CIP Optimization

Design, Implementation and Operation

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HYDE ENGINEERING OVERVIEW

- Bioprocess and GMP Manufacturing Focus
  - Process Engineering
  - Commissioning/Qualification
  - Cleaning/Process Validation
  - Compliance Engineering
- Highly Experienced staff
- Client Focused
- Founded 1993
- 275+ Staff, Engineers & Scientists
- 12 Offices - 6 in US, Ireland (2), Belgium, India (2), Singapore

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Phases of CIP Implementation

- Concept Design
  - Process/Facility Requirements and Constraints
  - Cycle Requirements
- Detailed Design
  - CIP Skids
  - CIP Circuitry
- Commissioning/Cycle Development
  - Skid Operations
  - Circuit Flow Paths
- Cleaning Validation
  - Initial Testing at Commercial Scale
  - Ongoing Monitoring of Cleaning Performance
- Benefits of Efficient CIP Design

CIP Concept Design

CIP Concept Design

- Process Requirements
  - Unit Operations
  - Interconnecting Piping
  - Containment/Contamination Control Requirements
    - Bio-Safety Level
    - Pre/Post Virus Removal
  - Production Targets (e.g., Lots/Year, Changeovers, etc.)
- Facility Constraints
  - PW and WFI Supply
  - Drain Capacities and Waste Treatment Requirements
  - CIP Skid Location and Space Requirements
    - Skids Preferably Located at or Below Elevation of Process Equipment Being Cleaned

CIP Concept Design

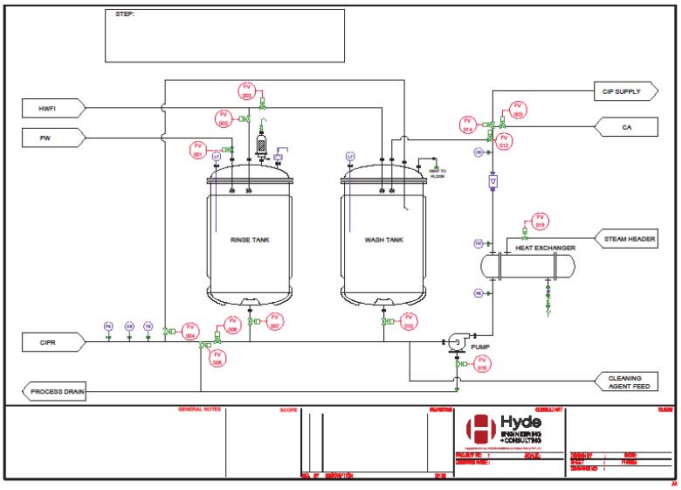
- CIP Cycle Requirements
  - Water Only Versus Chemical Cleaning
  - CIP Cycle Time Targets
    - Typically 2 Hours for Full Chemical CIP and 45 Minutes for Water Only Cycle
- Cleaning Efficiency Goals
  - Minimization of Water (PW and WFI) Consumption
  - Minimization of Cleaning Agent Consumption
  - Minimization of Waste Streams
  - Minimization of Number of Cleaning Cycles per Lot

CIP Detailed Design

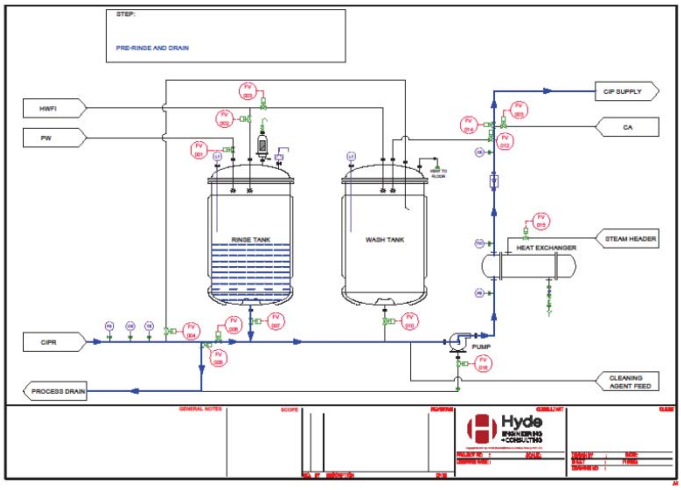
CIP Detailed Design

- CIP Skids
  - Tankage Requirements
    - Number of CIP Skid Vessels
    - Size of CIP Skid Vessels
    - Vessel Pressure Rating Requirements
  - Wash Solution Make-Up Methodology
    - Batching of Cleaning Solutions in the CIP Skid Tank
    - Formulation of Cleaning Solutions in the Cleaning Circuit
  - Control of Cleaning Critical Control Parameters
    - Required for Effective Cleaning
    - Required for Repeatable and Reliable Cleaning
    - Required for Efficient Cleaning

