a member of greencross GCEM

CIP (Cleaning In Place)

GCEM / QMT

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Leonid Shnayder, “Equipment Cleaning-In-Place in Modern Biopharmaceutical Facilities: Engineering Concepts and Challenges” Pharmaceutical Engineering, January/February 2005, Vol. 25 No. 1

David Greene, “Practical CIP System Design” Pharmaceutical Engineering, March/April 2003, Vol. 23 No. 2

Ryoichi Haga, “Cleaning Mechanism Study for Bio-Pharmaceutical Plant Design” Pharmaceutical Engineering, September/October 1997, Vol. 17 No. 5

1 Introduction

Definition

- Cleaning process system and equipments without major disassemble of components
- Flow of cleaning solution by pumping through the system
- To reduce or eliminate the possibility of cross contamination

Figure 2. CIP skid.

Regulation – cGMP, 21 CFR Part 211. 67

(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements

Introduction

Advantage

- Good reproducibility of the cleaning process because the cleaning parameters are defined.
- Dismounting of equipment is not necessary
- Low number of personnel

Disadvantage

- Usually high consumption of water and cleaning agent

2 Main Concept

I. CIP System Selection

II. Piping Networking Plan

III. CIP SKID Configuration

IV. CIP Cycle Operational Parameter Setting

V. Validation & Automation System Strategy

VI. Key Check points for supplier selection

2 Main Concept

I. CIP System Selection (Possible ways to improve the CIP Design)

1. Portable CIP Skid (Initial CIP Design)

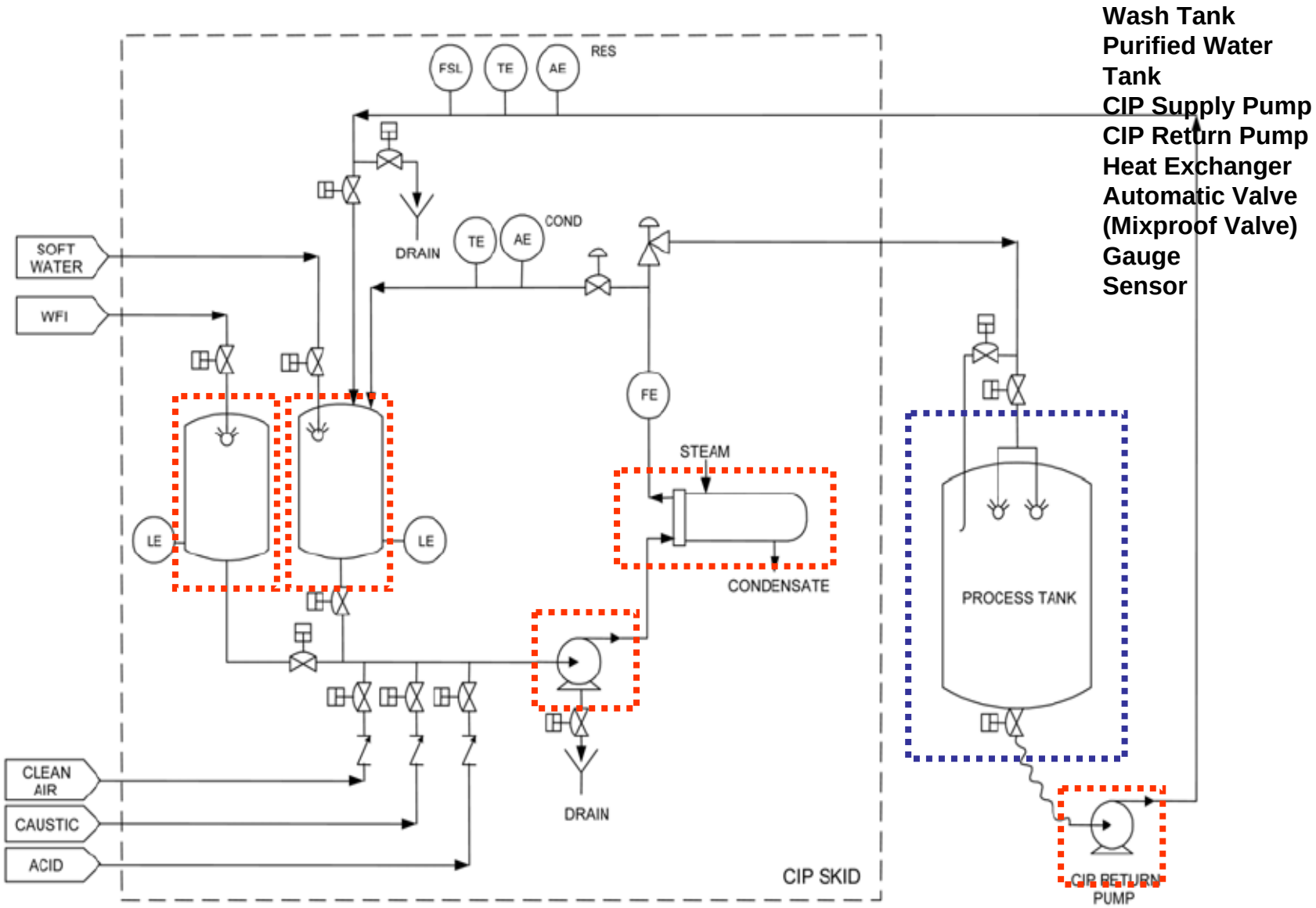
- + For small vessels those that do not need to be cleaned very often
- + Low capital cost & usage of water and chemical
- – Labor intensity, need to move it between various process area

