil times were examined and reduced
- Solvent volumes used in cleaning updated

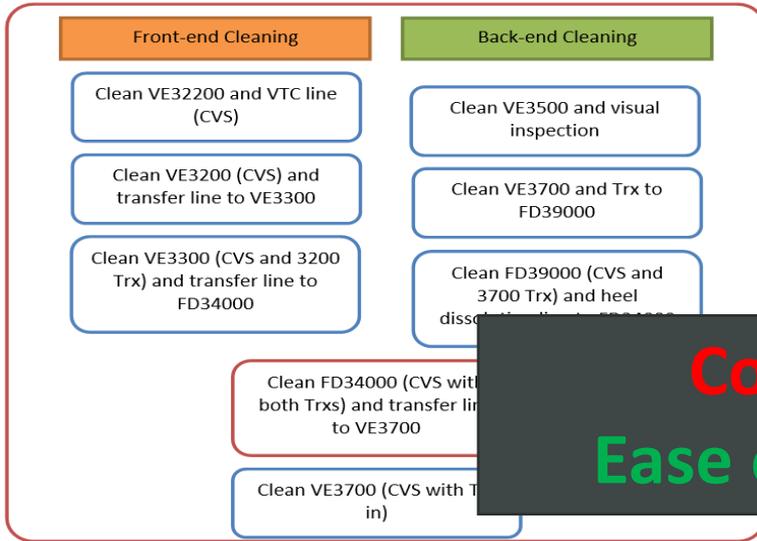


# Cleaning Record & Protocol

- The Cleaning Instruction Record (CIR) was split into 6 individual CIR's
- The Cleaning Verification Protocol documents were amalgamated into these CIRs.
- Removed the key wastes
- Incorporated the improvements
- Aim to improve cleanability and to increase the flow of the process
- Overall size of document was decreased



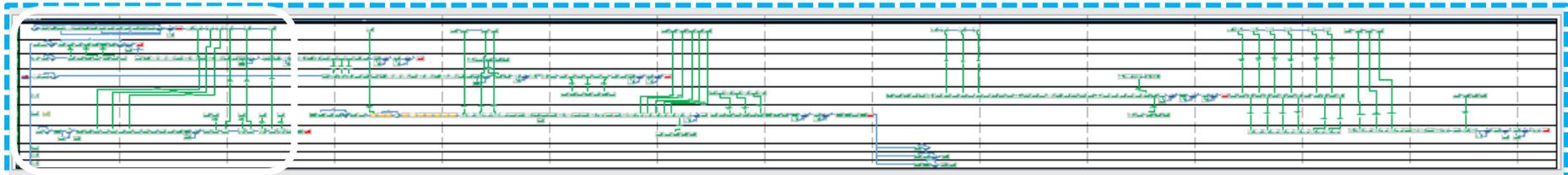
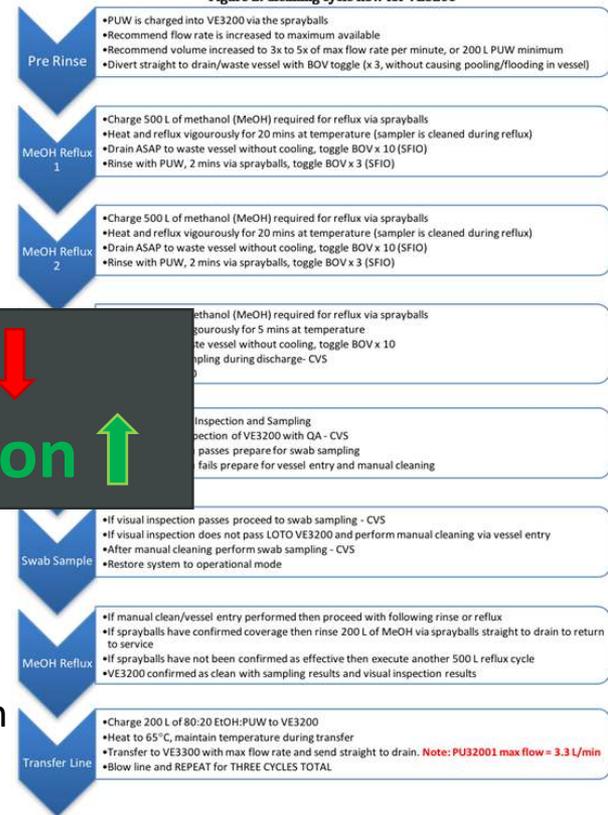
# Cleaning Process Flow ReBuild



