January 2017 Program

Case Study - New High Purity Water System Technologies Deliver Reliability & Sustainability for GSK
PRESENTERS

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- **TED DOMBROWSKI, Senior Project Engineer, Arcadis (on behalf of GSK)**
- **ROBERT HOEPPNER, Project Executive, Henderson Constructors, Inc.**
- **MIKE BILLUPS, Project Manager, Henderson Constructors, Inc.**
INTRODUCTION: BACKGROUND

CTM (Clinical Trial Materials) Facility

Manufactures purified drug substances for clinical trials worldwide
INTRODUCTION: BACKGROUND

- Insufficient Capacity for Future Expansion or Production Increase
- Costly Systems Not Energy Efficient
- Parts no longer Available
- Increased Plant downtime Risk due to insufficient equipment reliability

Existing HPW & WFI Systems Obsolete
INTRODUCTION: BACKGROUND

Project Scope

Replace 2 Obsolete Water Systems

HPW
High Purity Water
- New Reliable System Design
- Supply HPW to Biopharm Development Pilot Plant

WFI
Water for Injection
- Change System Configuration from 3 to 2 Pumps
- Replace WFI Control Panel
- Install Redundant VC Stills
INTRODUCTION: OBJECTIVES

PROVIDE RELIABILITY THROUGH REDUNDANCY

DELIVER SUSTAINABILITY
REDUCE WATER & ENERGY USAGE

INCREASE SUPPLY & STORAGE CAPACITY

REPLACE OBSOLETE EQUIPMENT

NO IMPACT TO ON-GOING OPERATIONS
INTRODUCTION: OBJECTIVES

RELIABILITY THROUGH REDUNDANCY

HPW
- Multi-Media Filters
- Softeners
- Carbon Filters
- RO/CDI Skid
- Tank Nitrogen Filters
- Distribution Pumps

WFI
- Vapor Compression Stills
- Tank Vent Filters
- Distribution Pumps

No Unplanned Downtime

re·dun·dant
serving as a duplicate for preventing failure of an entire system
INTRODUCTION: OBJECTIVES

INCREASE SUPPLY & STORAGE CAPACITY

CLINICAL TRIALS
- Need to be Adept & Flexible
- Accommodate Emerging Technologies in Manufacturing

HPW
- Generation and Storage Capacity
- Insufficient during Maintenance Activities

WFI
- Generation Capacity Bottlenecked
- Required Daily Water Usage Planning Activities

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INTRODUCTION: OBJECTIVES

OBSOLETE EQUIPMENT

Reverse Osmosis Pre-Treatment System (Built c.1987)

FRP High Purity Water Storage Tank 2000 Gallon (Built c.1987)
INTRODUCTION: OBJECTIVES

OBSOLETE EQUIPMENT

Multi-Effect WFI Still (5 MEF) (Built c. 1987)

(3) WFI Distribution Pumps
One pump on each floor
(Spares in Warehouse)
INTRODUCTION: OBJECTIVES

OBSOLETE EQUIPMENT

Softener Regeneration
Brine Tank

Softener Regeneration
Salt Pellets
Palletized 40 lb bags
Consumed 400-800 lb/day
# INTRODUCTION: OBJECTIVES

## NO IMPACT TO ON-GOING OPERATIONS

<table>
<thead>
<tr>
<th>Building 38</th>
<th>Building 5</th>
<th>Building 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopharm GMP Clinical Trial Production Manufacturing</td>
<td>Biopharm Development Pilot Plant</td>
<td>Safety Assessment Manufacturing</td>
</tr>
</tbody>
</table>

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INTRODUCTION: CHALLENGES

- LIMITED SPACE
- IMPACT TO ON-GOING OPERATIONS: PHASED APPROACH
- VENDOR COMMITMENT FOR EQUIPMENT DELIVERY
- INSTALL WINDOW & AVAILABLE DOWNTIME
- WFI CONTROL PANEL CHANGE OUT
INTRODUCTION: CHALLENGES

BUILDING 38
EXISTING MECHANICAL ROOM

Generation Equipment
Utilities
Access
EXECUTION

Introduction
- Background
- Objectives
- Challenges

Execution
- Design
- Construction
- Qualification

Results
- Benefits
- Lessons Learned
- Summary

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EXECUTION: DESIGN

VISIT OTHER GSK SITES

EQUIPMENT EVALUATION

SUSTAINABILITY EVALUATION

PROJECT LOCATIONS & CONSTRAINTS
EXECUTION: DESIGN

Other Site Tours (Gemba)