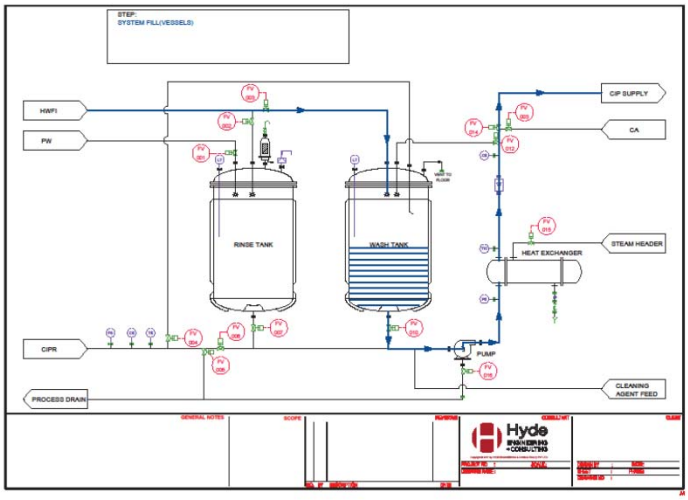
Typical CIP Skid P&ID



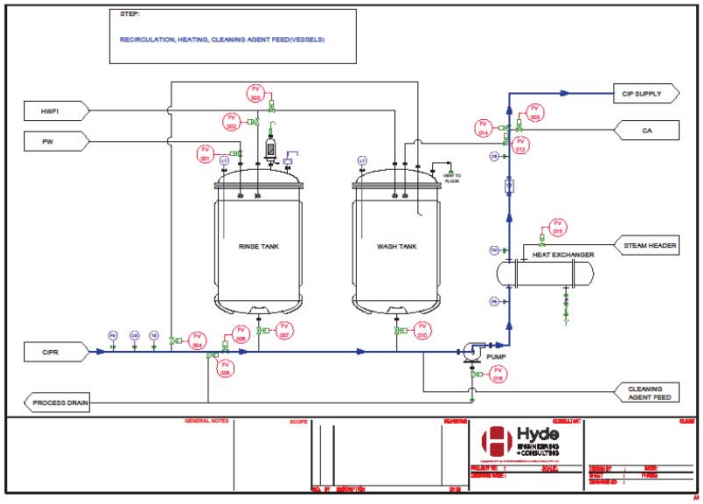
CIP Skid – Pre-Rinse and Drain



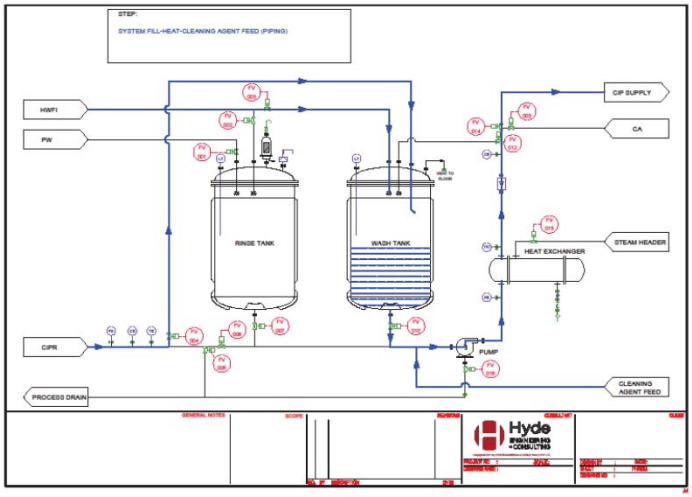
CIP Skid – System Fill Vessels



CIP Skid – Recirc, Heat and Cleaning Agent Feed - Vessels



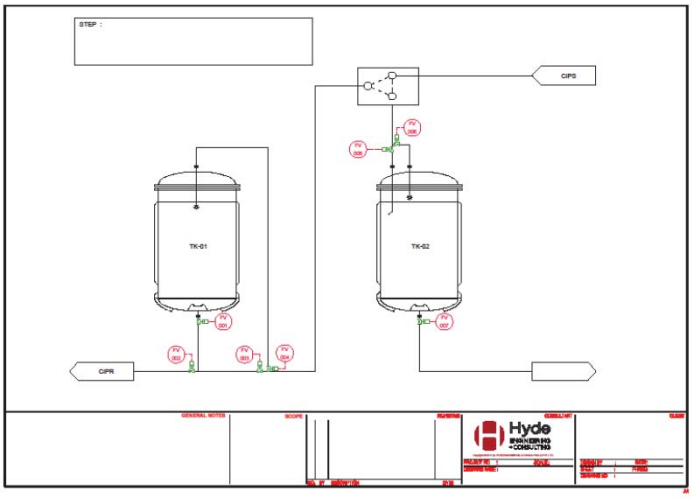
CIP Skid – Recirc, Heat and Cleaning Agent Feed - Piping



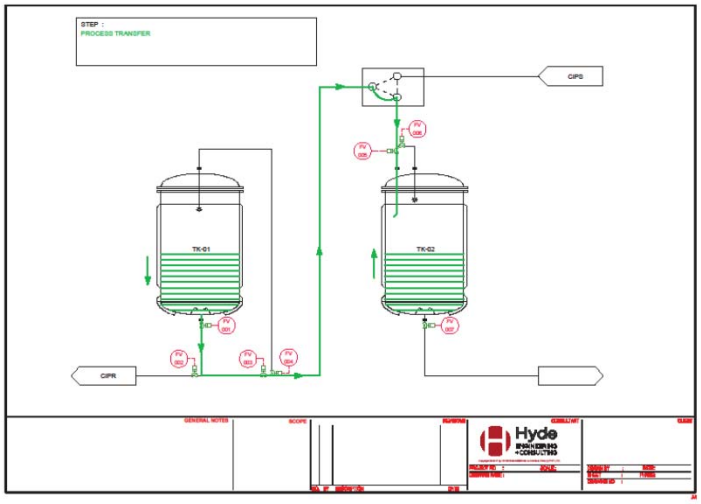
CIP Detailed Design

- CIP Circuitry
  - Cleaning of Vessels
  - Cleaning of Interconnecting Piping
    - Piping is Often Cleaned Independently from Vessels
    - Results in Increase of Cycles Per Lot Requirement by Factor of 2 to 3
    - Often Results in Significant Increase in Valves Required due to Leak Protection