Simplified Executive Overview,  
Parallel Workstreams

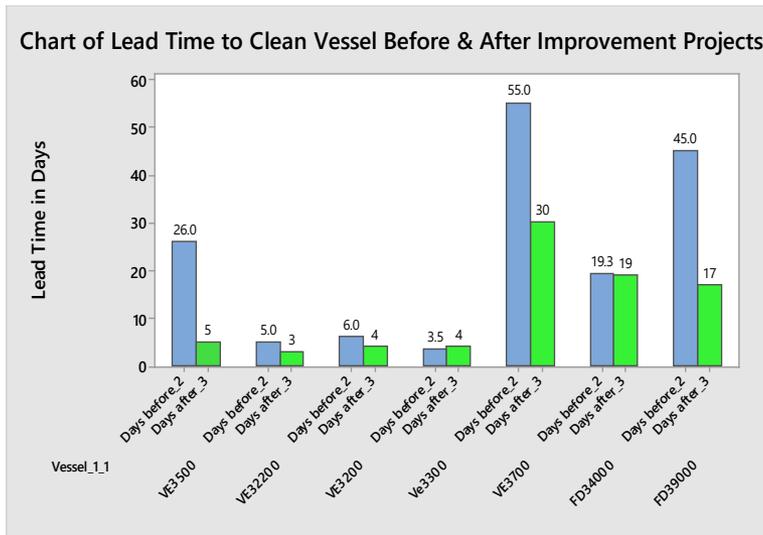
Simplified Detailed flow in  
Protocol for Execution

Figure 2: Cleaning cycle flow for VE3200



# Results

- Solvent usage 
- Boil time significantly reduced (up to 80%) 
- Failures eliminated in both VI and Sampling processes 
- Vessel entry was virtually eliminated 
- QC and QA engagement levels reduced 
- **Additional Batch Starts: up to 28**



Relevant Equipment System(s)	Aspect of Cleaning Assessment	2016 Results	2018 Results
VE-32200	Visual	Pass	Pass
VE-3200	Rinse	Fail	Pass
	Visual	Pass	Pass
	Swab	Pass	Pass
VE-3300	Rinse	Pass	Pass
	Visual	Fail	Pass
	Swab	Pass	Pass
FD-34000	Rinse	Fail	Fail*
	Visual	Fail	Pass
	Swab	Pass	Pass
VE-3500	Visual	Fail	Pass
VE-3700	Rinse	Pass	Pass
	Visual	Pass	Pass
	Swab	Pass	Pass
Misc Equip	Visual	Fail	Pass
FD-39000	Rinse	Pass	Pass
	Visual	Fail	Fail**
	Swab	Pass	Pass
CU-39000	Visual	Pass	Pass

\* TF-001 CVP/PRD/P2/035 FD34000 Rinse

\*\* TF-001 CVP/PRD/P2/037 FD39000 Visual



# Case Study 2

**Lonza, Spain**

**Install Additional Clean Utilities**



# Starting Issue

## Multi-product biologics facility

- Additional product incoming
- Increasing demand for existing product
- PW and WFI generation at max
- Waste treatment facility at max
- Find ways to increase capacity



# Phase 1 Key Focus – Water Consumption by CIP

Identified several opportunities to reduce water usage during CIP

- Pre-rinse
- Agitator Immersion
- Intermediate rinse
- Pre-final rinse
- Final rinse

But how to deliver?

- Production schedule is full
- Upcoming validation
- Right first time required
- Impact on existing product matrix



# How to Deliver?

## Statistical Leveraging of Existing Data

- Facility had been in production for many years
- MCS tracks data continuously as part of process monitoring
- Limitations of success can be read directly from existing data

### Method:

- Site quality engineers provide data
- External independent team extract and document key process data
- Intermediate SMEs verify data extraction
- CIP SMEs tabulate and perform statistical analysis
- Verification run at scale during product introduction



# Results

- Reduced water consumption by 29 %
- Prevented capital investment in additional utility infrastructure
- Enabled takt rate increase from 3.5 to 4.5 batches/week

## Key Inputs –

- Detailed site assessment
- Site was willing to try something new
- Remote, blind statistical analysis



# Case Study 3

## **Singapore, Biologics**

**We cannot achieve Takt rate!**



# CIP Optimization Case Study

## Overview

- Cell culture facility in Singapore (6 x 10K Bioreactors)
- 3 upstream and 2 downstream production lines
- Fixed stainless steel equipment cleaned by CIP Skids

## Problems

- CIP cycles fail to meet contact times. Repeated cycles run.
- CIP failures due to flow alarms
- Reduced production capacity due to excessive CIP duration
- Huge consumption of WFI and CIP chemicals