Site 1: Christ System

Site 2: Siemens: PreVUE®
# EXECUTION: DESIGN

## EQUIPMENT EVALUATION

<table>
<thead>
<tr>
<th>Options</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPW</strong></td>
<td></td>
</tr>
<tr>
<td>Single Pass vs. Double Pass RO</td>
<td>Single Pass</td>
</tr>
<tr>
<td>Polisher vs. None</td>
<td>Install Polisher</td>
</tr>
<tr>
<td>Carbon vs. Bi-sulfite vs. UV Light Filtration</td>
<td>Carbon Filtration</td>
</tr>
<tr>
<td>Service Type vs. Back Washable Carbon Filters</td>
<td>Back Washable</td>
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<tr>
<td>Hot Water vs. Chemical Sanitization</td>
<td>Hot Water Sanitization</td>
</tr>
<tr>
<td>FRP vs. SS HPW Storage Tank</td>
<td>SS Tank</td>
</tr>
<tr>
<td>High Recovery RO vs. None</td>
<td>High Recovery RO</td>
</tr>
<tr>
<td>Nitrogen Blanket on Storage Tank vs. None</td>
<td>Nitrogen Blanket</td>
</tr>
<tr>
<td>Bulk Brine vs. Day Tank</td>
<td>Both</td>
</tr>
<tr>
<td>Redundant vs. Single Storage Tank Filters</td>
<td>Redundant Filters</td>
</tr>
</tbody>
</table>
## EXECUTION: DESIGN

### EQUIPMENT EVALUATION

<table>
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<tbody>
<tr>
<td><strong>WFI</strong></td>
<td></td>
</tr>
<tr>
<td>Vapor Compression vs. Multi Effect</td>
<td>Vapor Compression</td>
</tr>
<tr>
<td>Separate Pump per Floor vs. Redundant Pumps</td>
<td>Redundant Pumps</td>
</tr>
<tr>
<td>Redundant vs. Single Storage Tank Filters</td>
<td>Redundant Filters</td>
</tr>
</tbody>
</table>
### EXECUTION: DESIGN

#### SUSTAINABILITY EVALUATION

<table>
<thead>
<tr>
<th></th>
<th>Single Pass RO</th>
<th>Single Pass RO with CDI</th>
<th>Double Pass RO</th>
<th>Double Pass RO with CDI</th>
<th>SPRO/DI followed by VC stills</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment Costs, estimated:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pretreatment Equipment</td>
<td>$800,000</td>
<td>$1,150,000</td>
<td>$1,200,000</td>
<td>$1,400,000</td>
<td>$804,000</td>
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<tr>
<td>WFI Still</td>
<td>$525,000</td>
<td>$525,000</td>
<td>$535,000</td>
<td>$535,000</td>
<td>$1,071,000</td>
</tr>
<tr>
<td>Total Equipment Cost</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operating Costs per day, estimated:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• <strong>Standard Operation</strong> with recirc and hot water sanitization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Standard Operation (note 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• <strong>Start/Stop Operation</strong> (Siemens S-3)</td>
<td></td>
<td></td>
<td></td>
<td>$601</td>
<td>$632</td>
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<tr>
<td>• <strong>Christ Aqua Standard Operation</strong> with high recovery, idle turndown and hot water sanitization</td>
<td></td>
<td></td>
<td></td>
<td>$517</td>
<td>$544</td>
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<tr>
<td>• <strong>RO/DI with VC Stills</strong> (note 6)</td>
<td></td>
<td></td>
<td></td>
<td>$495</td>
<td>$506</td>
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<tr>
<td>• VC Still</td>
<td>$215</td>
<td>$210</td>
<td>$205</td>
<td>$200</td>
<td></td>
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</tbody>
</table>

#### Operating Cost Comparisons

- **Wastewater Volume**:
  - **Standard Operation**: 12,624 gals, 13,299 gals
  - **Modified Standard Operation**: 16,198 gals, 16,900 gals
  - **Christ Aqua Standard Operation**: 3,120 gals, 2,200 gals

- **VC Still**
  - Resistivity / short life of polishing bed / pH adjustment necessary to eliminate ammonia
  - Water quality higher than needed for WDI

