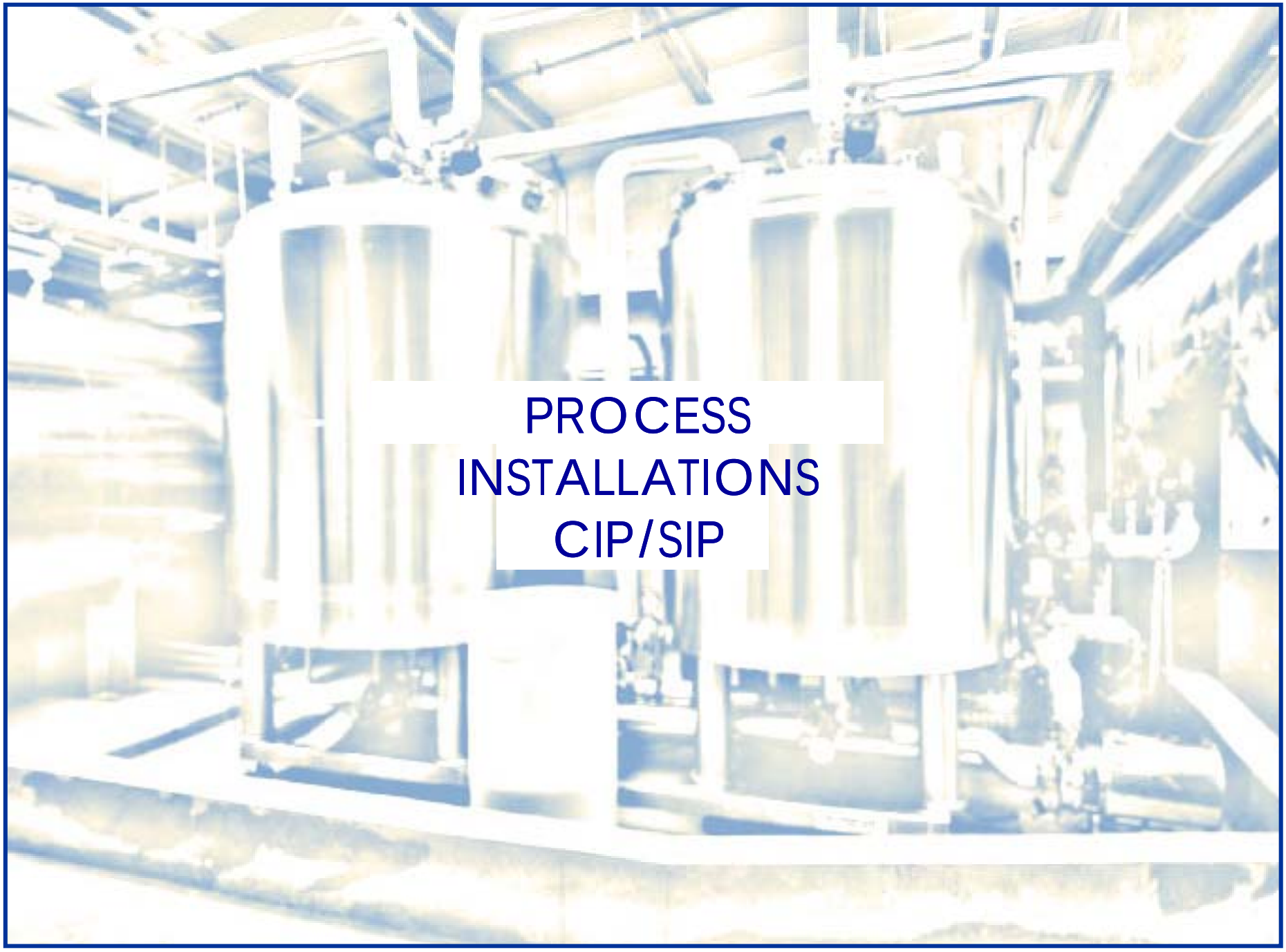
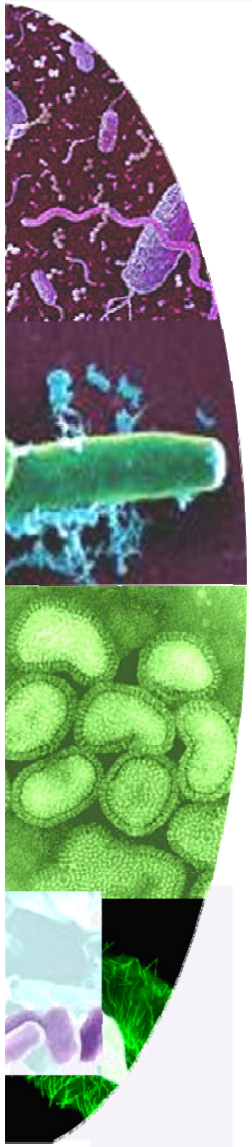

# CIP/SIP SYSTEMS

JORGE DOMINGO


PROCESS
INSTALLATIONS
CIP/SIP



The main aim is .....

# Minimize risks of
# CROSS CONTAMINATION

## Others Important CIP/SIP objectives

- End Product Quality
- Product Protection
  Microbiologically, against pirogen, etc.
- Protection against product ACTIVE INGREDIENT
  Internal & External
- Environmentally Friendly

# CIP-SIP

## ABBREVIATION

**CIP: CLEANING** IN PLACE

**SIP: STERILITATION** IN PLACE

**WIP: WASHING** IN PLACE

**COP: CLEANING** OUT OF PLACE

# WHY USE A CIP SYSTEM?

## CIP is better than other cleaning method

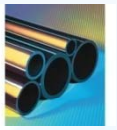
- Automated, with monitorised and controlled parameters
- Human error elimination
- Contaminated products elimination

## Operating Costs Reduction

- Direct Labor costs decrease
- Cleaning times reduction
- Less use of detergent/solvents/waters

## Safety

- Less Product Exposure (by workers)
- Avoid mechanical disassemblies and Tanks entries
- Less use of detergent/solvents/waters



## SCOPE AND EQUIPMENT FEATURES

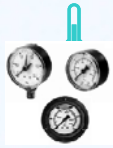
- List of Equipment and Facilities
- Full Documentation

## PROCESSES TEMPERATURE

- Define Maximum Temperature
- Define Minimum Temperature

## CHEMICAL PRODUCTS

- Determine products to be use in each cleaning step
- Determine acceptance criteria (pH, Conductivity)



## FLOW AND VELOCITY

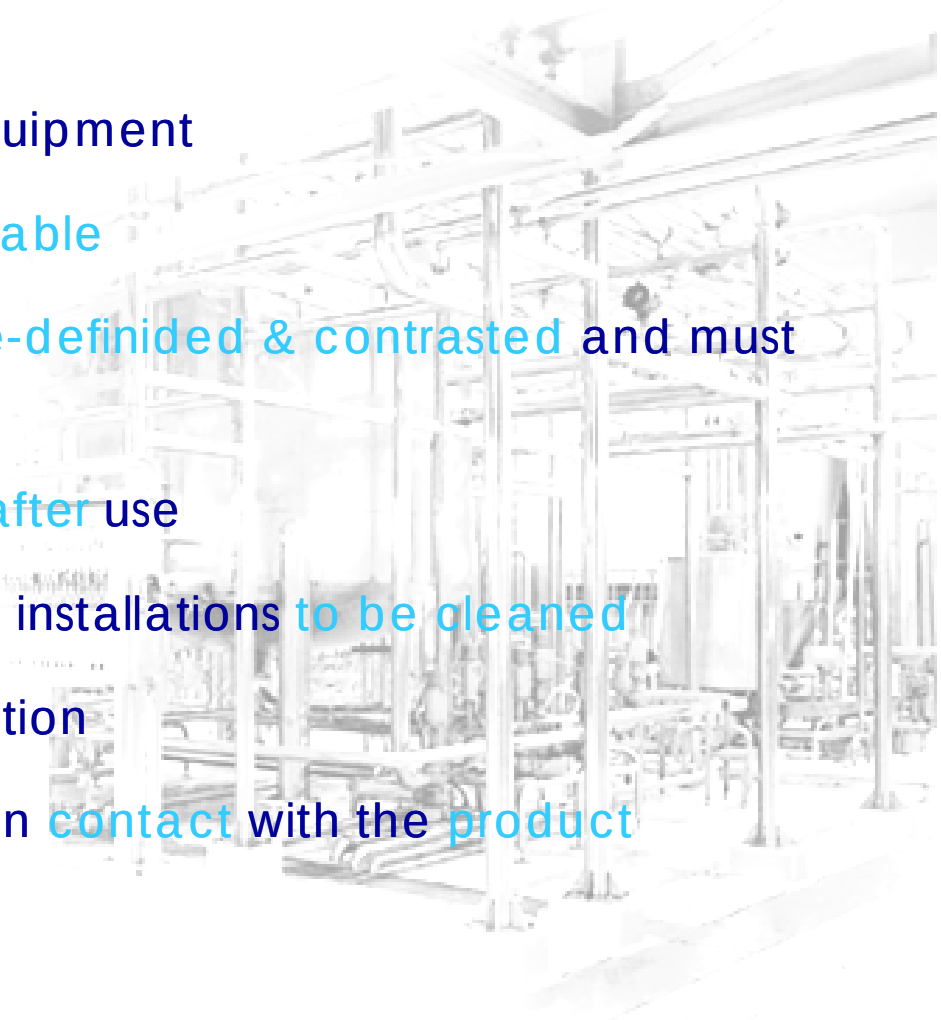
- Cleaning Flow
- Fluid velocity in pipe

## CLEANING CYCLE TIME

# CIP

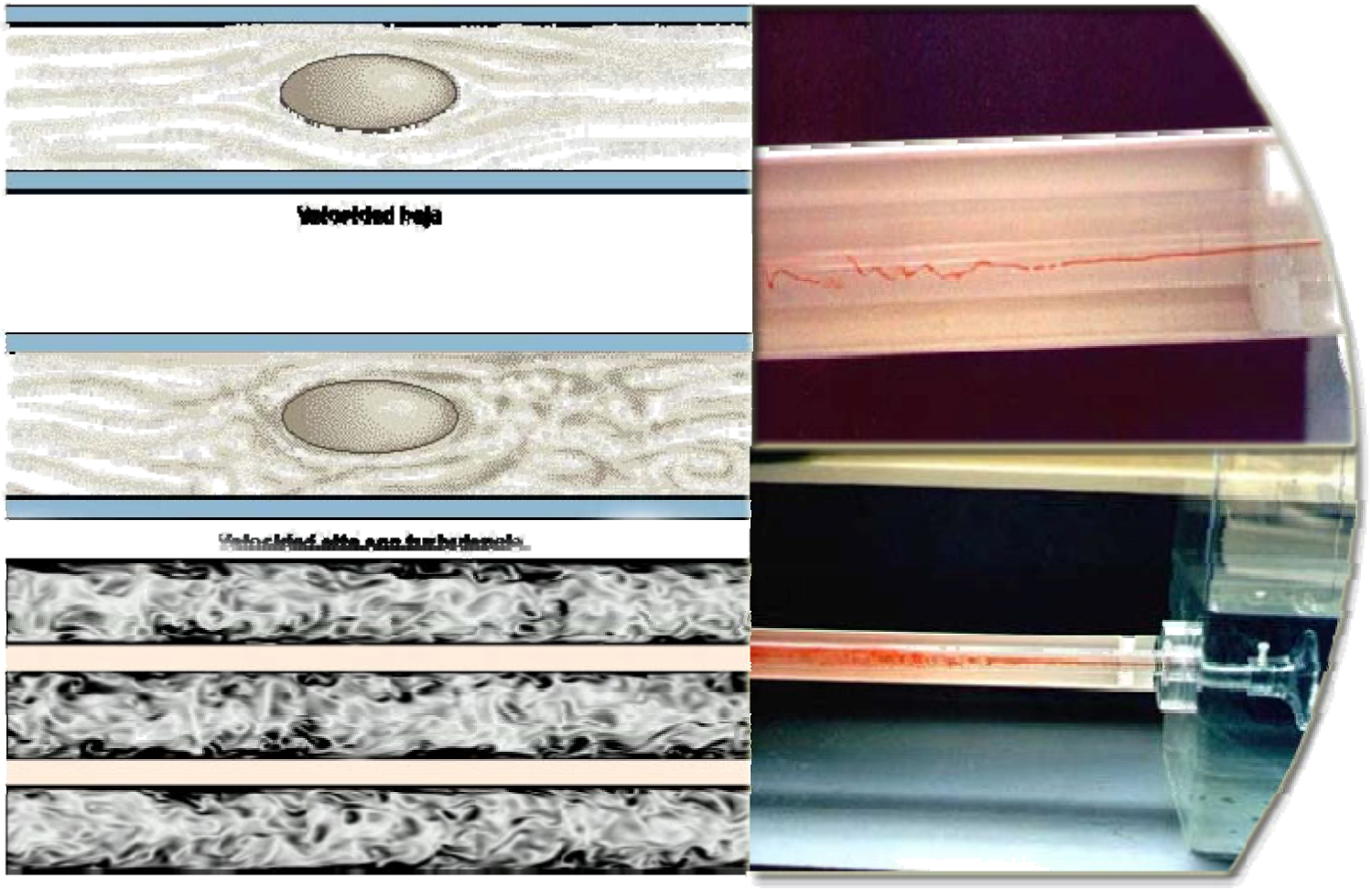
## BASIC CONCEPTS

- ✓ To clean is essential to ensure appropriate installation and equipment
- ✓ Cleaning Steps must be repeatable
- ✓ Cleaning Protocols must be pre-definided & contrasted and must be reliable
- ✓ Clean equipment before and after use
- ✓ Design process equipment and installations to be cleaned
- ✓ Proper cleaning products selection
- ✓ Ensure exposure of all surfaces in contact with the product



