Module #3 – Risk Evaluation and Control - Cleaning Process Development

- Chemistry and Physics of Cleaning
- Cleanability Studies (determination of Hardest to Clean)
- Comparison and Selection of Cleaning Agents
- Determination of "C-Value" and "Time-to-Clean"
- Using Design of Experiments to determine the "Cleaning Design Space"
- CASE STUDY – Presentation of Cleaning Plan

ASTM E3106
6. Cleaning Risk Assessment

- 6.5 Risk Identification
  - 6.5.1 Process residue hazards
  - 6.5.2 Equipment design ***hazards? No- Source of Variation***
  - 6.5.3 Procedural ***hazards? No- Source of Variation***

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6.5 Risk Identification

6.5.1 Process residue hazards

6.5.2 Equipment design ***hazards? No- Source of Variation; Likelihood of residue***

Potential hazards presented by equipment design should also be considered, such as the possibility of product buildup. Equipment should be designed to facilitate cleaning, inspection, and monitoring.

6.5.3 Procedural ***hazards? No- Source of Variation; Likelihood of residue***

Before use, cleaning procedures should be subjected to risk assessments, for example, cleaning FMEA or other risk management tools, to minimize risk of failure (for example, to ensure that product buildup is avoided), improve the cleaning procedures, and make the cleaning procedures more reliable and robust.

Risk Assessment-
Cleaning process evaluation and development

- Knowledge of Equipment Design/Cleanability
  - Concentration or dispersion of contamination
  - “Hot spots”-underside of agitator
  - Transfer of contamination -Common surface area
  - “Critical sites”,concentration points-filling
- Nature of Cleaning Process
  - Reproducible? Manual vs. Automated
  - Under Control? Process control and process indicators
  - Effective, Consistent? Residue removal capability

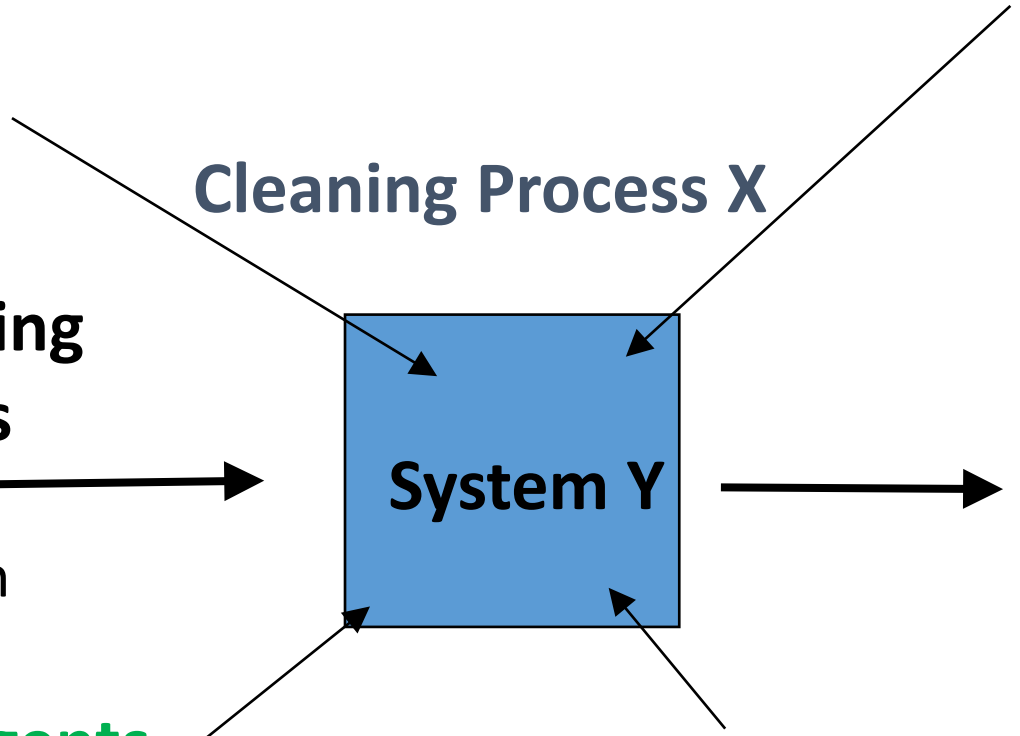
Cleaning process Evaluation/Selection

- **Agent-Cleaning chemistry/thermodynamic requirements**
- Method- fluid, hydrodynamics, coverage
- Procedure:
  - Sequence, duration, interval, technique
  - manual; automatic
- Measurement:
  - sampling, analytical

Cleaning Validation Design Space

Methods, Conditions, Parameters (CPPs)
Pressure, Temp, flow, rpm, concentration, timing, position