- **Wastewater Volume Reduction**
  - Reduction of 1,300 gals
EXECUTION: DESIGN

PROJECT LOCATIONS & CONSTRAINTS

Only Feasible Solution:
Utilize existing Courtyard between B5 & B38 (14’ W x 110’ L)
EXECUTION: DESIGN

PROJECT LOCATIONS & CONSTRAINTS

Top of Courtyard Looking NORTH

Bottom of Courtyard Looking SOUTH
EXECUTION: DESIGN

2-Story Mechanical Room Design
EXECUTION: DESIGN

2-Story Mechanical Room Design
EXECUTION: DESIGN

NO IMPACT TO ON-GOING OPERATIONS

PHASE 1
Construct Addition & Install HPW System

PHASE 1A
Install WFI Pumps & Control Panel

PHASE 2
Demo Old HPW System
Install WFI VC Stills
Demo Old Still

Phased Construction/Qualification Approach

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EXECUTION: DESIGN

Construct 2-Story Addition for HPW

- Between 2 Buildings
- Adjacent GMP Operations
- Limited Access
EXECUTION: DESIGN

PHASE 1

Construct 2-Story Addition for HPW

- Between 2 Buildings
- Adjacent GMP Operations
- Limited Access
EXECUTION: DESIGN

SYSTEM CONSIDERATIONS

Energy Efficiency
S3 Technology & Pump VFDs

Reduce Water Usage
S3 Technology & High Recovery RO

Bulk Brine Tank System

WFI: Pump Schemes
Fathom Software
Complexity of Flows – Multiple Floors

Online TOC, Conductivity & Microbial Detection

Choose Vendor that Supplies Customizable PLC Controllers:
- Normalized Differential Pressure to determine cleaning interval
- Softener Regeneration is based on Hardness
- Softener Regeneration Rinse is based on Conductivity
EXECUTION: DESIGN

PHASE 1A - WFI

OLD SYSTEM

- No Redundancy
- Difficult to Control Flow
- Maintenance requires Shutdown
- Single Pump affected
- Tank Temp and other Floor Availability

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EXECUTION: DESIGN

PHASE 1A - WFI

NEW SYSTEM

- Redundancy
- Control From Worst Case
- Pump Maintenance = No downtime
- VFD’s to manage fluctuations
- Individual Loops can be Isolated

Generated from Fathom Modeling
EXECUTION: DESIGN

WFI CONTROL PANEL

- 20 Year Old System
- No ‘Plan B’
- Desktop Simulation Only

GREATEST RISK

- Extensive Pre-Planning
- Instruments = 86
- I/O Points = 106
EXECUTION: DESIGN

HPW GENERATION SUMMARY

LATEST TECHNOLOGY

WATER & ENERGY EFFICIENT

AUTOMATED: SANITIZATION CYCLE

SEQUENCED CHANGE OVER

ALWAYS ONLINE
EXECUTION: CONSTRUCTION

PHASE 1

Existing Courtyard

1st Floor Slab Installation

Stone & Soil Excavation

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EXECUTION: CONSTRUCTION

TEMPORARY PROTECTIONS

Maintain Building Integrity during Removal of Building Façade

Removal of the façade exposed Utilities above occupied space inside

Installed Temporary Partition Walls in Active Areas & Issued Change Control

Updated Qualified Flow Drawings Continually During Construction
EXECUTION: CONSTRUCTION

PHASE 1

Building Structure Construction

Large Crane due to Limited Access
EXECUTION: CONSTRUCTION

PHASE 1

Installation of HPW Equipment
EXECUTION: CONSTRUCTION

Outdoor Bulk Brine Tank

2nd Floor HPW
EXECUTION: CONSTRUCTION

PHASE 1

1st Floor
Dual RO Skids

1st Floor
HPW Tanks & Pumps
EXECUTION: CONSTRUCTION

PHASE 1

2nd Floor Dual Softeners & Multi-Media Filters

2nd Floor Dual Carbon Filters
EXECUTION: CONSTRUCTION

PHASE 1A

B38 Mechanical Room
Existing WFI Pumps to Demo

B38 Mechanical Room
New WFI Pumps
EXECUTION: CONSTRUCTION

B38 Mechanical Room
HPW System to Demo

Access Doors to B38 Mechanical Room
EXECUTION: CONSTRUCTION

PHASE 2

New WFI Stills at FAT Sugarland, TX

New WFI Stills in B38 Mechanical Room
Vendor Qualification Documents Reformatted to GSK Standards PRIOR to Factory Acceptance Test (FAT)