# Major Issues

Hyde team performed site assessment and underlying issues were identified

- Too many CIP circuits
- Too many sub-paths in each CIP circuit
- Inadequate flow control
- Once-through” CIP circuits wasting wash solution



# Solution: Combined CIP Circuits

- Consolidation of CIP circuits to reduce overall quantity
- Equipment circuits combined with process line circuits
- Total circuits reduced from  $> 200$  to  $<100$



# Solutions: Flow control

- Existing system poor flow control, wasteful of CIP fluids.
- Added flow control using VSD on CIP supply pump
- Eliminated problematic flow control valve and CIP bypass from system
- Allowed for efficient start up and commissioning of CIP cycles

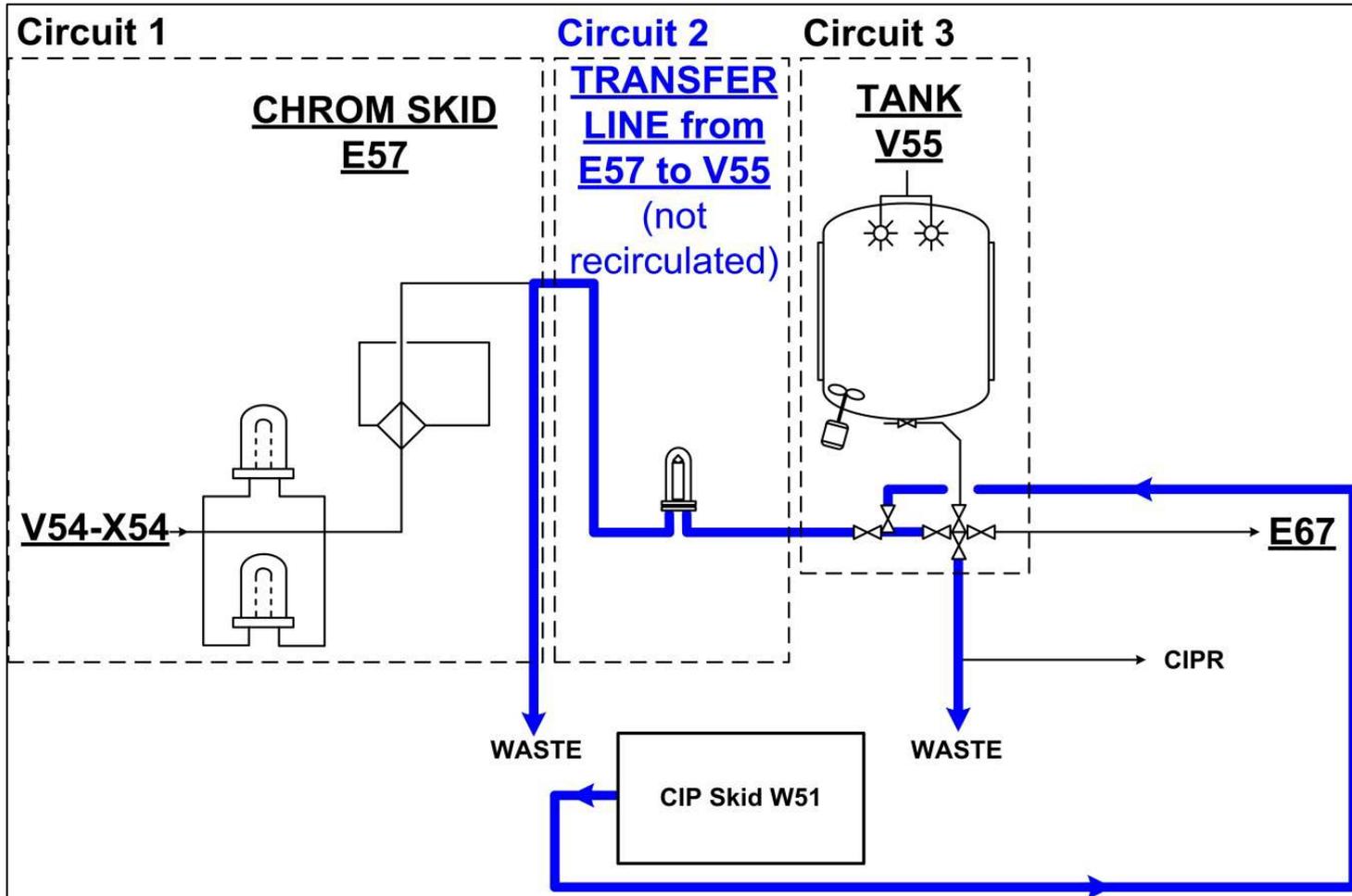