# CIP

## TURBULENT AND LAMINAR FLOW

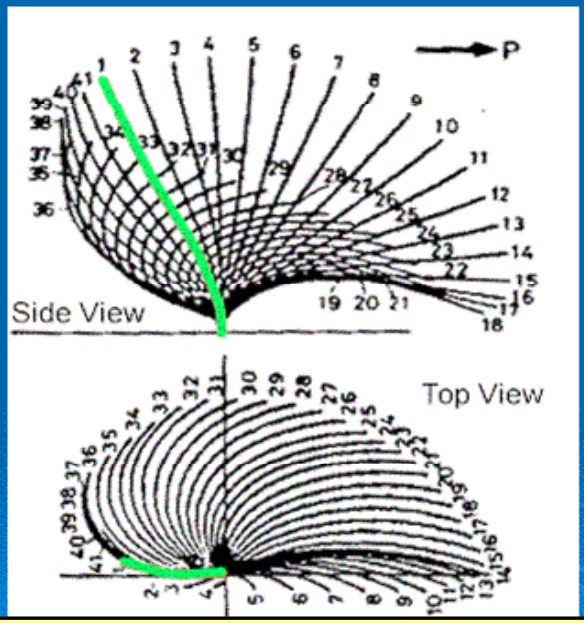


# Low Reynolds Number = Laminar Flow

$$Re = vR\rho / \eta$$

V = velocity
R = characteristic distance
ρ = density
η = viscosity

For bacteria,
Re = .00003




| | |
|---|---|
| **Re<2000** | **LAMINAR FLOW** |
| **2000<Re<4000** | **TRANSICION FLOW** |
| **Re>4000** | **TURBULENT FLOW** |

# CIP

## EJEMPLO

**CASO A)**

$V_1$=2,5m/s

$D_1$=25,4mm

U=$10^{-6}$ $m^2/s$

**CASO B)**

$V_2$=0.5m/s

$D_2$=25,4mm

U=$10^{-6}$ $m^2/s$

$$Re = V \times D/U$$

V: velocidad (m/s)
D: diámetro (m)
U: Viscosidad cinem ($m^2/s$)

**Re=63500 Re=12700**

**Saving Water in 5 minutes:**

t=5min / $V_1$=2.5 m/s / $V_2$=0,5m/s

$\sigma = (D^2 \times \pi) \times 4^{-1}$ = 5.08 cm2

$Q_1 = V_1 \times \sigma$= 1,26 l/s

$Q_2 = V_1 \times \sigma$= 0,26 l/s

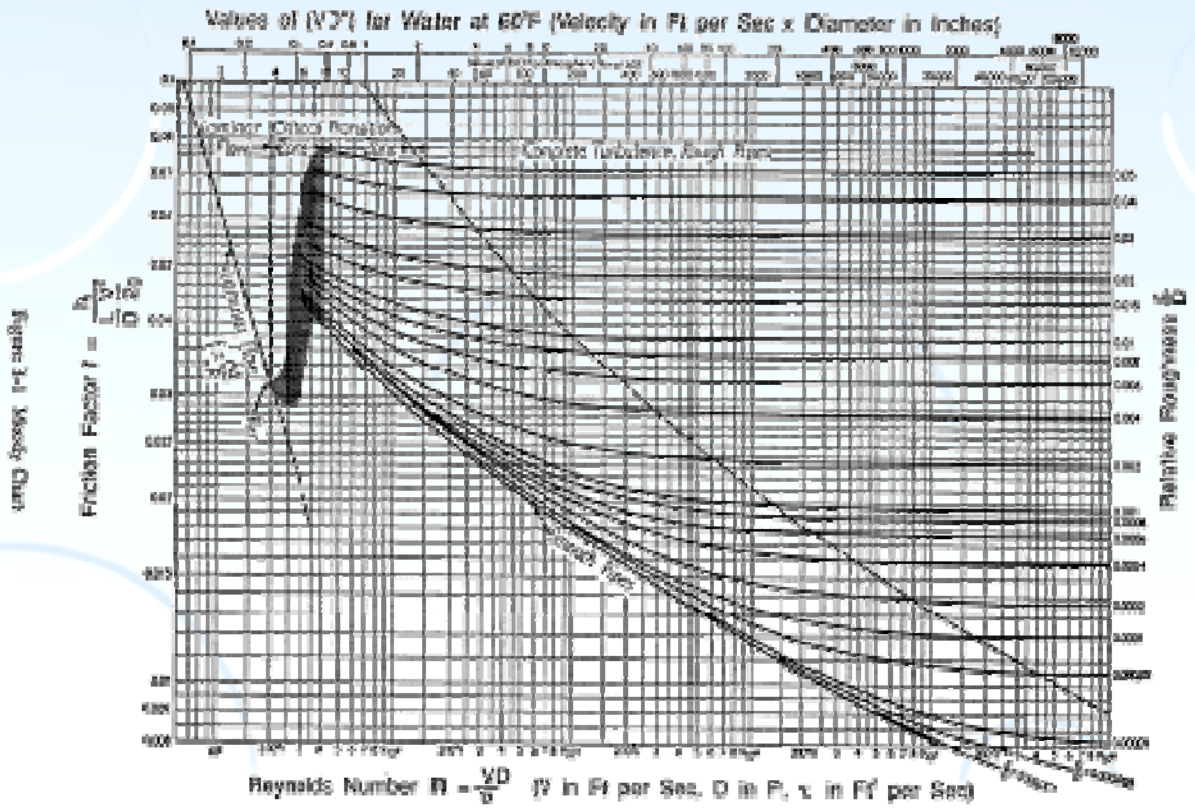
→

δ1(Qxt)= 380 litros
δ2= 76 litros

$\delta_1 - \delta_2$=304 liters/5min

# CIP

## MOODY'S DIAGRAM

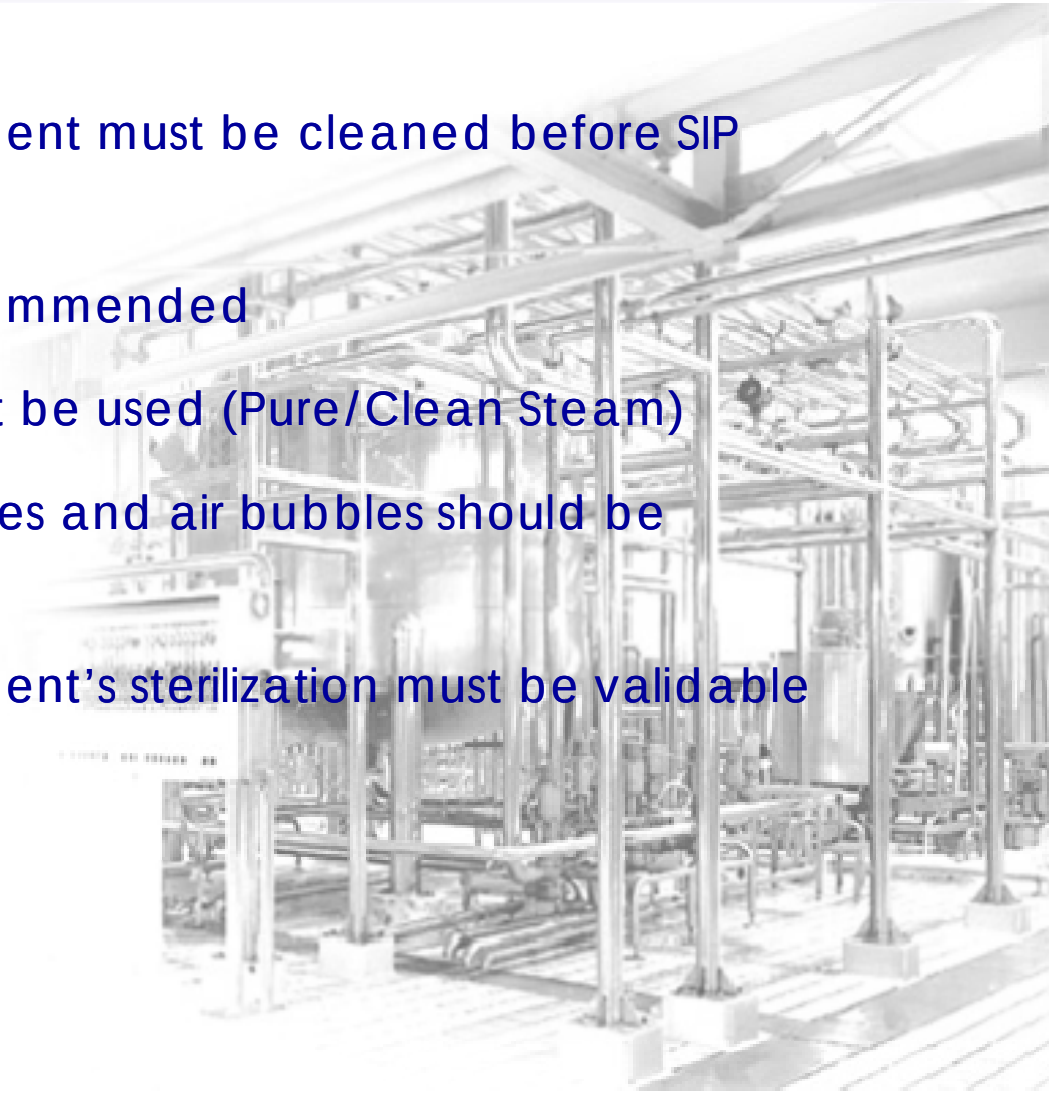



**Variables: Friction Factor, Reynolds Number, Roughness**

# SIP

## BASIC CONCEPTS

- ✓ Installations and equipment must be cleaned before SIP process
- ✓ Thermal sterilization recommended
- ✓ High Quality Steam must be used (Pure/Clean Steam)
- ✓ Using steam, condensates and air bubbles should be eliminated
- ✓ Installations and equipment's sterilization must be validable



# CIP-SIP

## NORMATIVAS DE APLICACION

- **EUROPEAN PHARMACOPEIA**
- **USP**
- **EUROPEAN GMP**
- **FDA CFR 21  210/211**
- **ICH, Q7A (APIs)**
- **ASME BPE**
- **ISPE** Vol4:Water and steam
- **GAMP** 4/5(Good Automated Manufacturing Practices)
- **ASTM, ASME, CEN, ISO (material)**. Certificates must comply with **EN 10204 (Certificate 3.1B), ASTM E1831**.