  - Circuitry Layout Strategies
    - Clean Vessels with Outlet Piping in Reverse Flow
    - Clean Filter Housings Inline
    - Ultimate goal is to Have no Circuits That are Just Piping
    - Clean and Dirty Hold Time Considerations

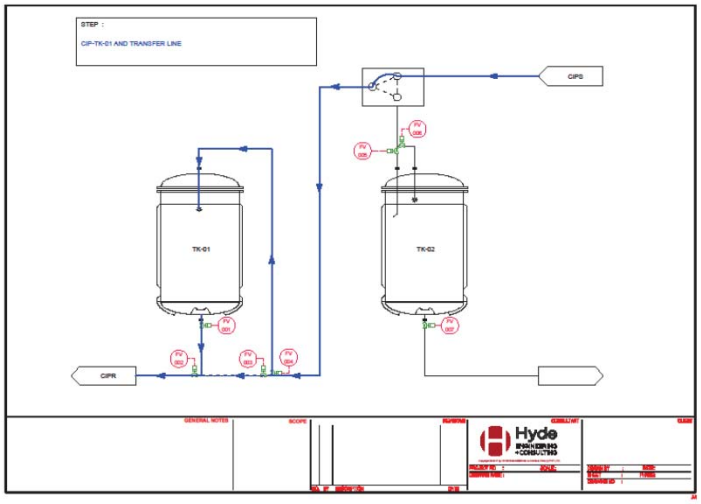
Process Vessels P&ID



Process Vessels – Process Transfer



Process Vessels - CIP



CIP Commissioning and Cycle Development

Commissioning and Cycle Development

- Determination of Cleaning Critical Control Parameters (CCCPs)
  - Supply Flow Rate
  - Supply Pressure
  - High Range Conductivity
  - Low Range Conductivity
  - Cleaning Solution Temperature
- Establishment of Cycle Setpoints
  - Rinse Durations
  - Wash Durations
  - Airblow/Drain Durations