2. Fixed CIP Skid

- + Reduce usage of water and chemical
- + Reduce labor by automation
- – Need special effort to find suitable area

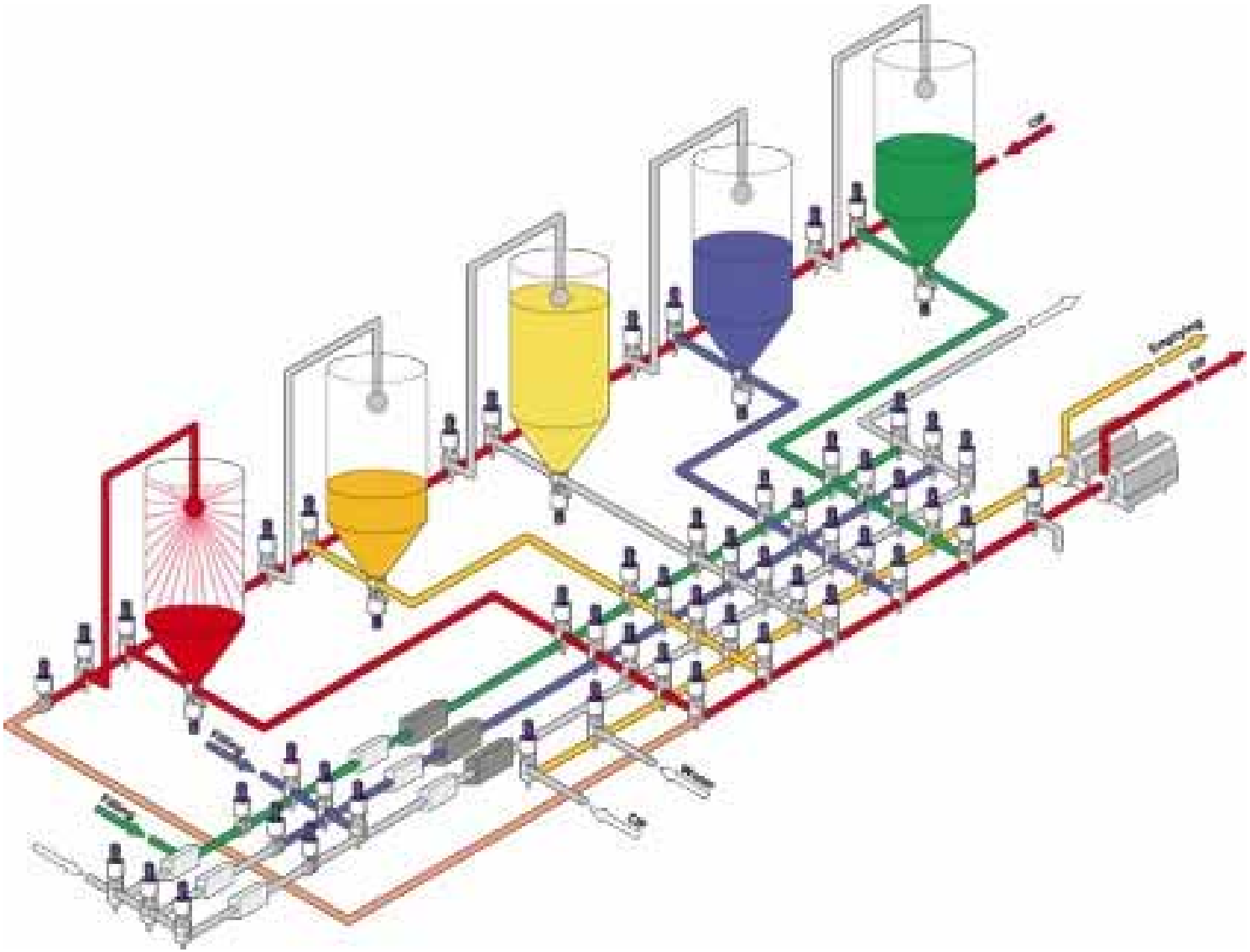
2 Main Concept

3. Dedicated System (Typical CIP System)



2 Main Concept

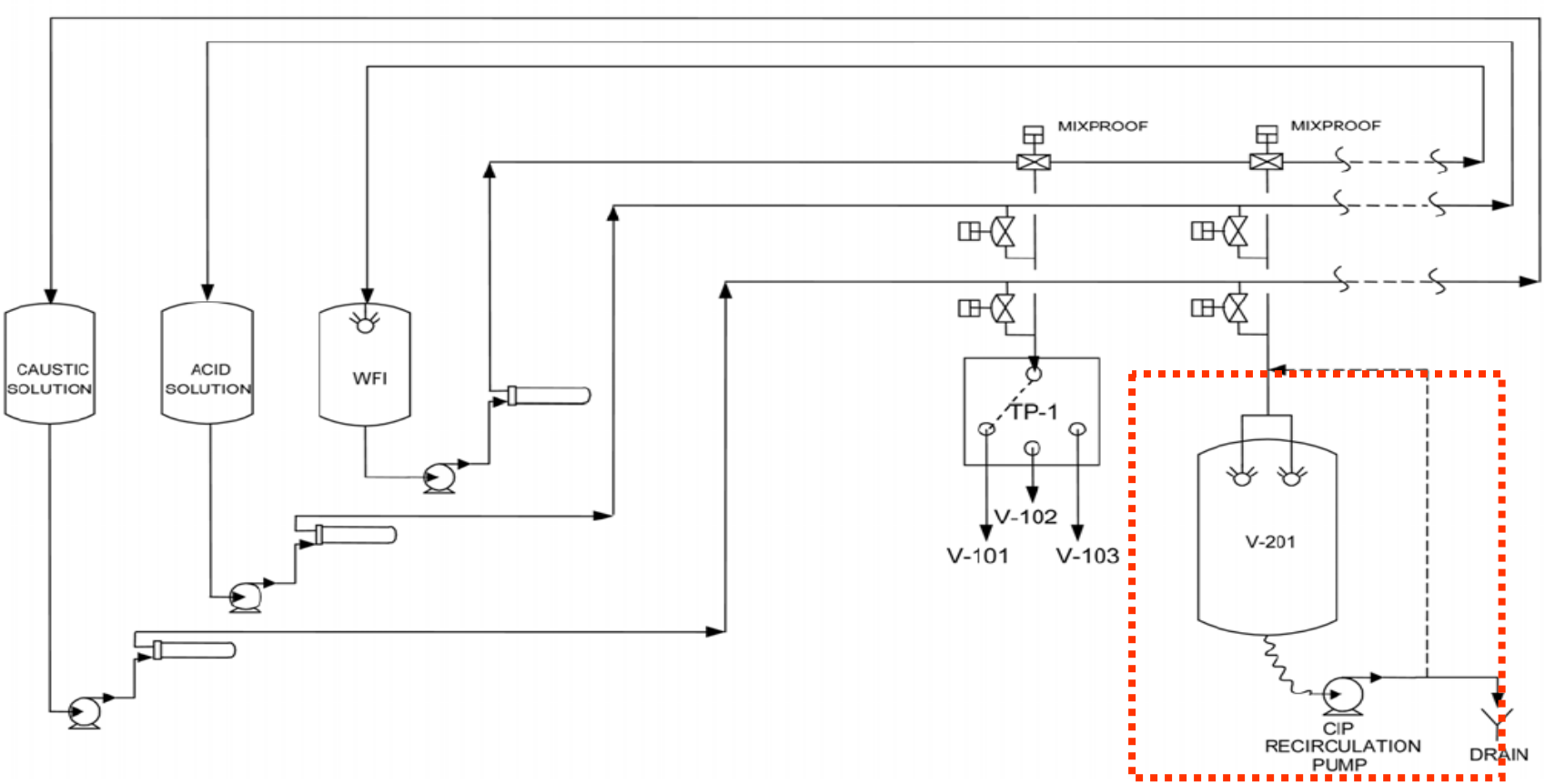
4. Multi-use System



2 Main Concept

5. Alternative CIP Approach – Separate Distribution Piping

- + Less equipment need
- + No CIP return piping work
- + Reduce risk of cross contamination
- + Reduce CIP cycle time
- – Reduced flexibility to modify the recipe, Higher usage of chemicals