**EXECUTION: CONSTRUCTION**

**LEVERAGED QUALIFICATION APPROACH**

**PEOPLE**
- Qualification Team:
  - Validation
  - Engineering
  - Facilities
  - QA

**EQUIPMENT CHECK**
- Resolve issues prior to shipment
- Equipment Still at Factory

**DURATION**
- Reduced Document Development Time by 3 weeks
- Duplicated FAT during SAT
EXECUTION: CHALLENGES

CONSTRUCTION

- Constrained Area within the Middle of Operating Buildings
- S3 Design Not Turn-Key
- Polisher Tank Delivery
- Sartorius Filter Housings
- Delivery of High Purity Equipment
- Installation of High Purity Equipment
- DI Tank Filters
- Failure of PQ1 Testing (Plan B)

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## EXECUTION: QUALIFICATION

### VALIDATION DOCUMENTATION

<table>
<thead>
<tr>
<th>EXTENSIVE DOCUMENT MANAGEMENT</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Validation Master Plan (HPW/WFI) including 3 Validation Interim Reports</td>
</tr>
<tr>
<td>5</td>
<td>User Requirement Specs</td>
</tr>
<tr>
<td>14</td>
<td>Change Controls</td>
</tr>
<tr>
<td>27</td>
<td>Installation Operation Qualification Documents</td>
</tr>
<tr>
<td>10</td>
<td>Standard Operating Procedure Updates</td>
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<tr>
<td>22</td>
<td>Functional Design Specifications</td>
</tr>
<tr>
<td>3</td>
<td>Factory Acceptance Test / Site Acceptance Test</td>
</tr>
<tr>
<td>2</td>
<td>Design Qualifications</td>
</tr>
</tbody>
</table>
RESULTS: BENEFITS

- INCREASED SUPPLY & CAPACITY
- IMPROVED RELIABILITY & DELIVERED SUSTAINABILITY
- LOWER OPERATING EXPENSE
RESULTS: BENEFITS

IMPROVED SUPPLY TO CLINICAL OPERATIONS

Redundant HPW & WFI

Increased Capacity & Reliability

B38  B5  B4
RESULTS: BENEFITS

- **Water Consumption**
  - Reduced ~11,000 gallons per day / ~4,050,000 gallons per year
  - Cost savings of ~$32K per year (Water & Sewer)
  - Supports GSK’s strategic goal to reduce Water Consumption

- **Electrical Energy**
  - Pumping operations reduced by 88%
  - Cost Savings of ~$28k per year

- **Carbon Emissions**
  - Annual carbon emissions reduction of 348 TONNES CO2
  - Supports GSK’s strategic goal to reduce Carbon Footprint

- **Operations**
  - New System supplying HPW to Biopharm Development Pilot Plant
  - Eliminated Resin Bed Train Service
  - New Bulk Brine & Online Microbial Detection Systems
  - Cost Savings of ~$170,000 per year
RESULTS: BENEFITS

Future Operating Savings

Reduces Regulatory Sampling

Doesn't Eliminate

Online Microbial Detection System

Synchronized Optical Monitoring

Particulate Size

Microbial Fluorescence

Bioburden/Endotoxin

20% (96) Samples/Year

Only 4th System Installed in US

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RESULTS: LESSONS LEARNED

COULD HAVE DONE BETTER

- Procurement Management
- WFI Batcher Orifices
- WFI Still & Clean
- Steam Supply Pressure
- PQ1 Failure / ‘Plan B’

WHAT WENT WELL

- Full Control Replacement: Demo Simulation of functionality
- Integration of Automation Contractor
- Selection of Construction Contractor
RESULTS: SUMMARY

SUCCESS!

CONSTRUCTED & VALIDATED IN LESS THAN 1 YEAR

TWO VALIDATED SYSTEMS & NEW GENERATION EQUIPMENT

MINIMAL IMPACT TO ON-GOING OPERATIONS
RESULTS: SUMMARY

OBJECTIVES EXCEEDED!

- INCREASED RELIABILITY
- LOWER OPERATING EXPENSE
- MINIMIZED DOWNTIME
- DELIVERED SUSTAINABILITY
RESULTS: SUMMARY

OBJECTIVES EXCEEDED!

We kept the Trains on the Tracks
QUESTIONS