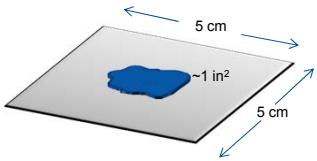
Establishment of CCCPs at Lab Scale

- Test Plan
  - Author an experimental test plan describing the approach used to conduct bench scale cleaning process developmental studies for post production residues
- Cleaning Agent Selection
  - Test each residue using a designed experiment to screen alkaline, neutral, and acidic post production residues over a range of typical cleaning process temperatures to determine an appropriate cleaning agent for a particular post production residue

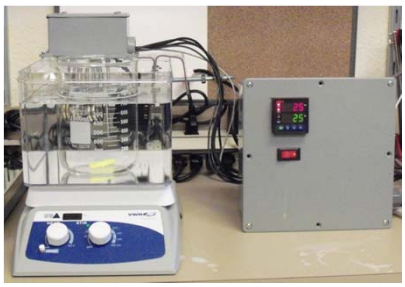
Establishment of CCCPs at Lab Scale

- Cleaning Process Design Space Exploration
  - Using the appropriate cleaning agent, explore combinations of temperature, turbulence, and concentration to assess the response of removal rate over typical ranges of these process variables via a DOE based study
- Worst Case Residue Evaluation
  - Compare the removal rates of selected post production residues to empirically determine which are worst case with respect to the cleaning process

Establishment of CCCPs at Lab Scale



- Consistent soiling
  - Amount of material
  - Reproducible surface area
  - Control "Dirty Hold Time"



•Cleaning Process Control

•PID Temperature Control

•Controlled Agitation

•Precisely Formulated cleaning solutions

Determining Reynolds Number

ρ- density
μ- viscosity
N – Impeller speed in revolutions per second
D – Impeller Diameter

$N_{Re} < 2100$ Laminar

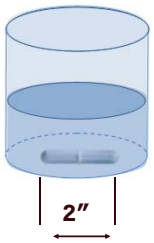
$N_{Re} > 3000$ Turbulent

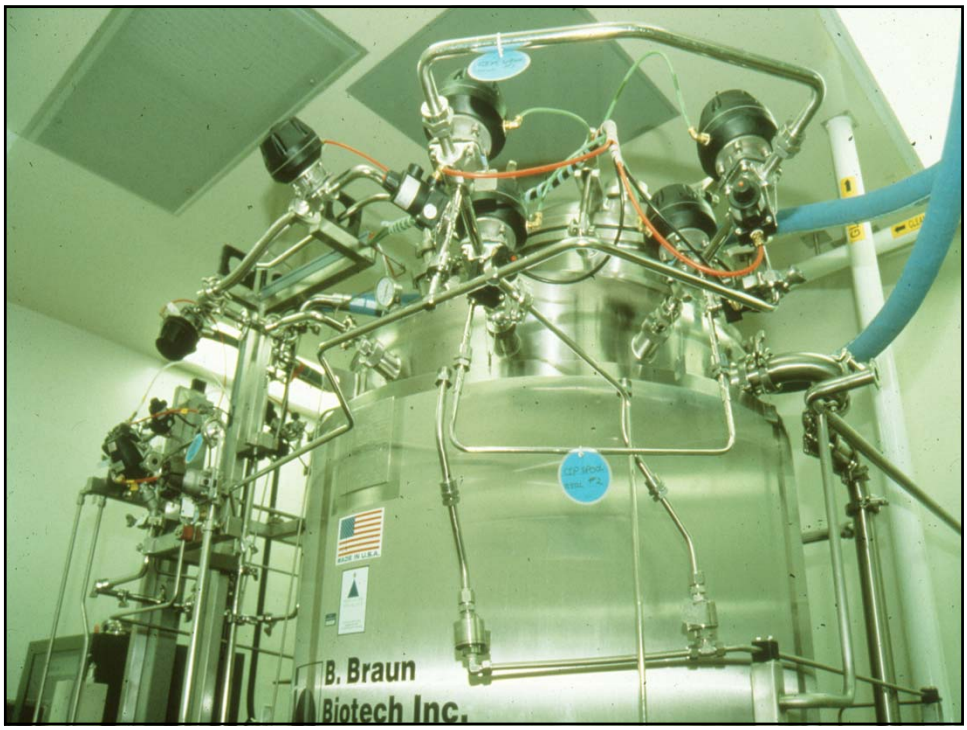
Example:

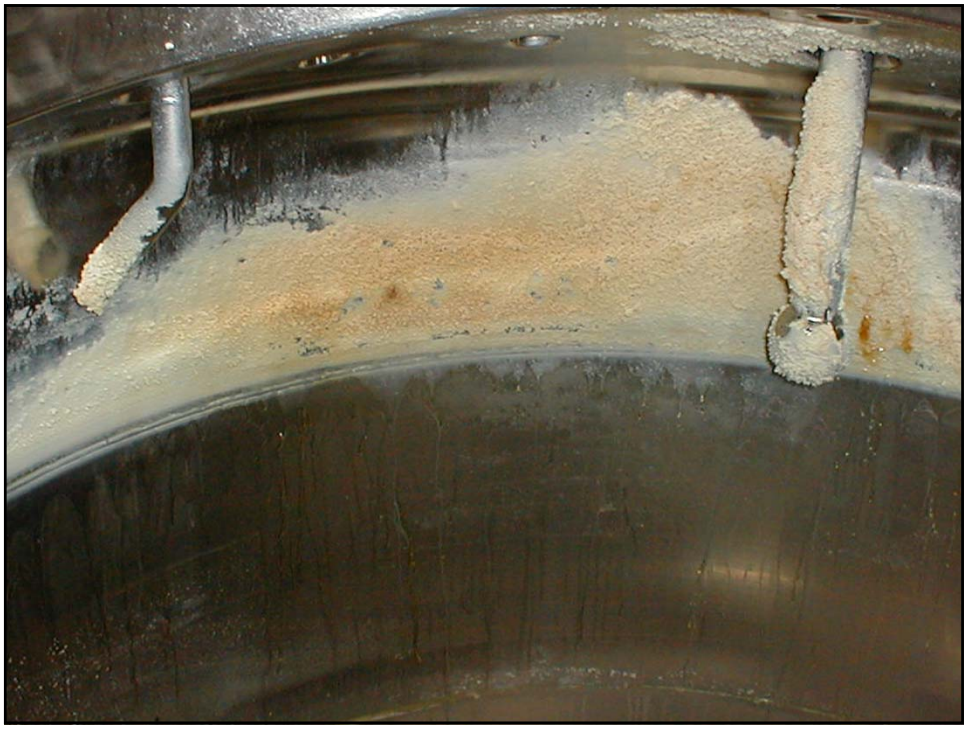
T=25ºC
D = 2" (0.0508 m)
ρ = 997 (kg/m^3)
μ = 0.0089 poise
N = 64 rpm (1.07 rps)
N_{Re} = 3082

Agitated Immersion:

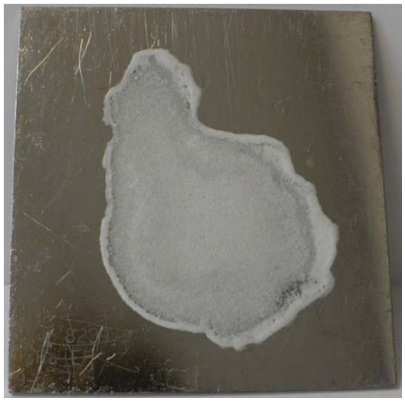
$$N_{\mathrm{Re}} = \frac{D^2 N \rho}{\mu}$$