# CIP-SIP

## TECHNICAL ISSUES

- **Manufacturing processes must be studied individually for a good sterilization and cleaning recipe definition**
- **Have cleaning/sterilization procedure's drafts, as well as an Effectiveness analysis; before starting the CIP/SIP detail engineering**
- **Specific production equipment must have special cleaning procedures contrasted with the manufacturer or use they**
- **Right material and component choice, as well as other features**
- **Monitoring and recording** of defined critical parameters
- **Warnings and alarms must be defined**

## Termo sensores:

Tubos de Browne: tubos de vidrio cerrados con 0,15 ml de un fluido rojo que cambia a verde al aumentar el calor

Tiras de papel impregnadas con esporas: bioindicadores. Se incuban luego del tratamiento para evaluar la supervivencia

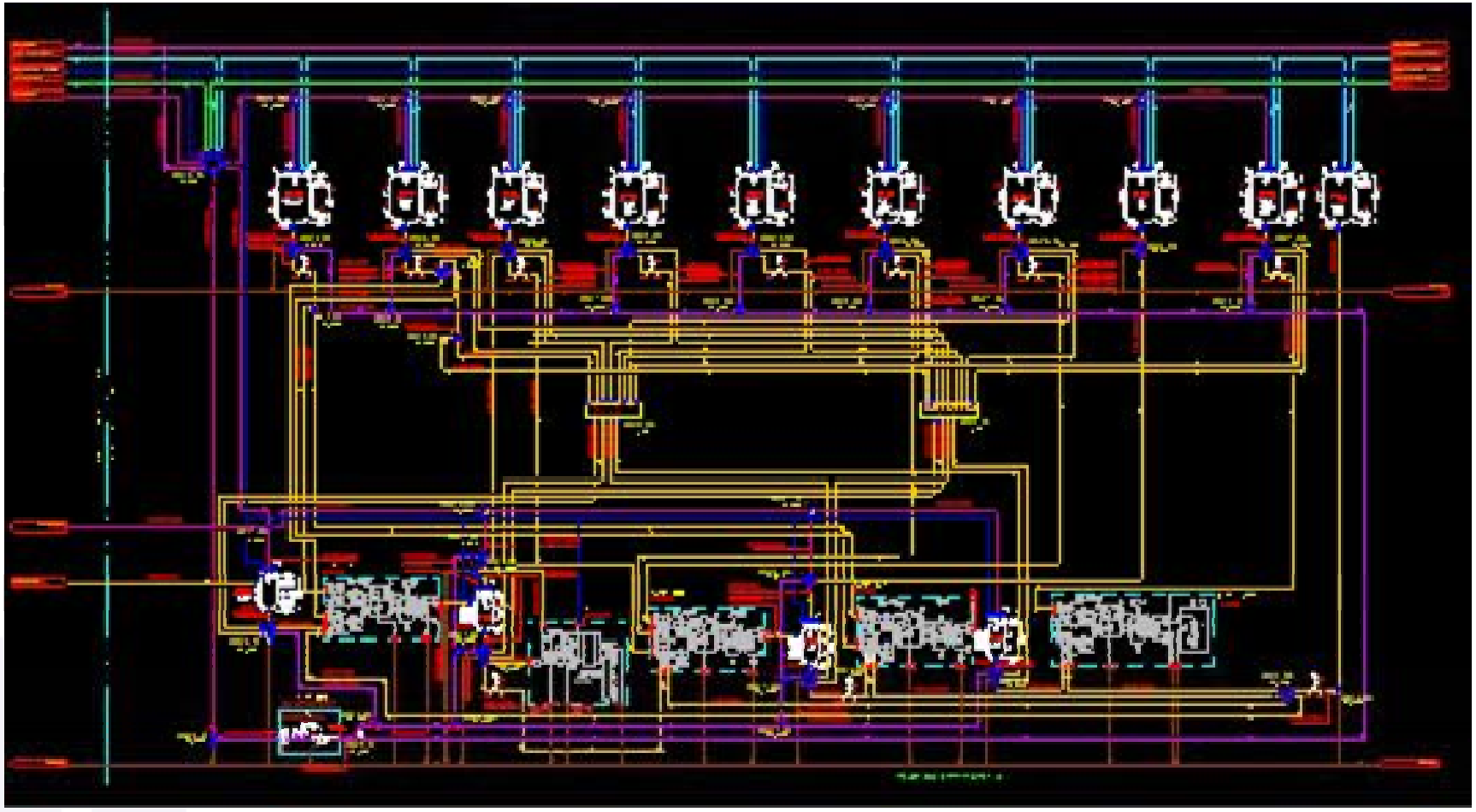
Tiras indicadoras: responden al calor húmedo entre 115-123ºC. Indican la dosis de calor por distancia recorrida de un colorante azul

Cinta adhesiva de autoclave: indica que el vapor, a un mínimo de 120ºC, alcanzó la cinta cuyas rayas se tornan de blancas a negras. No asegura esterilidad sino que un objeto ha sido procesado mediante vapor.

# INSTALACIONES DE LIMPIEZAY ESTERILIZACIÓN DE EQUIPOS E INSTALACIONES "IN SITU"

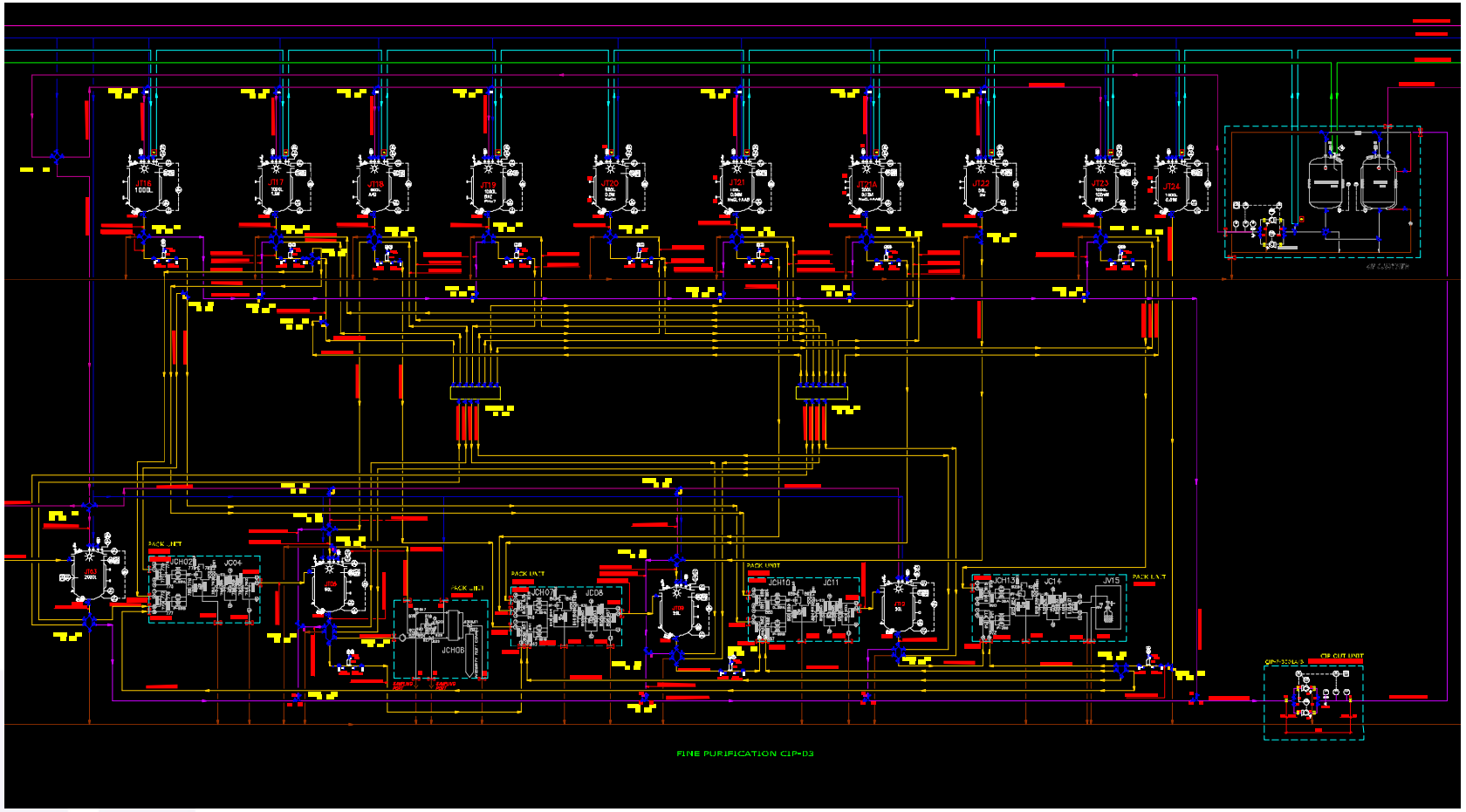
# CIP-SIP

## CONFIGURACIÓN INSTALACIONES DE PROCESO



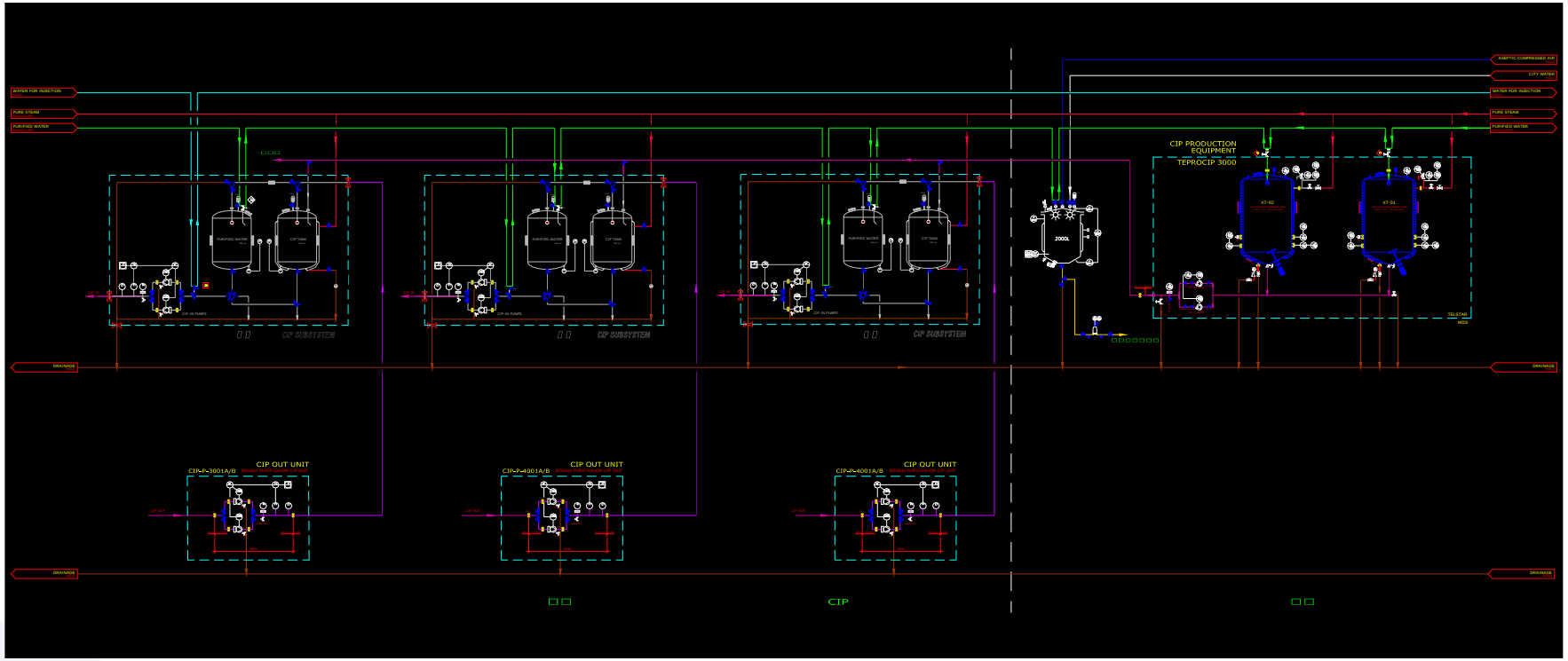
# CIP-SIP

## INTEGRACION EN EL PROCESO



# CIP-SIP

## SISTEMAS



# CIP-SIP

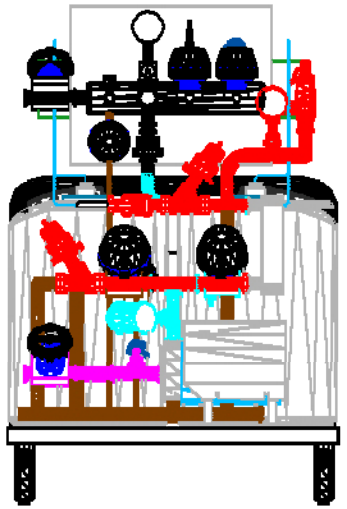
## TYPE UNIT

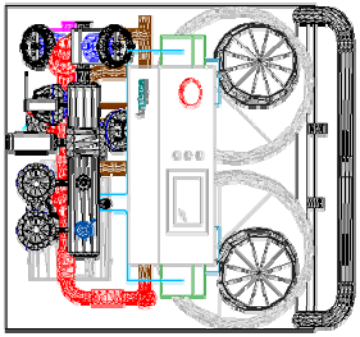
**Fixed Units:** To Provide service from a technical area through CIP piping lines (CIP supply and return

**Mobile Units:** Compact units, no need fixed piping. Can be use to clean different reactors

# CIP-SIP

## UNIDADES MÓVILES- ESQUEMA





# CIP-SIP

## VESSELS

- ✓ **Storage Tank**:. Can be installed to store the water of the last rinse. Will be installed depending the CIP unit use and the water cost (depends of each project/facility)
- ✓ **Preparation Tank:** Has the enough capacity to clean the worst. Cleaning solutions will be recirculated in that thank until the correct pH and temperature are reached.
- ✓ **Chemical tanks:** Acid and base are stored and later are pumped into the preparation tank.

# CIP-SIP

## PUMPS

- ✓ **CIP-IN Pump:** Will be calculated to give the optimal flow and pressure. Installed at the preparation tank outlet, this pump will be used to recirculate the cleaning solution (until the temperature and pH are reached) and to pump the solution to the reactors that must be cleaned.