Facility, Systems, Tools & Equipment



DHT, Starting Conditions
Quality, Composition

Output CQAs, Attributes
Surface Quality, residues, bacteria
Bioactive Residue A
Surface (µg/cm2);
Rinse (mg/L);

Media, agents, consumables

Procedure-
sequence, duration, interval, control

Adhesion

- Molecular
- Eectrostatic
- capillary

Residues

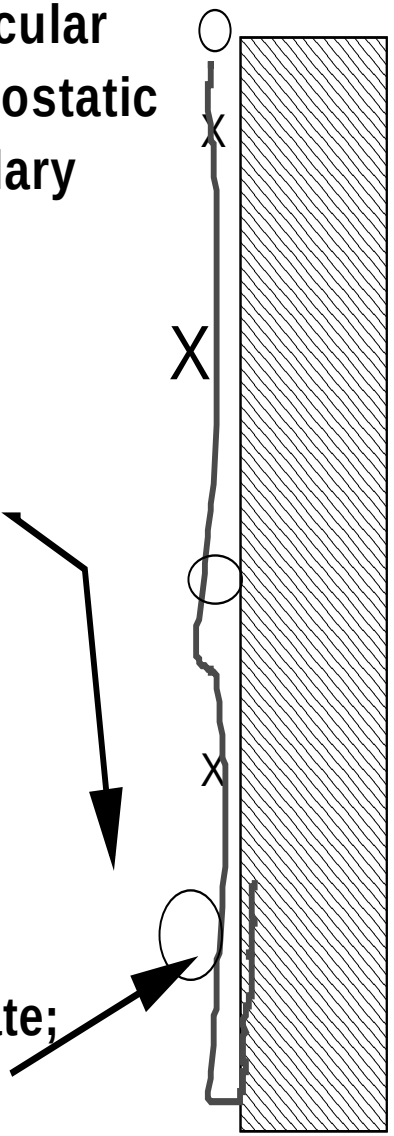
- Type
- Quantity
- Physical Form
- Drug Class

Decon Process

- Agent
- Applicator
- Hydraulics
- Temp&Time

Measurement

- in agent; from substrate; on substrate



Substrate

- Material Type
- Purpose
  - Dedicated
  - Multi-Use
  - Class
- Porosity/finish
- Accessibility

BASIC CONTROL MECHANISMS

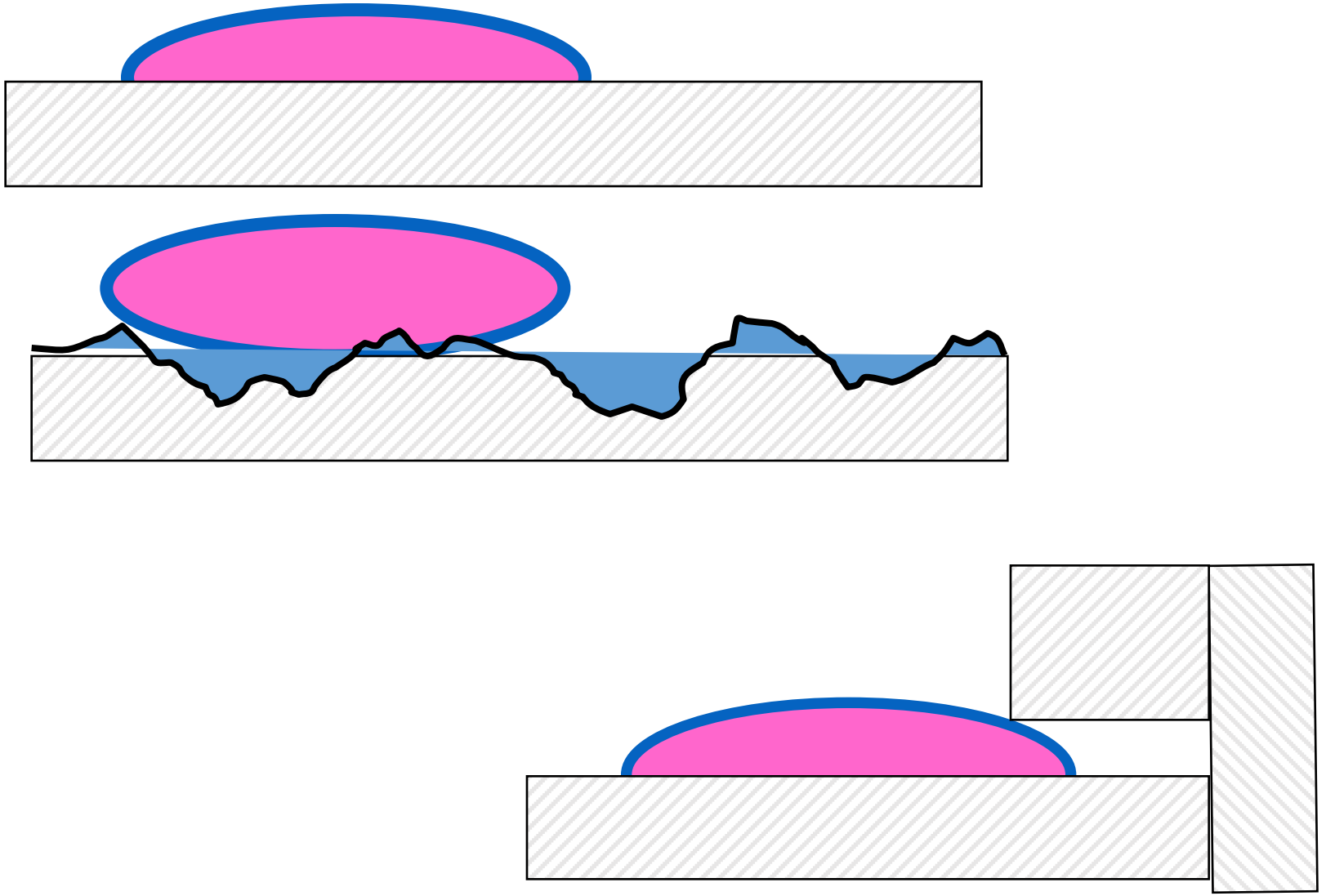
- Barrier-
- Deactivation
- **Removal –”cleaning”**
  - physical
  - **Chemical/liquid extraction**