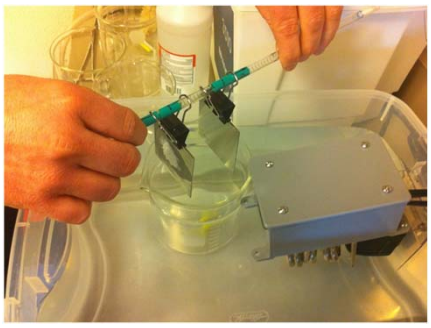
Coupon Soiling

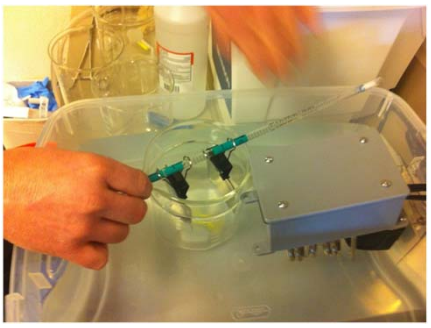


Representative Post-Production Residue Applied to Coupon

Soiled Coupon Dried to Simulate Post-Production Conditions

Coupon Testing





Gravimetric Assessment

Laboratory Microbalance

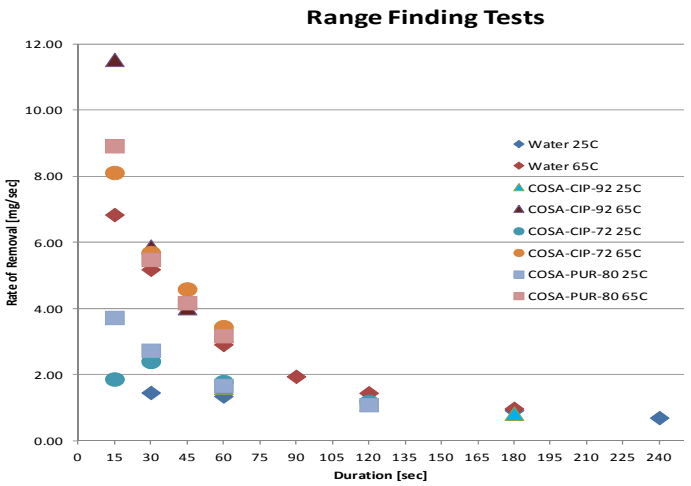
Accuracy ±0.00005 grams

Tare mass of coupons

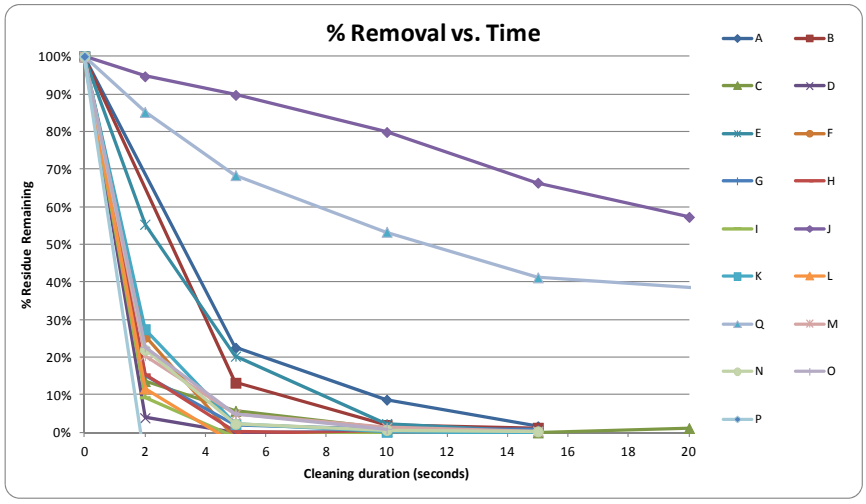
Amount of residue spiked on coupons

Amount of residue remaining after cleaning assessment

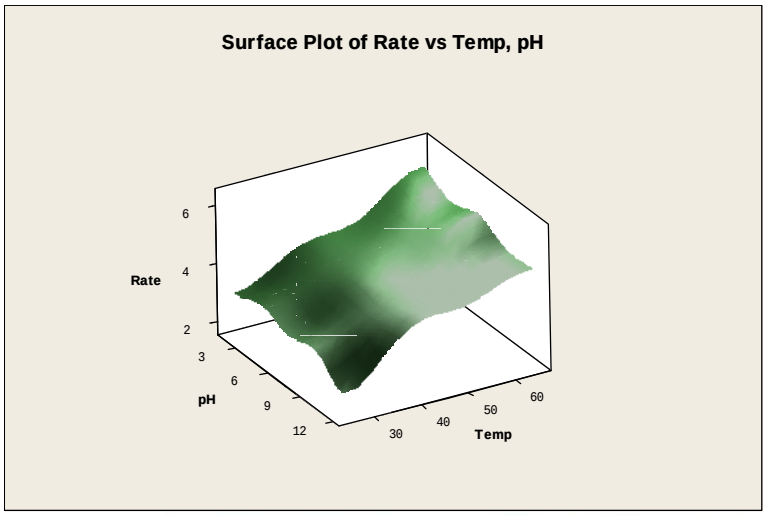
Range Finding Results



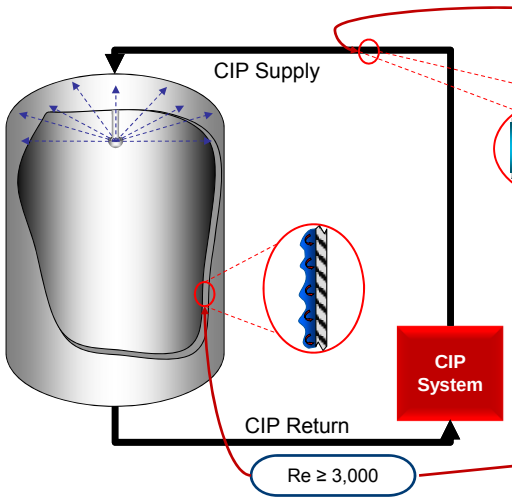
Worst Case Residue Identification



Surface Response Plot



Establishment of CIP Setpoints for Cleaning Vessels and Piping



Variable	Low Level (-)	High Level (+)
Concentration	1%	2%
Temperature	25°C	65°C
Energy N_{Re}	3,000	34,000

Commissioning and Cycle Development

- Protein Containing Residues