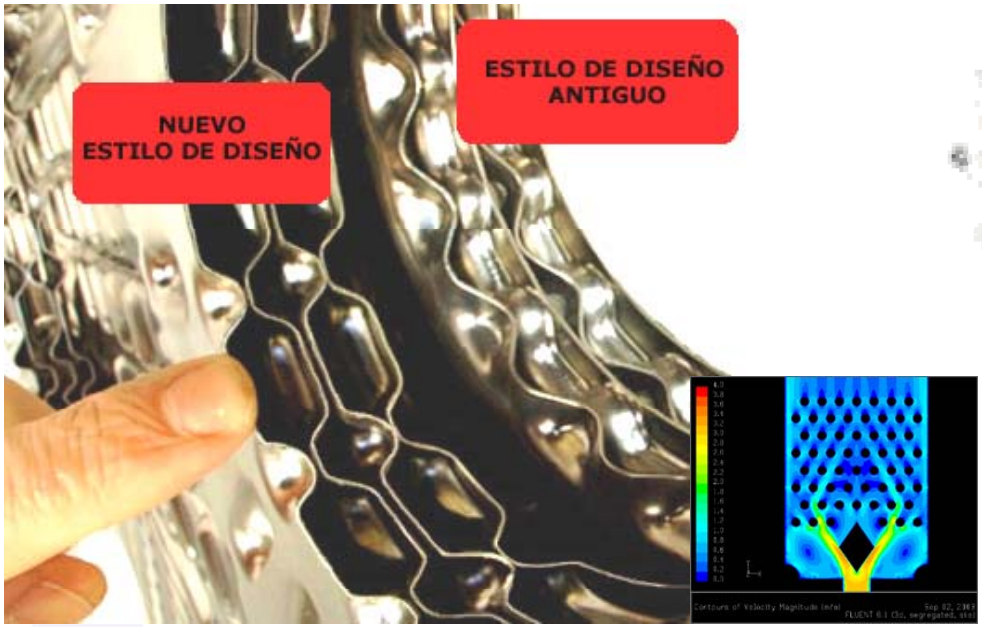
- ✓ **CIP-OUT Pump:** Allows full equipment draining as well as recirculation of the cleaning solution

- ✓ **Dosing Pump:** Used to pump ( controlled dosing) the cleaning solution to the preparation tank

# CIP-SIP

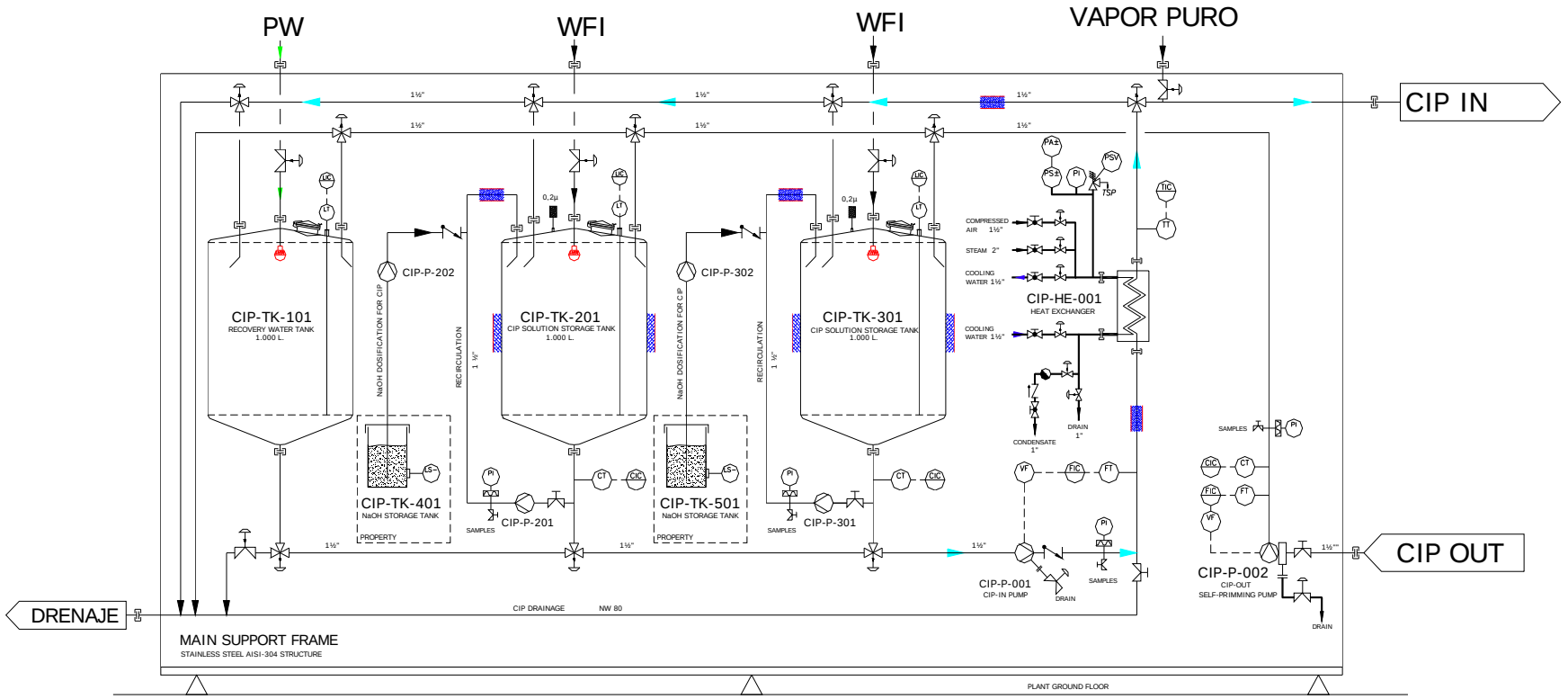
## HEAT EXCHANGER

- ✓ Its main objective is to put the cleaning solution at the proper temperature.
- ✓ Double plate and tubular are the most used