2 Main Concept

II. Piping Networking Plan

Important Features

- Need to be configurable
- No dead legs

URS : < 3D

- No Pressure drop and hold up volumes
- Return Line Slope 1% minimum for gravity drain and removing air pocket
- Water & Chemical Consumption Consideration (minimize pipe line)
- Sanitary Material : SUS 316L, 0.38 μm (Ra max)

URS : SUS 316L, 0.75μm

Multiple Transfer Panels in Series

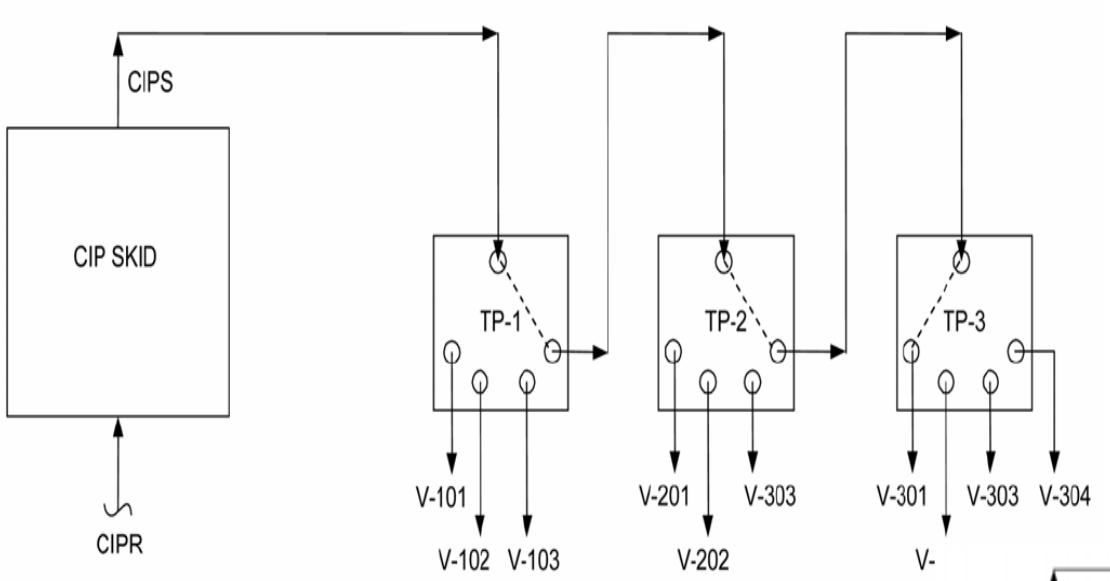
Master Transfer Panels

Valve Manifold

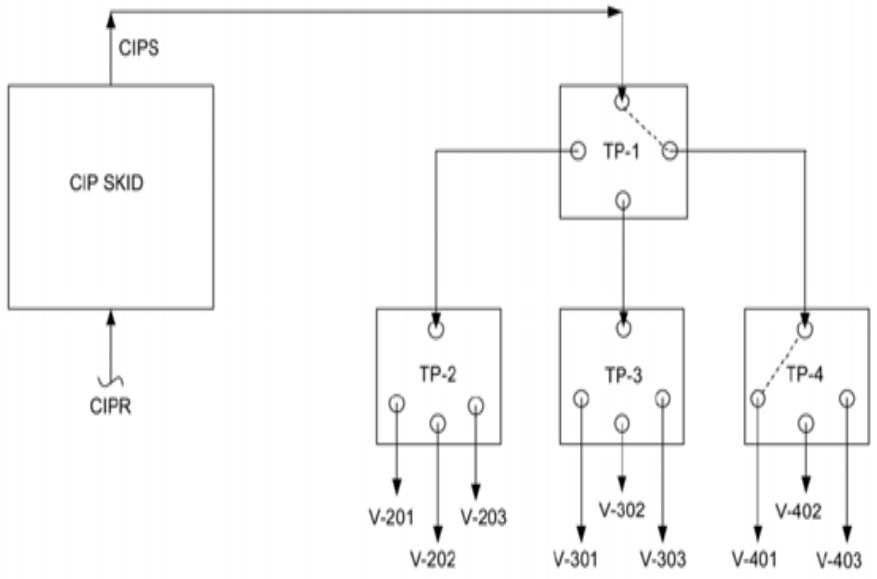
Loop Header

2 Main Concept

Multiple Transfer Panels in Series



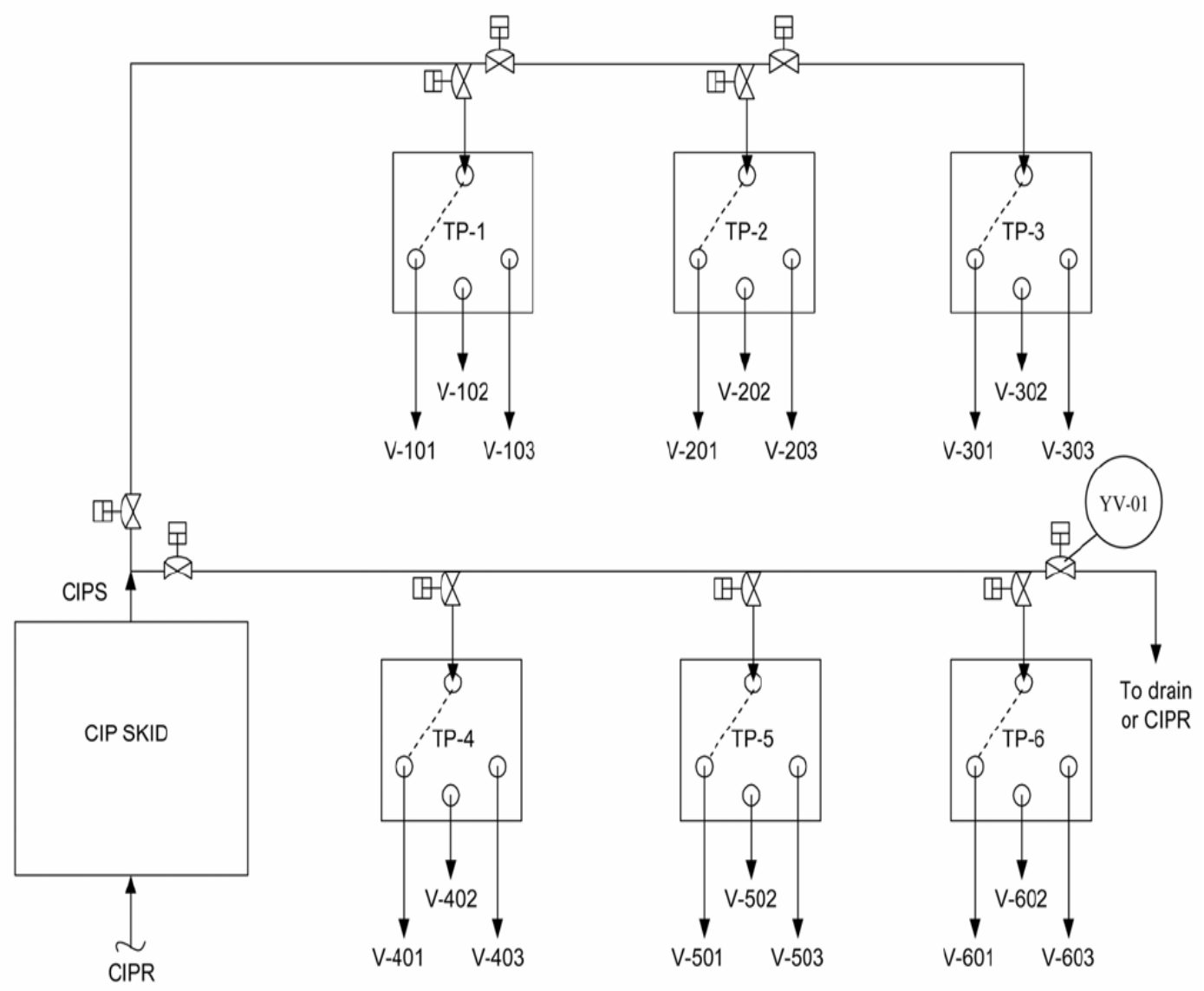
Master Transfer Panels