  - Full CIP (Rinses, Alkaline Wash and Acid Wash)
- Buffer Containing Residues
  - Typically Rinse Only
  - Periodic Full CIP for Maintenance Purposes
- Cleaning Cycle Critical Parameters Grouped by Residues
  - Media, Buffer, Cell Culture and Harvest, and Purification
  - Residue-Based CCCPs Provide for More Effective and Economical Cleaning
  - "One Cycle Fits All" Approach Very Inefficient and my also be Ineffective

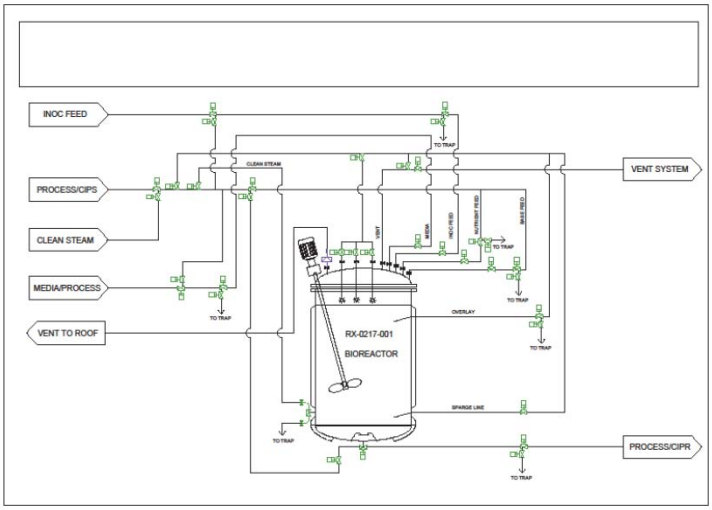
Cycle Development at Commercial Scale

- Input of Critical Cleaning Control Parameters (CCCPs)
  - Analysis of CIP Cycle Operational Sequence
  - Input of CIP Cycle Parameters into Control System Setpoint Format
- Hydraulic Balancing Equally Important to Implementation of CCCP Values
  - CIP Supply and Return Flow Rates Must be Equal
- Cleaning Efficacy Confirmed with Concurrent Process Validation and Cleaning Validation Runs