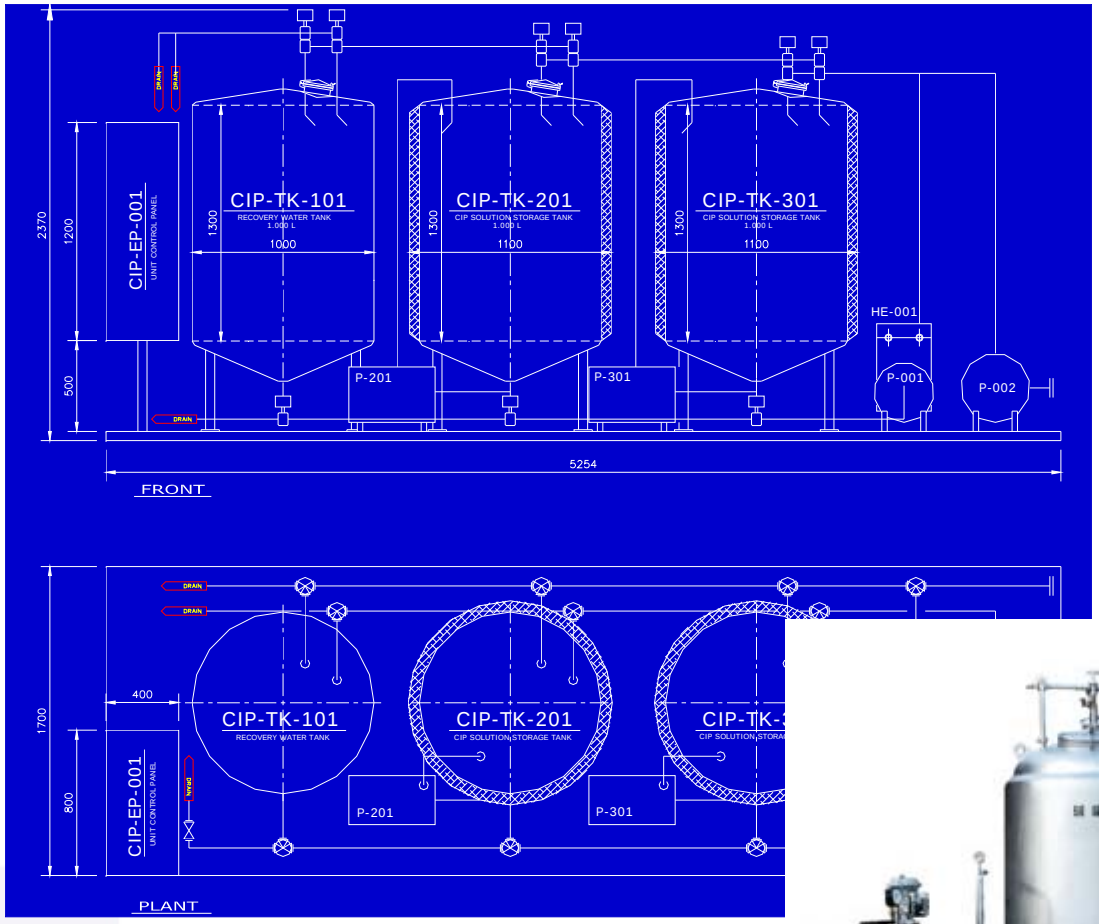

# CIP-SIP

## UNIDADES FIJAS-DIAGRAMA



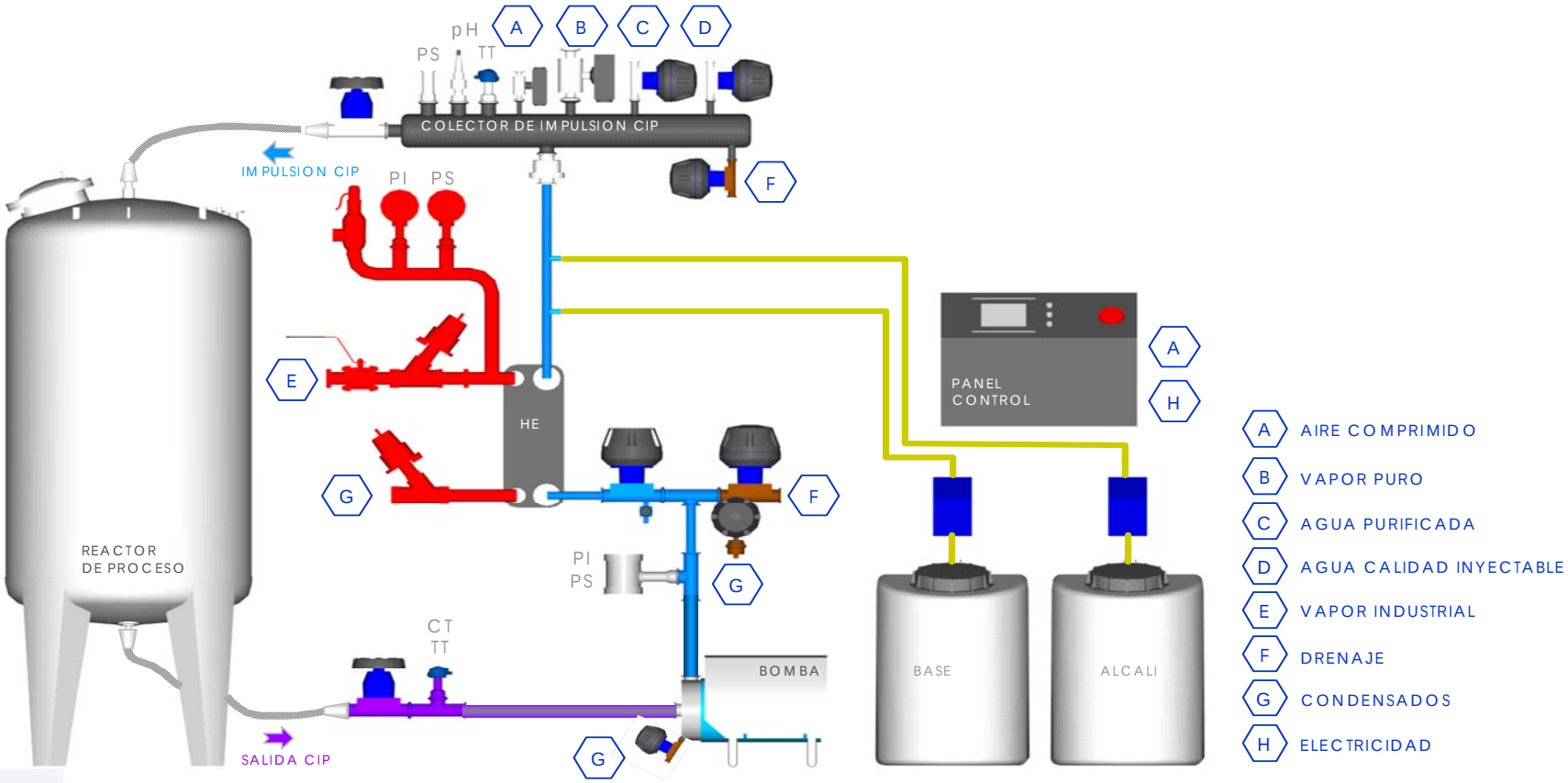
# CIP-SIP

## FIX UNIT




# CIP-SIP

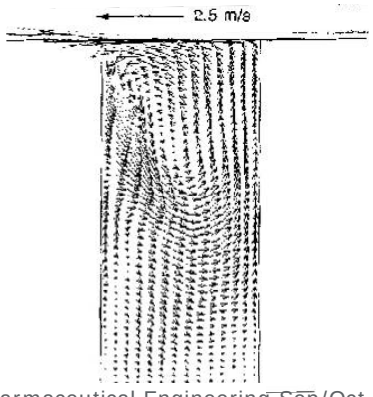
## UNIDADES MÓVILES- ESQUEMA



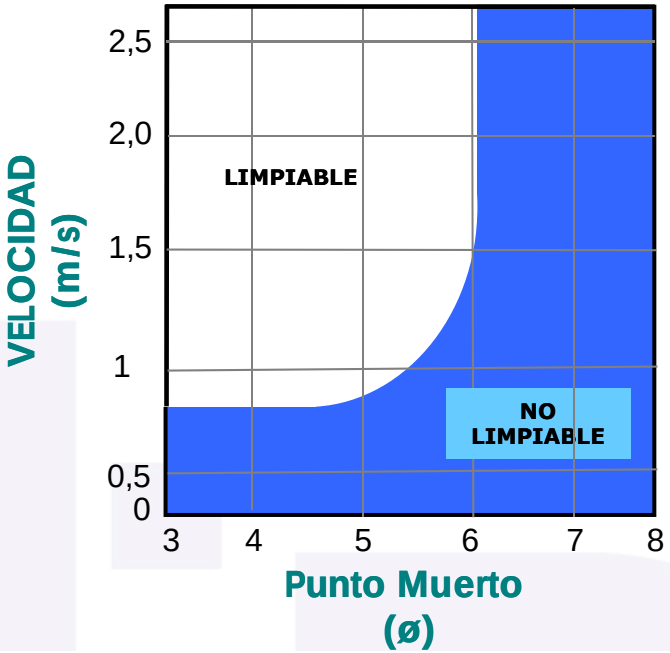
## Caudales Rociado Depósitos

| Caudales Recomendados para la limpieza de depósitos verticales<br>ASME BPE 97 (Rev.2005) Tabla SD-7 | | | |
|---|---|---|---|
| Diámetro Interior | | Caudal | |
| **Pies** | **mm** | **Galones/min** | **l/min** |
| 1,5 | 457 | 12 a 14 | 45 a 53 |
| 2 | 610 | 16 a 19 | 60 a 72 |
| 3 | 914 | 24 a 28 | 90 a 106 |
| 4 | 1.219 | 31 a 38 | 117 a 134 |
| 5 | 1.524 | 39 a 47 | 148 a 178 |

# Velocidad en Tuberías




Pharmaceutical Engineering Sep/Oct 97
Rioichi Haga, Sei Murakmi, Steven Ostrove




## Caudales Recomendados para Asegurar Régimen Turbulento en tuberías

ASME BPE 97 (Rev.2005) Tabla SD-6

| Diam. Ext. | | Diam. Int | | Caudal | |
|---|---|---|---|---|---|
| **Pulg.** | **mm** | **Pulg.** | **mm** | **Gal/min** | **l/min** |
| 0,5 | 12,7 | 0,37 | 9,4 | 1,7 | 6,5 |
| 0,75 | 19,1 | 0,625 | 15,9 | 4,8 | 18 |
| 1 | 25,4 | 0,875 | 22,2 | 9,4 | 35 |
| 1,5 | 38,1 | 1,375 | 34,9 | 24,0 | 90 |
| 2 | 50,8 | 1,850 | 47 | 42,8 | 162 |
| 3 | 76,5 | 2,875 | 73 | 102 | 386 |

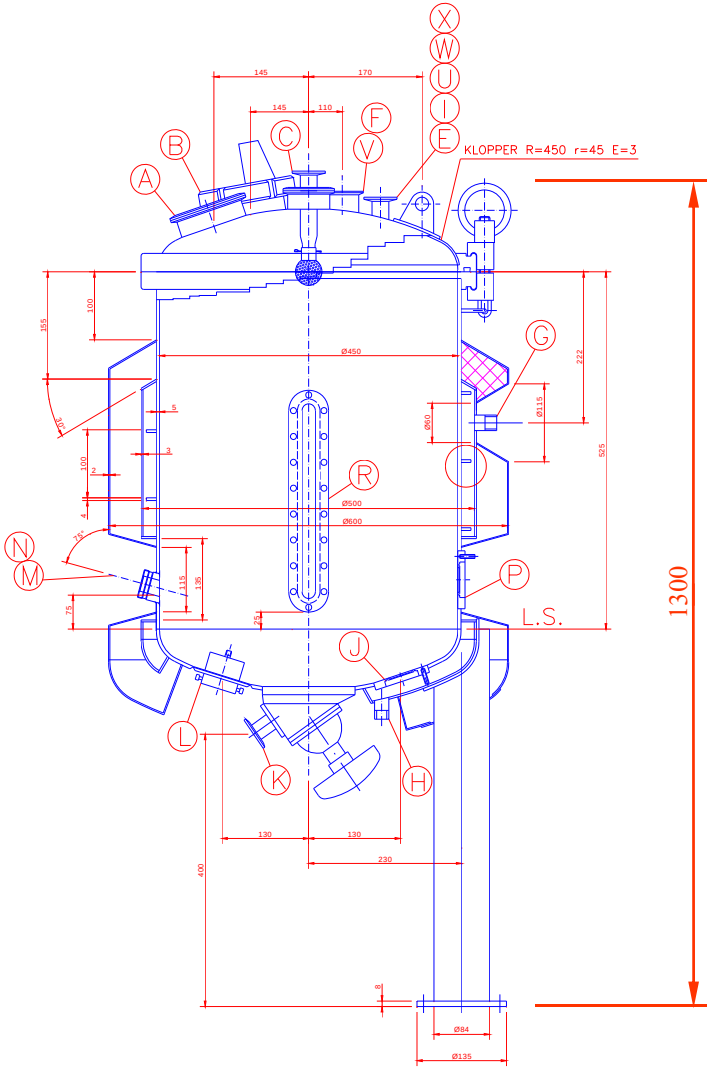
# CIP-SIP

## CIP/SIP TYPYCAL PROTOCOL

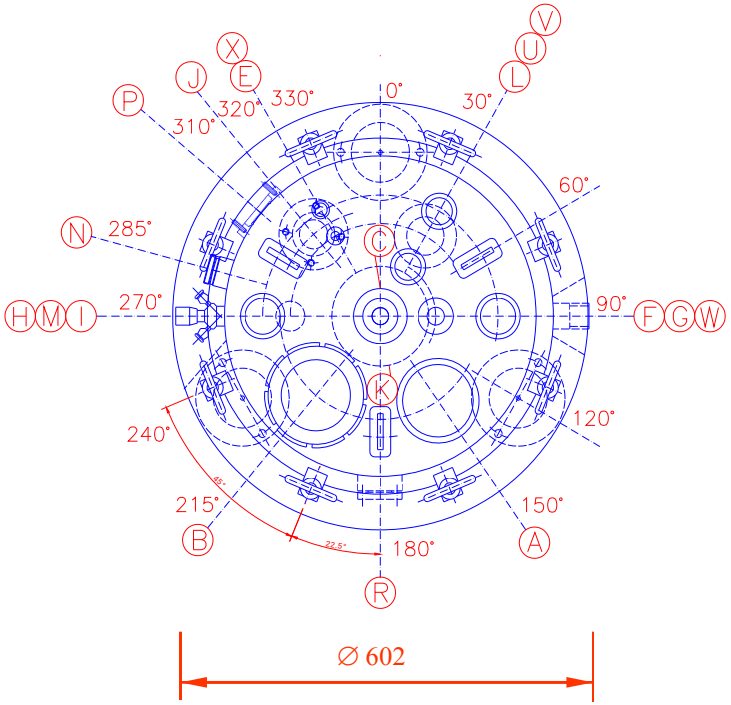
| First Rinse | Cleaning | pH adjust | Rinse | Final Rinse | SIP | Aplication |
|---|---|---|---|---|---|---|
| PW | PW + Álcali | Acid Dosing | PW | WFI | PS | Injectables, Steriles |
| SW | SW + Álcali | Acid Dosing | SW | PW | Opcional | Sólids, Líquids , Creams |
| Temperature Time | Temperature Time Conductivity | Conductivity | Time Temperature Conductivity | Time Conductivity | Time Pressure Temperature | Parameters to be controlled |

# CIP-SIP

## EQUIPMENTS AND INSTALLATIONS




FRONT VIEW




PLANT VIEW

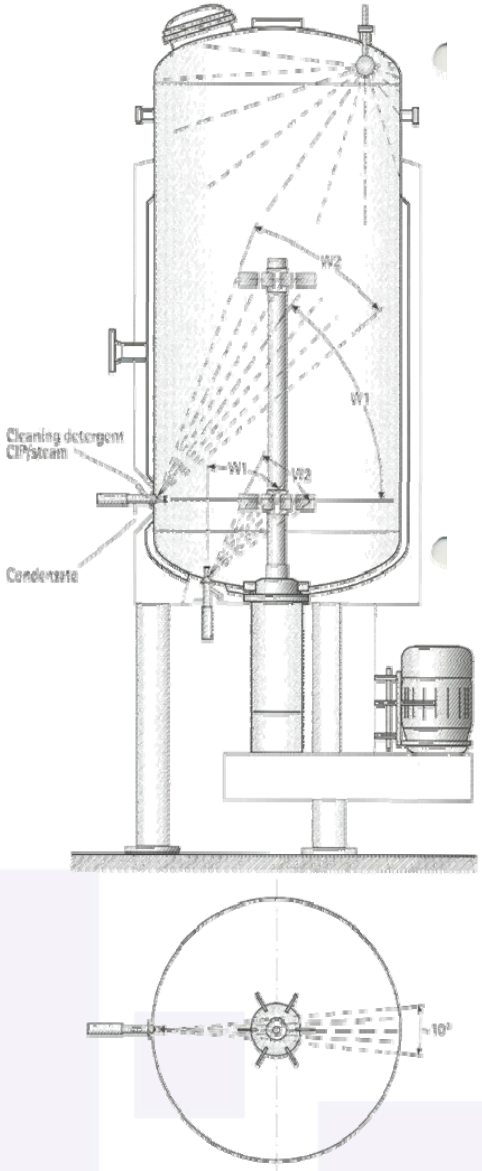
# CIP-SIP

## COMMON PROBLEMS

- ✓ **Equipment and installation bad designed**
- ✓ **CIP fluids drain**
- ✓ **To ensure that the cleaning solution/SIP is in contact with 100% of the surfaces**
- ✓ **Bad choice of cleaning spray**
- ✓ **Hard to clean products**
  (gelatins, fats, concentrated products, …)
- ✓ **Installation drying**
- ✓ **To have appropriated services**
  (quality waters, pure steam, clean compress air,…)
- ✓ **A great equipment variety to be cleaned**

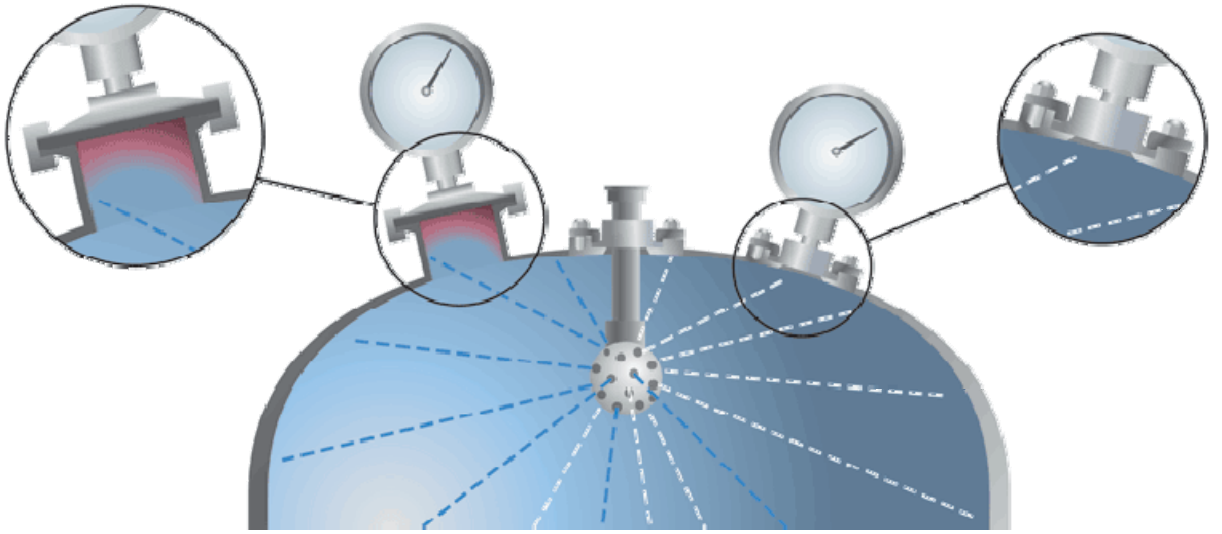
# CIP-SIP

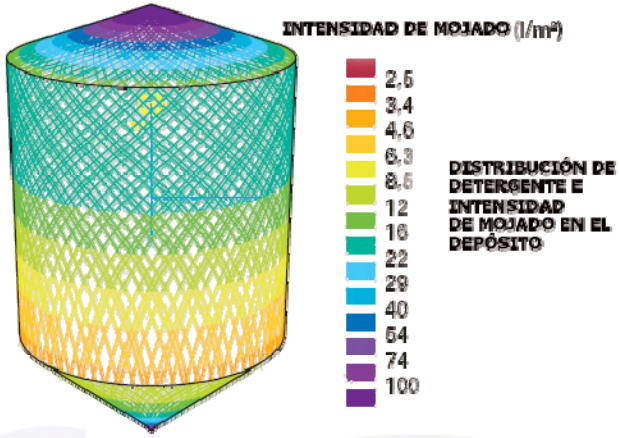
## EQUIPMENT AND INSTALLATION CONSIDERATIONS