Removal by Liquid Extraction

- Penetration
- Extraction
  - Solvency, dissolution
  - surfactant/emulsification
  - Reaction- oxidation, saponification, electrochemical
- Suspension
  - emulsification
  - Dispersion
  - Sequestration

Transfer from surface to liquid phase

Penetration:

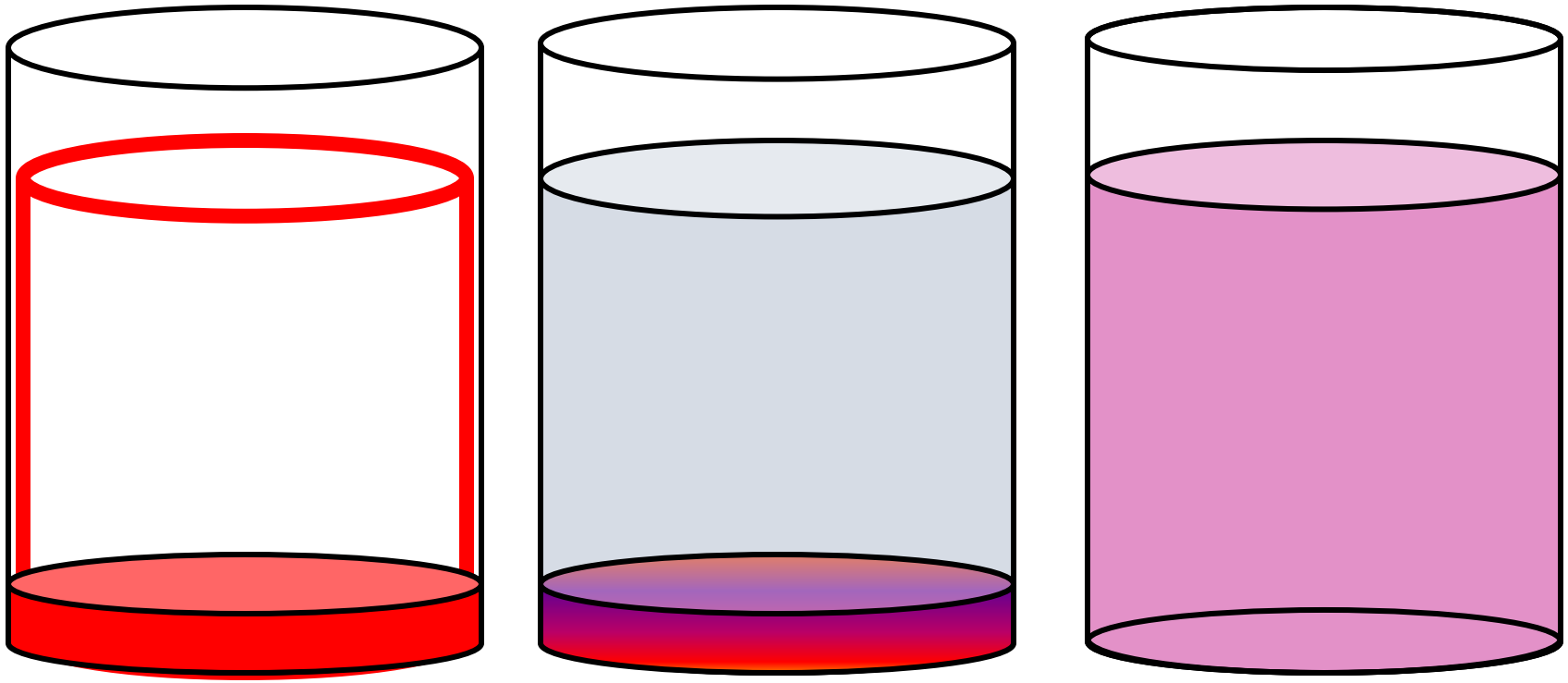