2 Main Concept

Valve Manifold

Loop Header



2 Main Concept

III. CIP SKID Configuration

Tanks — Wash Tank | Rinse Tank | Caustic Tank | Acidic Tank

Pumps — Supply Pump | Return Pump | Local Recirculation Pump

Heat Exchanger

URS : Tubular Heat Exchanger

Mixproof Valve, Gauge, Sensor, Hose

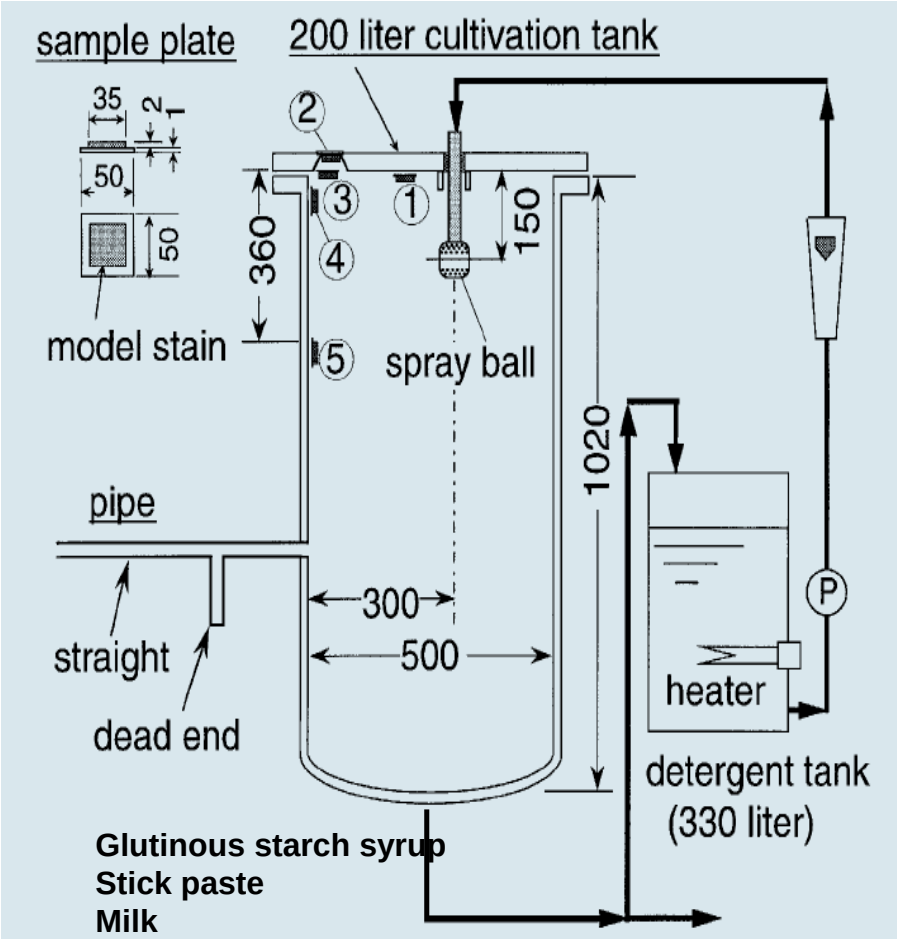
URS : Conductivity Sensor, Double check

Spray Ball & Nozzle

2 Main Concept

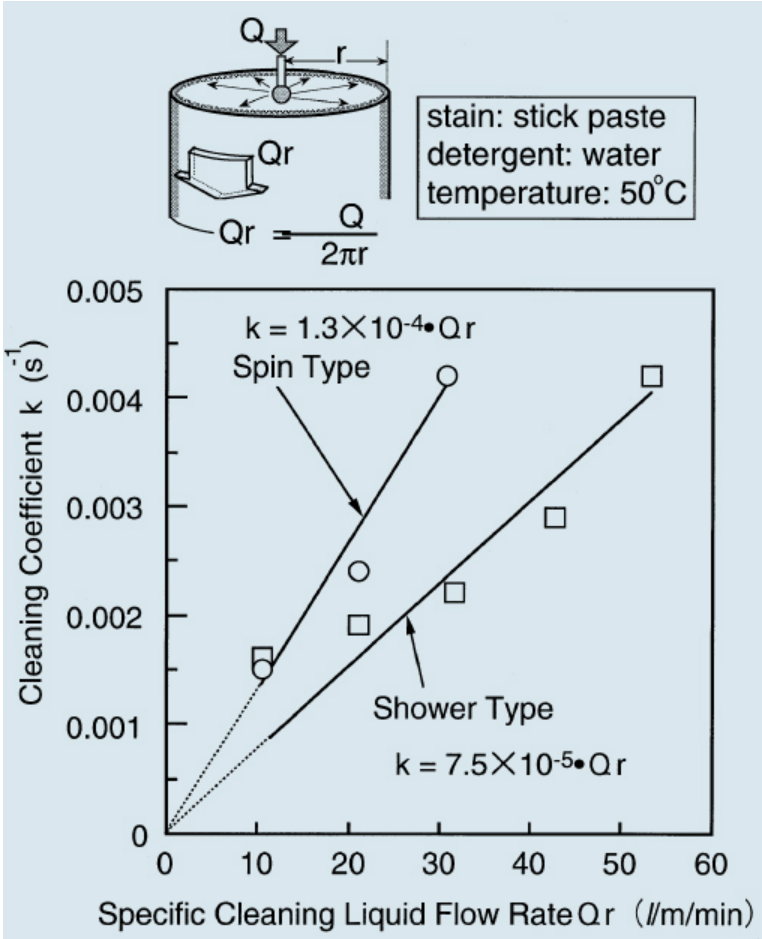
Spray Ball & Nozzle

Type of spray-ball



Glutinous starch syrup
Stick paste
Milk
Bovine serum albumin

Spin type vs. Shower type

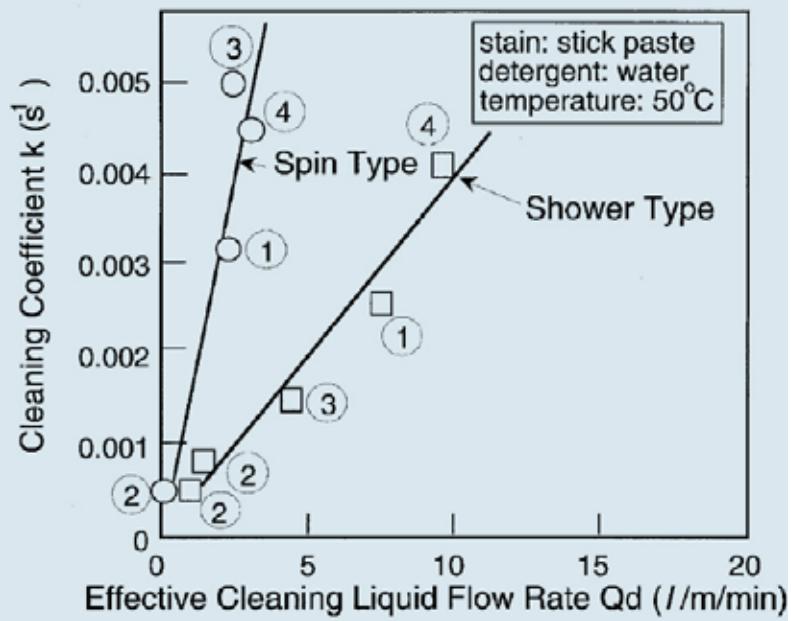