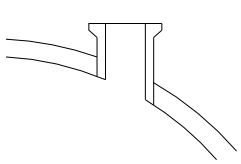
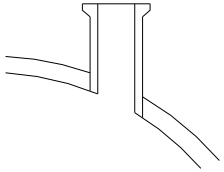
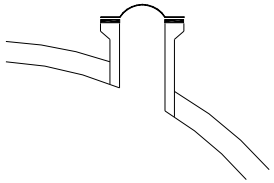
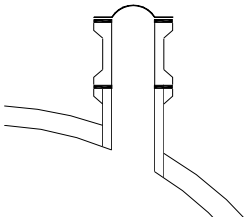
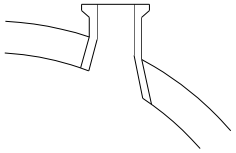
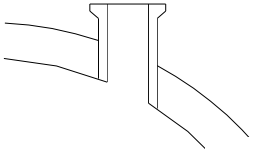
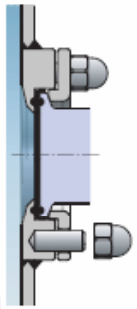
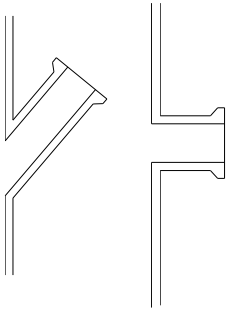



A ferrule
TC connection

NA-Connect®
flush mounted





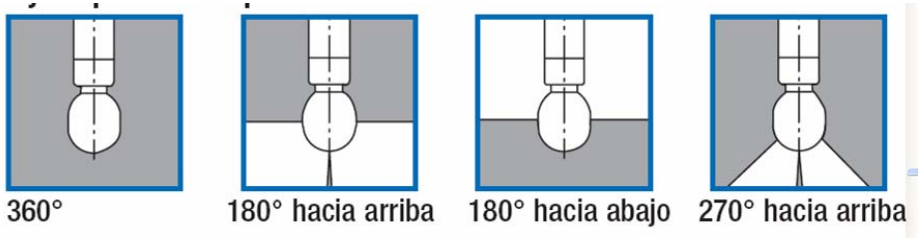
| *CORRECTO* | *INCORRECTO* |
| --- | --- |
|  |  |
|  |  |
|  |  |
|  |  |

# CIP-SIP

## SPRAY DEVICES

**ADVENTAGE:**

- Maintenance Free
- Easy control
- Less Power needed (Pump)




**DISADVENTAGE:**

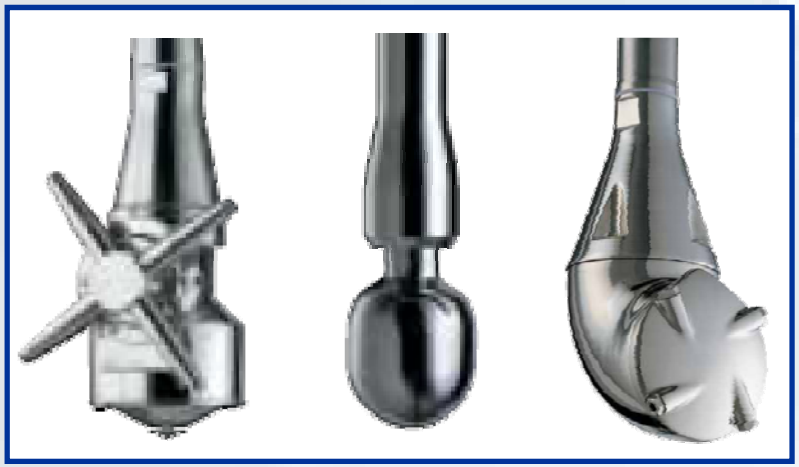
- More water used
- More cleaning times
- Less mechanical wear

# CIP-SIP

*Spray systems*

**ADVANTAGE:**

- Less water waste
- Longer cleaning distances

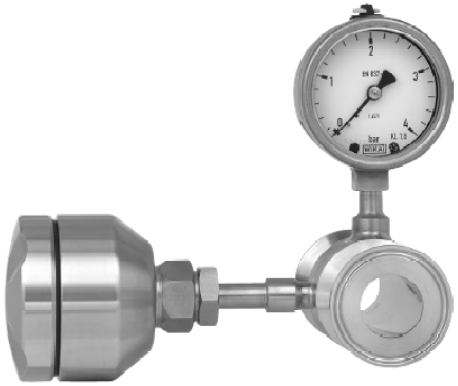


**DISADVANTAGE:**

- Higher Pump Power
- Dificul to know if bloqued
- Higher cost
- Higher maintenance