Bioreactor Example

- Not all components may be cleaned simultaneously
  - Many components to be cleaned in this complex CIP Circuit
    - Cleaning vessel with sprays
    - Cleaning multiple lines to bioreactor
  - CIP system can only provide a limited flow rate to the bioreactor
  - Bioreactor has limited drain rate
- Clean components in sets with toggle sequences:
  - Toggle CIPS valves to clean sets
  - Clean all sets of components sequentially
  - Use short toggle times and repeat toggles to get required contact time
  - Base Exposure Times for Piping on Residue to be Removed
    - Gas Lines Versus Product or Media Containing Lines

Bioreactor Example



Cleaning Validation

Cleaning Validation Trends

- Utilization of FDA 2011 Process Validation Guidance Approaches for Bases of Cleaning Validation Program
- Extensive Utilization of Risk Analysis and Management to Establish Focus Areas for Cleaning Validation and Ongoing Monitoring
- Development of Existing and New In-Process Material Residue Matrix from Laboratory and Pilot Scale Cleaning Data
- Usage of Residue Matrix Data for Determination of Extent of Full Scale Cleaning Validation Testing (e.g., Utilization of Laboratory Derived Data and Residue Matrices Rather Than Three Full-Scale Runs for Validation of Cleaning for New Products)

Cleaning Validation Trends

- Generation of Product Inactivation Data to Justify Analytical Methodologies and Residue Limits for Multi-Product Facilities
- Residue Limits not Based Upon MAC Calculations Unless Residues Contain Significant Levels of Active Drug Product
- Usage of PAT Methodologies and Data for Basis of Initial Cleaning Validation Studies and On-Going Monitoring for Defining Re-Validation Requirements

Multi-Product Cleaning Validation Trends

- Re-Use of Elastomers Between Manufacturer of Different Products
- Utilization of “Normal” Cleaning Cycles Between Manufacturer of Different Products
- Limited Cleaning Verification Between Manufacturer of Different Products if Justified by Existing Lab and Pilot Scale Cleaning Data

Benefits of Efficient CIP Design

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Case Study – Mab Facility

- CIP Systems
  - Large CIP Vessels Sized to Batch CIP Solutions
  - CIP-100 Only Cleaning Agent Used
- CIP Circuits
  - Piping and Vessels Cleaned Separately
  - Piping Circuits Cleaned “Once-Through”, e.g., CIP-100 Solution Not Recirculated
- Performed Optimization Study
  - Analyzed CIP Parameters and Operational Sequences
  - Combined Piping and Vessel Cleaning
  - Eliminated Once-Through CIP-100 Washes

WFI Consumption

Operational Mode	Number of Cycles Per Lot	WFI Usage (L) Per Lot	Number of Lots per Year	WFI Usage (L) per Year
Vessels and Piping Cleaned Separately	70	816,000	120	100,368,000
Vessels and Piping Cleaned Separately Optimized	70	530,400	120	65,239,000
Vessels and Piping Cleaned Together	30	408,000	120	50,184,000
Vessels and Piping Cleaned Together Optimized	30	269,000	120	33,121,000

WFI Consumption

Operational Mode	Number of Cycles Per Lot	Skid Usage (H) per Lot	Number of Lots per Year	Skid Usage (H) per Year
Vessels and Piping Cleaned Separately	70	408	120	50,190
Vessels and Piping Cleaned Separately Optimized	70	238	120	29,275
Vessels and Piping Cleaned Together	30	224	120	27,600
Vessels and Piping Cleaned Together Optimized	30	149	120	18,380

WFI Consumption

Operational Mode	Number of Cycles Per Lot	CIP-100 Usage (L) Per Lot	Number of Lots per Year	CIP-100 Usage (L) per Year
Vessels and Piping Cleaned Separately	70	5,900	120	736,000
Vessels and Piping Cleaned Separately Optimized	70	3,950	120	482,950
Vessels and Piping Cleaned Together	30	2,600	120	324,720
Vessels and Piping Cleaned Together Optimized	30	1,750	120	213,070

Questions?

Please use the microphone indicated so our recording includes audio of your question

Contact Information

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