# Solutions: Flow path optimization

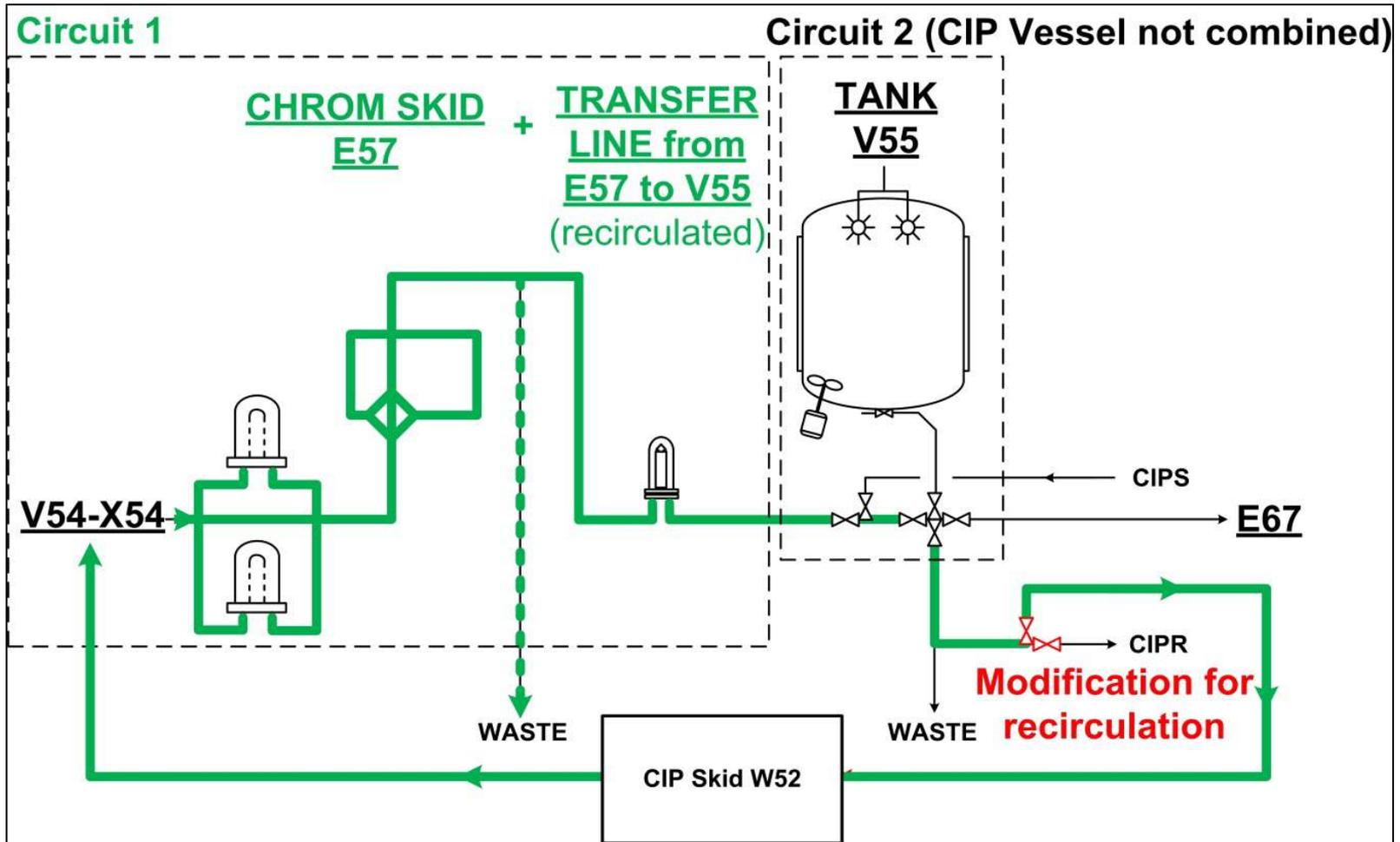
- Existing circuits cycle through many paths, time consuming.
- Hydraulic analysis performed to identify optimal combinations of flow paths.
- Single flowrate for all paths to reduce stress on supply pump
- Flow paths sequenced to avoid pressure spikes in transitions.
- Reduction in cycle duration and rinse volumes realized.



# CIP Circuit Pre-Optimization



# CIP Circuit Post -Optimization



# Results & Recommendations

## Results

Per annum savings

- 40 million litres WFI
- 400,000 litres CIP-100
- 20,000 hours of CIP running time

## Recommendations

- Don't leave CIP circuit design too late!
- Upfront hydraulic analysis saves time in commissioning





## Q & A

Thank you.

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