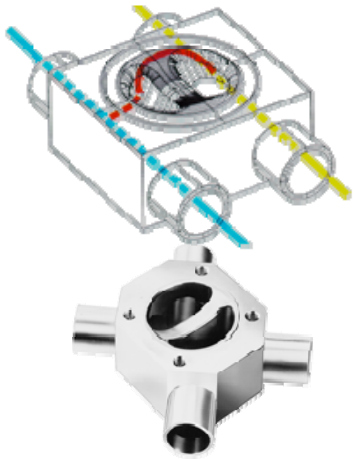
# CIP-SIP

## INSTRUMENTATION



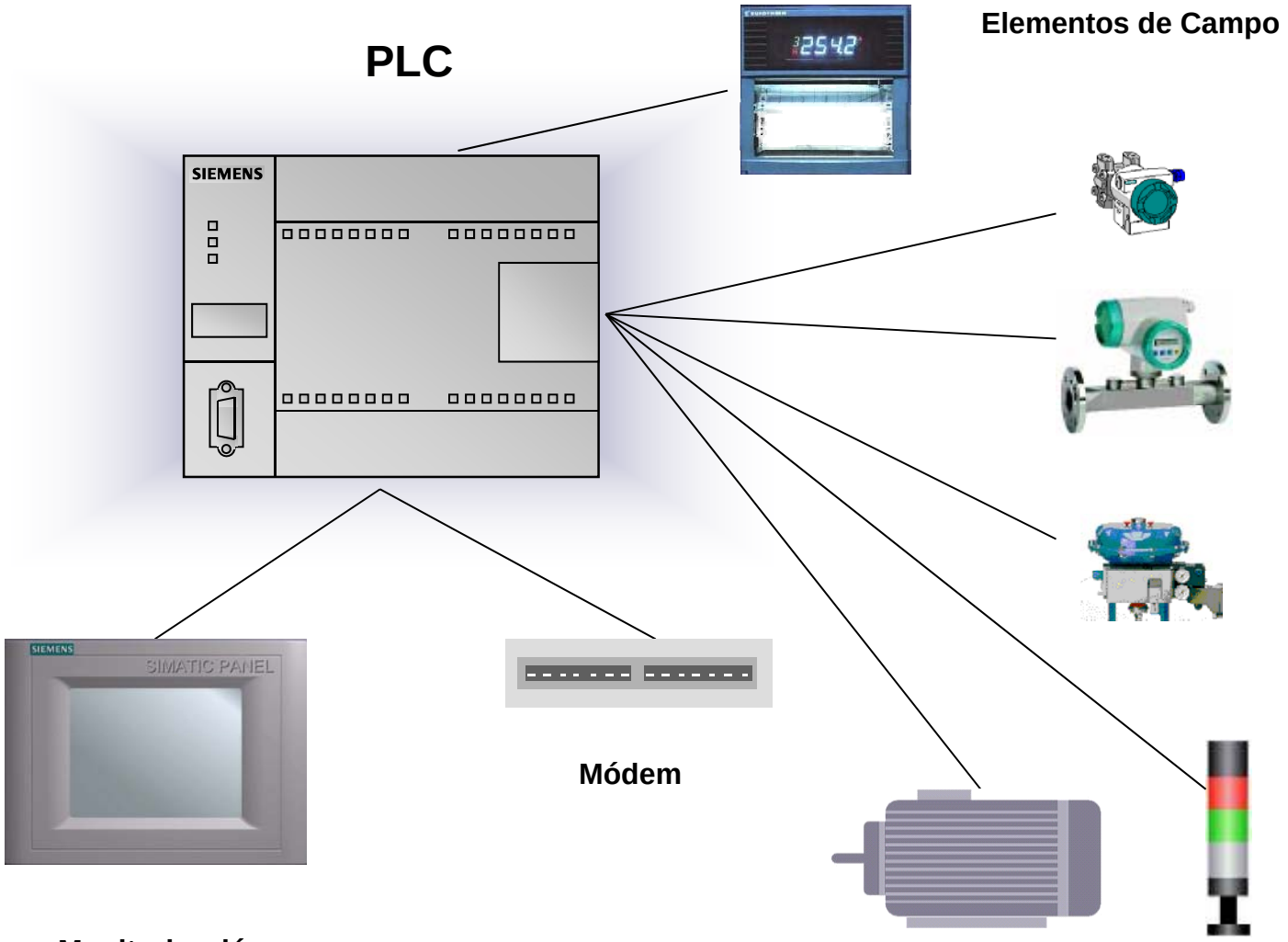
# CIP-SIP

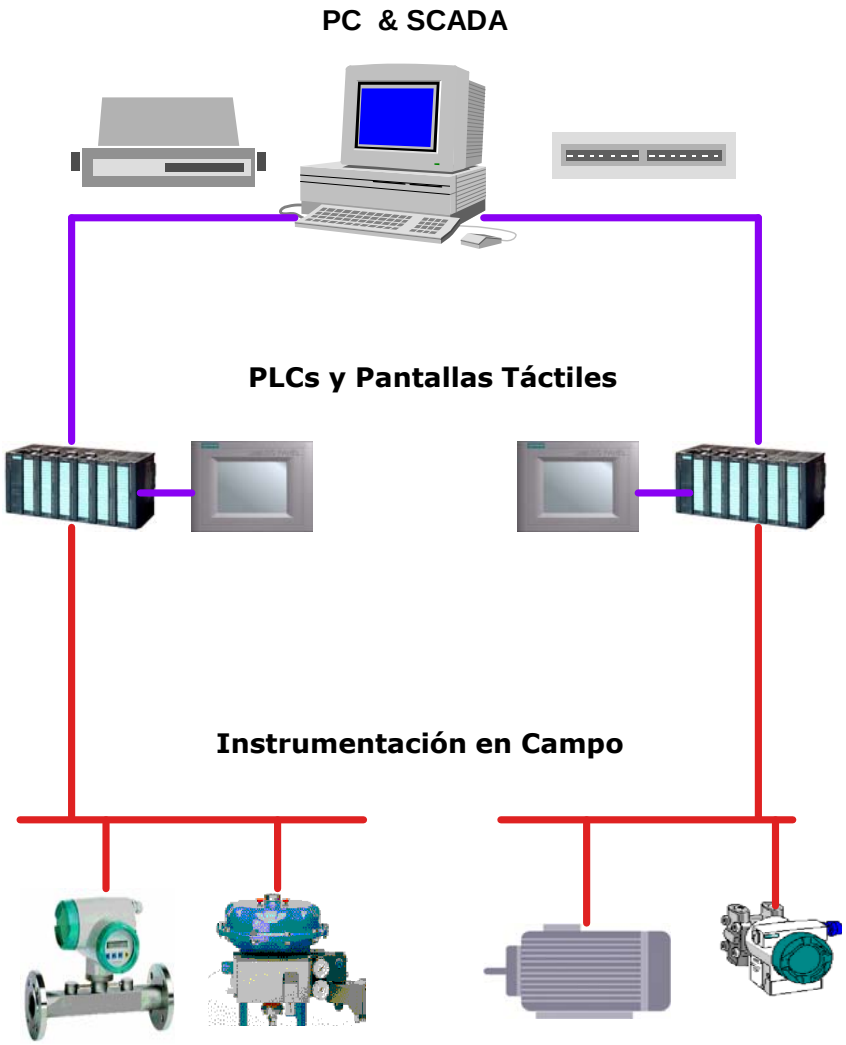
## VALVLES



# CIP-SIP

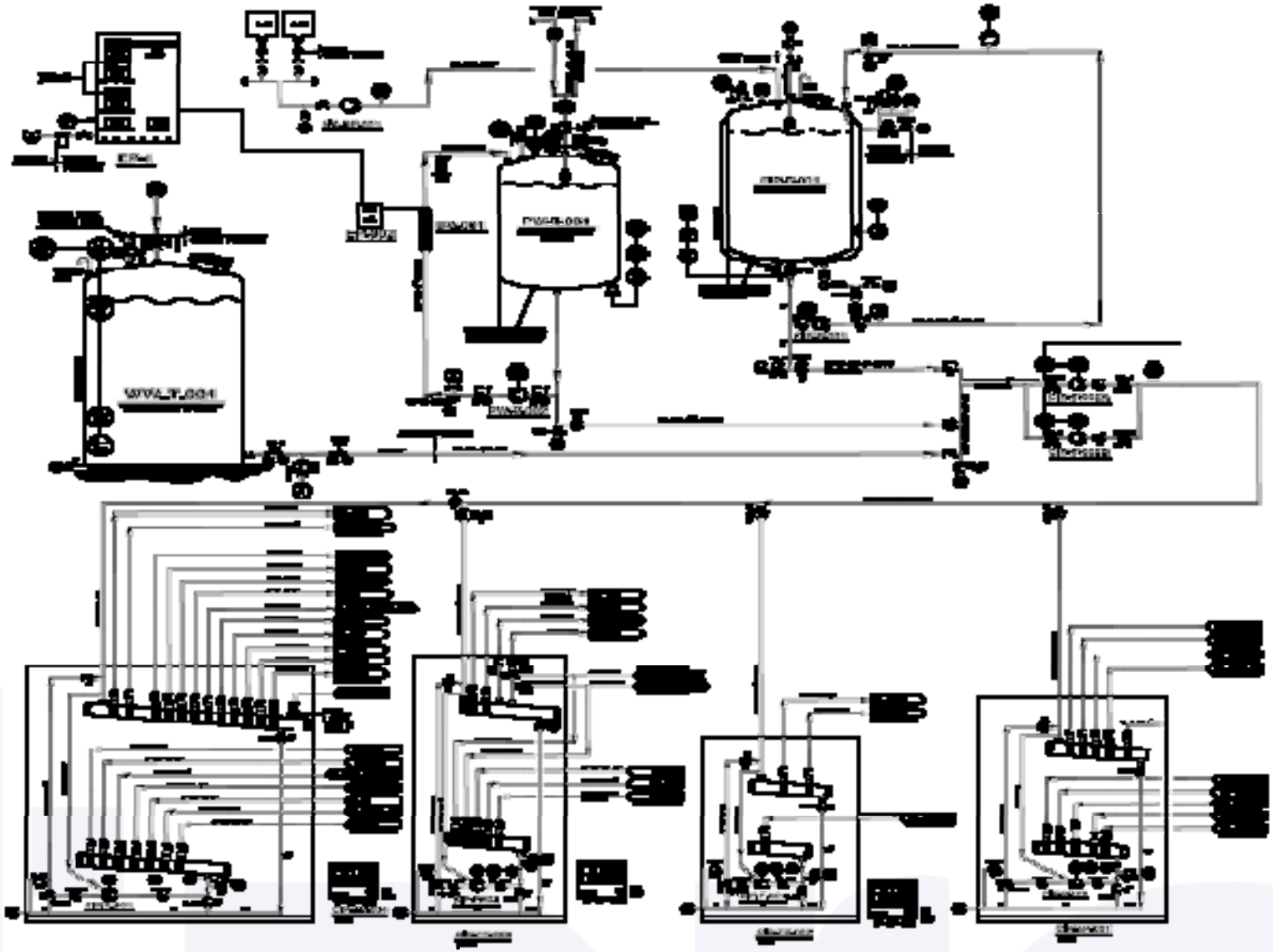
## CONTROL SYSTEM




PC & SCADA
PLCs y Pantallas Táctiles
Instrumentación en Campo

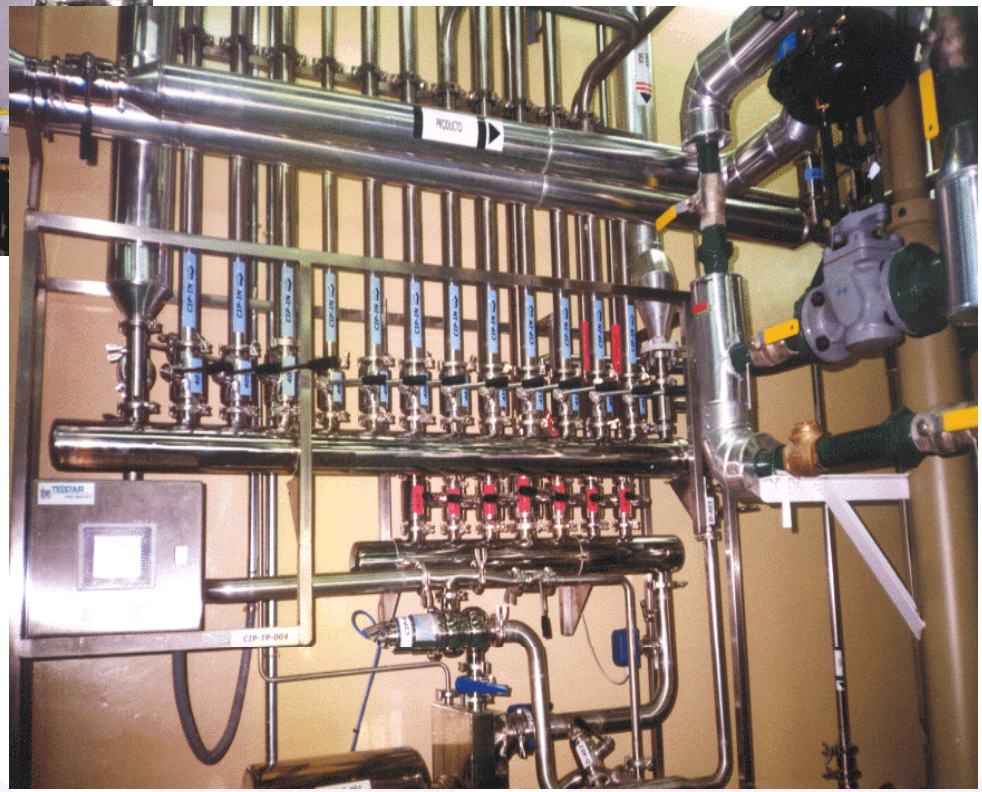
# CIP-SIP

## CASE1- APIs



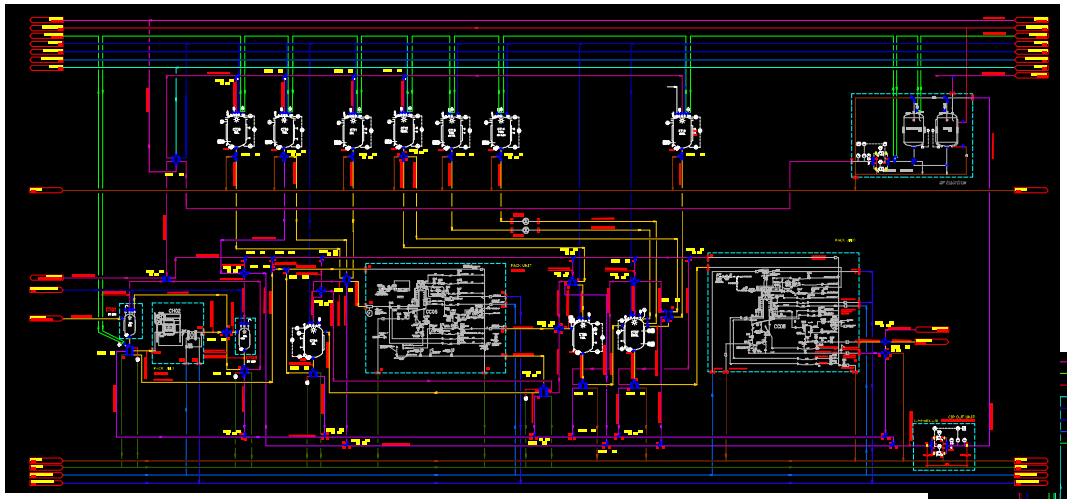
# CIP-SIP

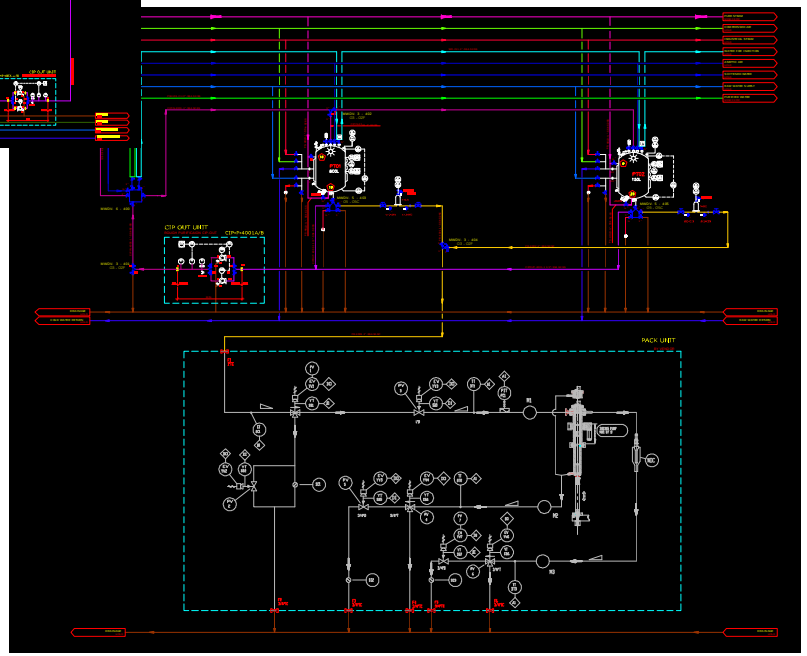
## CASO1- Planta de Producción APIs



# CIP-SIP

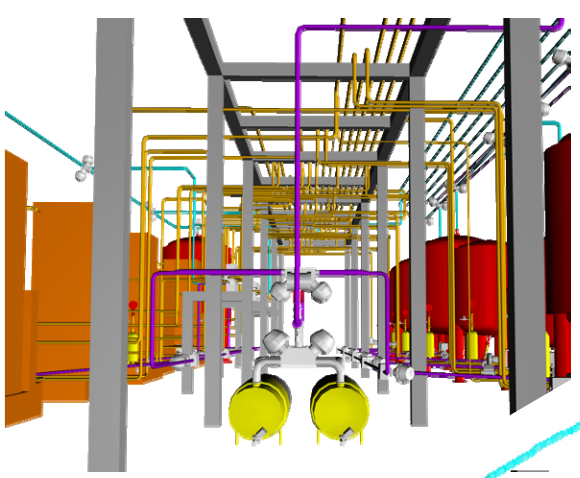
## CASO1- Planta de Biotecnologia

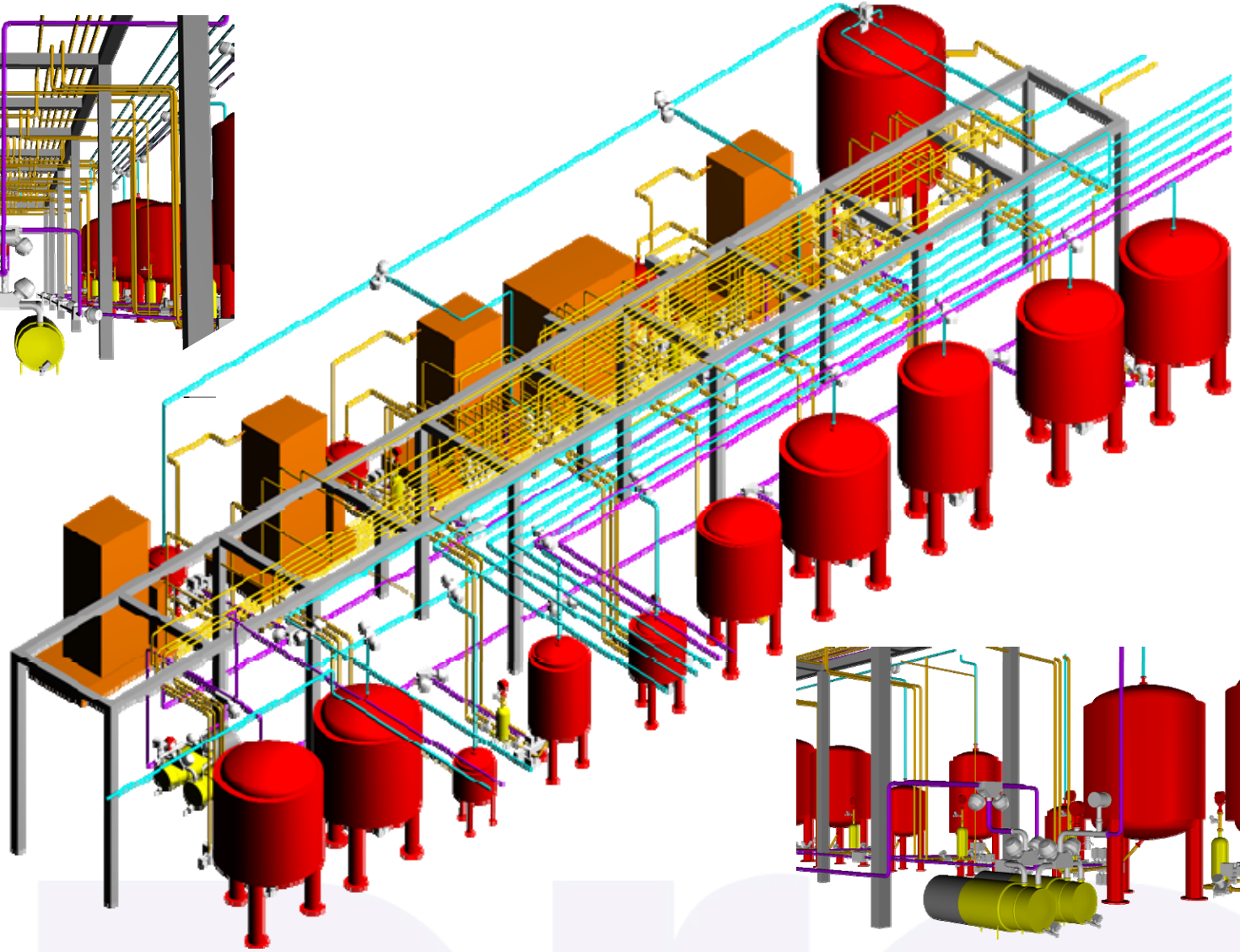




# CIP-SIP

## CASO1- Planta de Biotecnologia



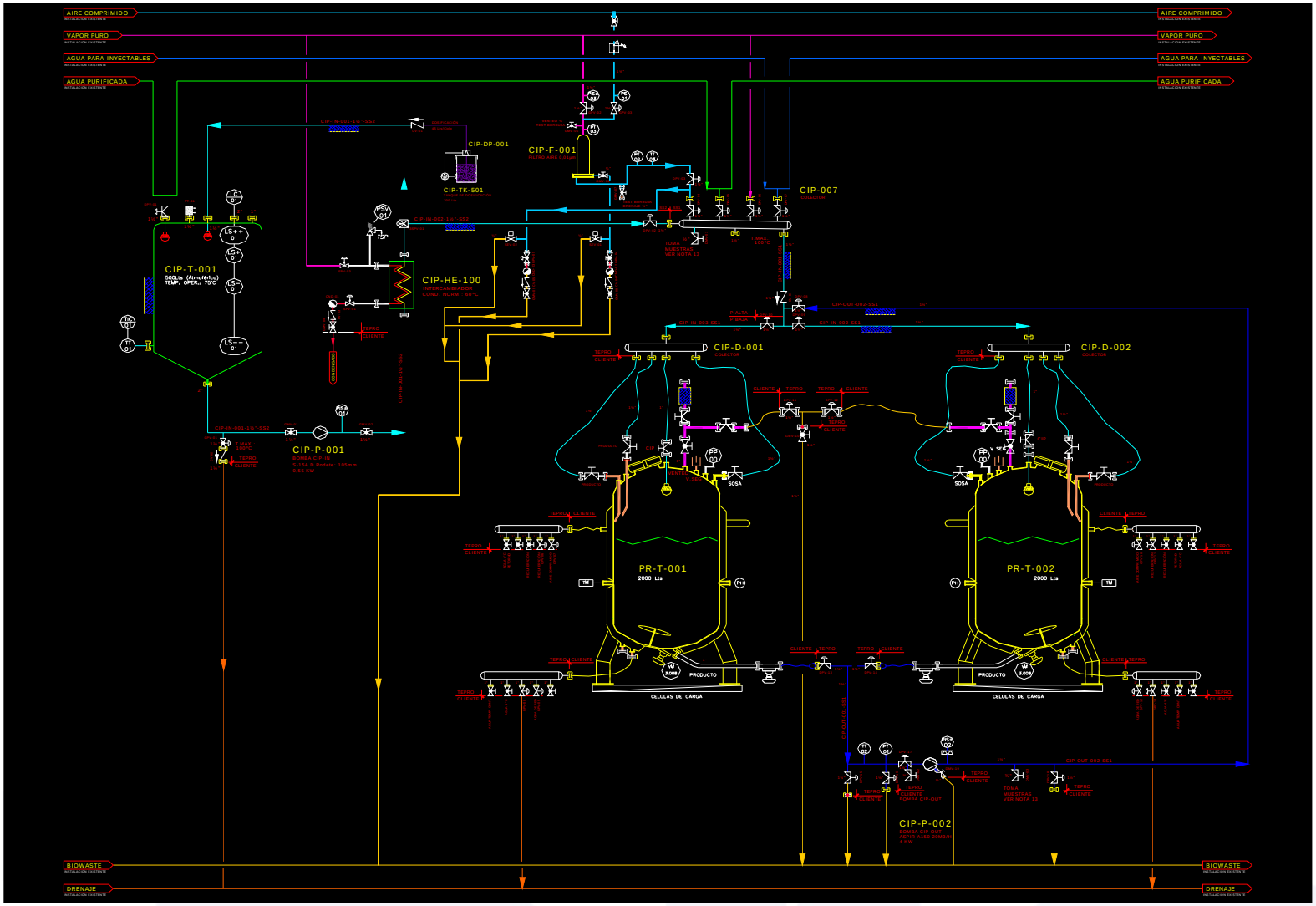


# CIP-SIP

## CASO1- Planta de Biotecnología

# CIP-SIP

## CASO1- Planta de Biotecnología

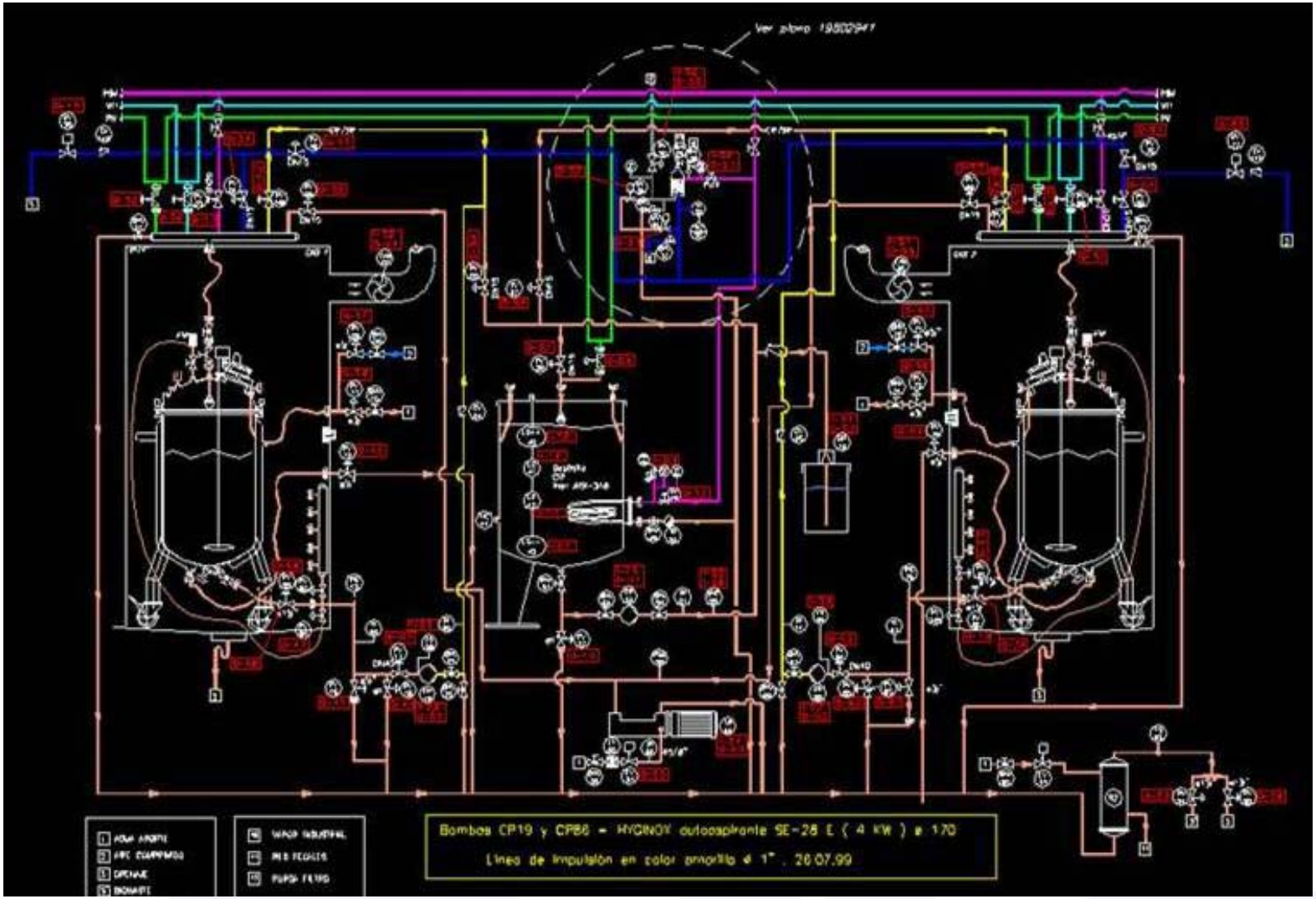


# CIP-SIP

## CASO1- Planta de Biotecnología


# CIP-SIP

## CASO1- Planta de Biotecnología



# CIP-SIP

## CASO1- Planta de Biotecnología

# CIP-SIP

## RUEGOS Y PREGUNTAS

# SOLUCION TEST

1) El principal objetivo de los sistemas CIP/SIP es reducir el riesgo de contaminación cruzada en los equipos e instalaciones de proceso
**VERDADERO**

2) Es recomendable que los sistemas de proceso a limpiar/esterilizar estén lo mejor definidos posible antes de acometer el análisis y diseño de los sistemas de limpieza
**VERDADERO:** Iniciar el diseño de un sistema CIP/SIP sin conocer con suficiente detalle las características de las instalaciones-equipos a limpiar provocará problemas de eficacia

3) Utilizaremos siempre los parámetros de velocidad recomendados independientemente del régimen de circulación (laminar, turbulento o transición) que resulte
**FALSO:** Se deberá verificar que el régimen de circulación es turbulento en cualquier caso

4) Los parámetros fundamentales a la hora de diseñar un sistema CIP/SIP son la “repetiiblidad” de los procesos, la fiabilidad y la monitorización-reporte de los parámetros críticos
**VERDADERO:** Estos factores se deben garantizar en cualquier circunstancia, incluso sacrificando otros factores importantes cómo eficiencia, precisión, etc…

5) En los sistemas que combinen CIP y SIP, se recomienda estudiarlos de forma combinada