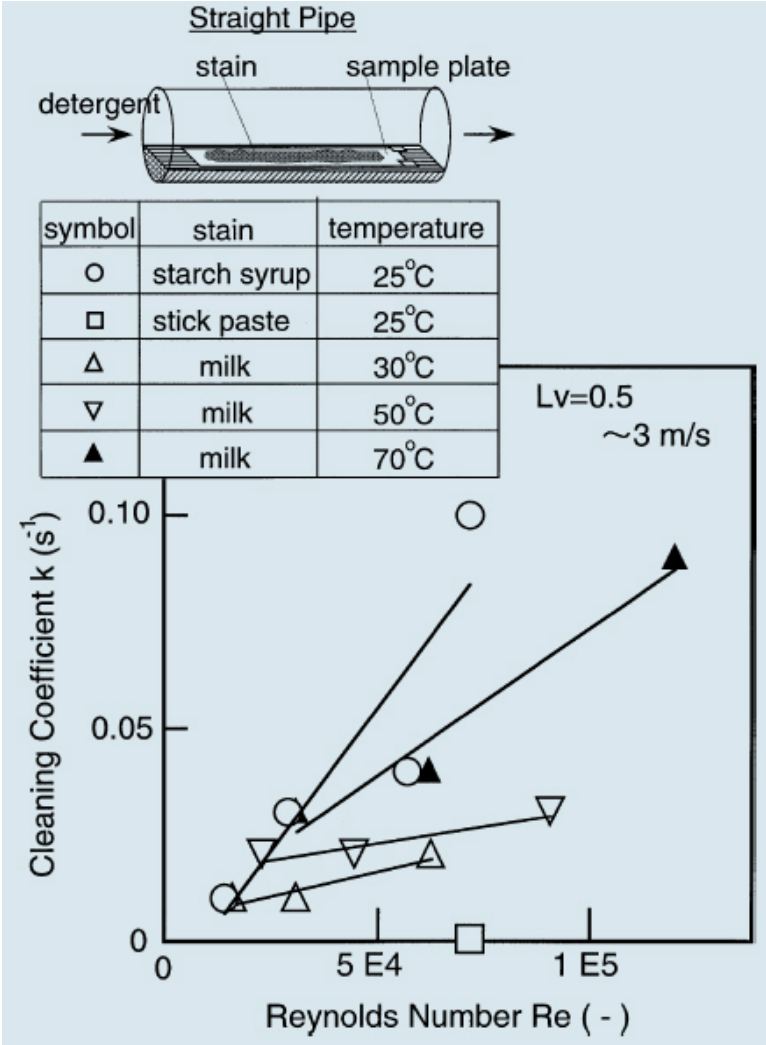
Tank wall cleaning Result

2 Main Concept

Spray Ball & Nozzle

Position Sensitivity



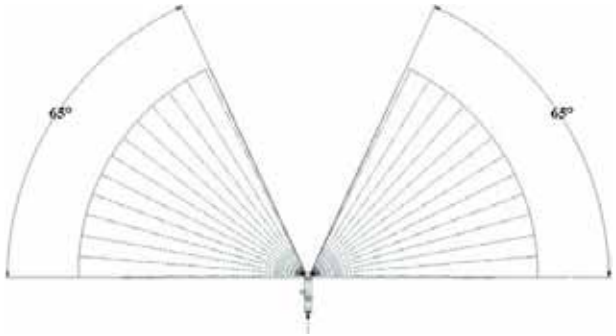


Pipe inner Surface
Flow rate
Temperature
The residues' physical and chemical properties
(viscosity, solubility)

2 Main Concept

Spray Ball & Nozzle

URS : Line Velocity ; > 2 m/s



Type
Quantity
Location
+
Performance Simulation

How to validate it !!

2 Main Concept

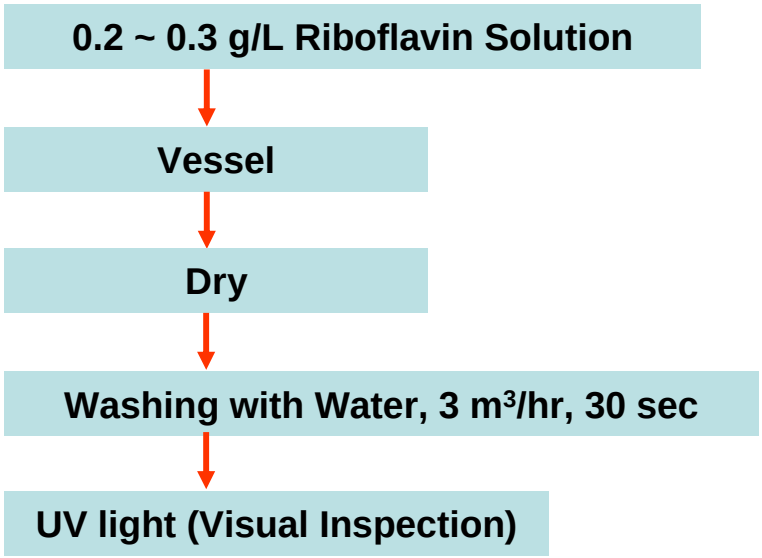
IV. CIP Cycle Operational Parameter Setting

Cycle Type	Solution Type & Concentration	Operational Parameter Time	Temperature	Flow Rate
Pre-Rinse	PW	5 min	25℃	3~5 m^3/hr
Caustic Wash	0.1M NaOH	5 min	60 ~ 83 ℃	??
			URS : 60 ~ 80 ℃	
Air Blow				
Rinse				
Acid Wash	0.1M Phosphoric Acid	5 min	60 ~ 83 ℃	??
	URS : 0.1M Citric Acid			
Air Blow				
Rinse				
Final Rinse	WFI	5 min	60 ~ 83 ℃	??
Air Blow	Clean Air	5 min	Clean Air	??
Acceptance Criteria	1 ~ 3 %	N/A	± 3℃	± 10%
			URS : ± 0.25 ℃	

2 Main Concept

V. Validation & Automation System Strategy

Riboflavin Coverage Test
(Example of FAT Test Item)



URS : Sampling port for final washed solution

URS : Monitoring Temp. Pressure, Flow Rate, Conductivity (± 2%)

- **Automation system must be validated**
- **Documentation for IQ & OQ**

- P&ID
- Dimensional Drawings
- Complete set of Electrical Drawings
- Functional Design Specification
- Maintenance manuals and spare parts list for all components
- Welding & Inspection Documentation
- Material Certificates for all process components

3 Conclusion

VI. Key Check Points for supplier selection

1) System 구성의 다양한 해결책을 가지고 있는가?

2) GMP 및 Sanitary Piping의 이해력

3) Spray Ball의 Design Specification 및 Operation parameter (온도, 시간, 유량)
에 대한 과학적인 근거 자료 및 simulation 결과를 제공할 수 있는가?

4) System 구성에서 Utility Consumption 등 경제적 측면을 고려 하였는가?

5) Washing performance 등의 검증 방법과 GMP Documentation
(Computer System Validation) 능력을 갖추었는가?

6) Tank 제작업체, Pipe 담당 업체, Automation 업체와의 협력 방안은 마련 하였는가?