**VERDADERO:** Se recomienda que los sistemas CIP/SIP se estudien en conjunto para aprovechar las sinergias entre ambos

6) Es necesario realizar un estudio del impacto que podrán tener las características de los distintos fluidos CIP/SIP en los equipos-accesorios-instalaciones de proceso
**VERDADERO:** Los procesos CIP/SIP pueden ser suficientemente agresivos como para dañar partes de los sistemas a limpiar, esto debe ser evaluado y reportado durante el diseño

# SOLUCION TEST

7) Aunque no estén en nuestro alcance de suministro, será conveniente estudiar las características de los equipos de proceso que estarán incluidos en los sistemas CIP/SIP
**VERDADERO:** Deberemos analizar con el mayor detalle posible las características de los sistemas a limpiar antes de iniciar el diseño CIP/SIP, principalmente para reportar cualquier posible punto de difícil limpieza que podamos encontrar en los sistemas a limpiar

8) Una vez definidos los sistemas CIP/SIP, es imprescindible realizar una revisión de los datos de consumo de servicios y en particular aquellos que sean críticos (aguas farma, aire comprimido estéril, etc…)
**VERDADERO:** Es imprescindible que se realice una revisión de los datos estimados de consumo especialmente de fluidos críticos, dado que las estimaciones iniciales pueden no ser correctas (caudales, presiones, temperaturas, …)

9) En una instalación de proceso compleja, puede ser muy recomendable combinar sistemas CIP/SIP fijos con unidades móviles
**VERDADERO:** Los sistemas móviles aportan gran flexibilidad que puede ser muy importante para realizar CIP/SIP de ciertas partes de los procesos. Así mismo tienen un importante impacto en el aspecto económico (a la baja) frente a los sistemas fijos

10)Para alargar los periodos en los que el equipo se considera limpio-estéril, se puede considerar el mantener los sistemas presurizados con gases adecuados
**VERDADERO:** Esta práctica, habitual en ciertos equipos (BFS) puede ser muy útil para alargar los periodos en los cuales los equipos se consideran (validado) limpios/estériles. Deberá ser realizado siempre mediante el uso de gases de características adecuadas.