Removal by Chemical Extraction

- Penetration
- Extraction
  - Solvency, dissolution
  - surfactant/emulsification
  - Reaction- oxidation, saponification, electrochemical
- Suspension
  - Solubility
  - Dispersion
  - Sequestration

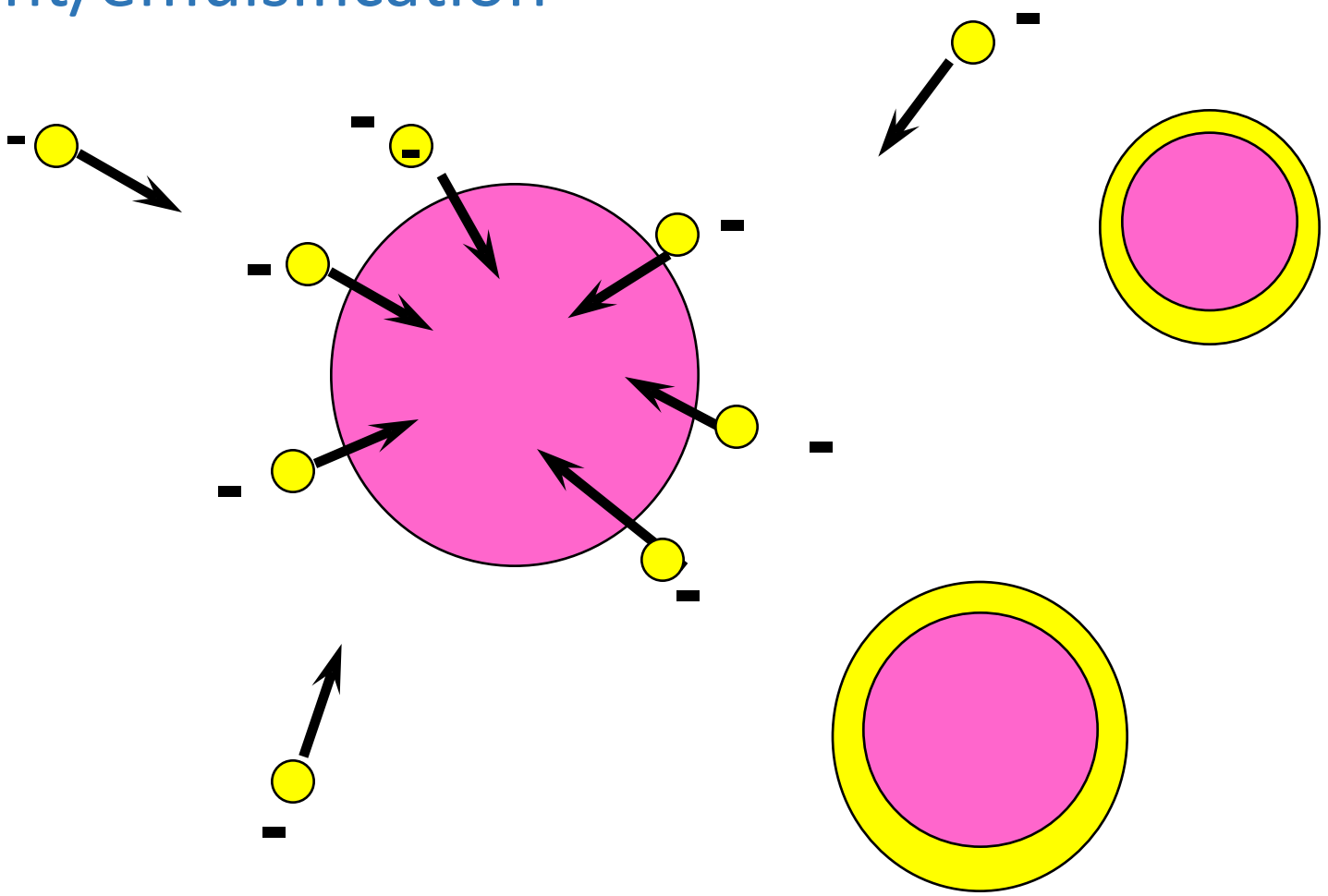
Transfer from surface to liquid phase

Extraction: Solvency, dissolution



EXTRACTION

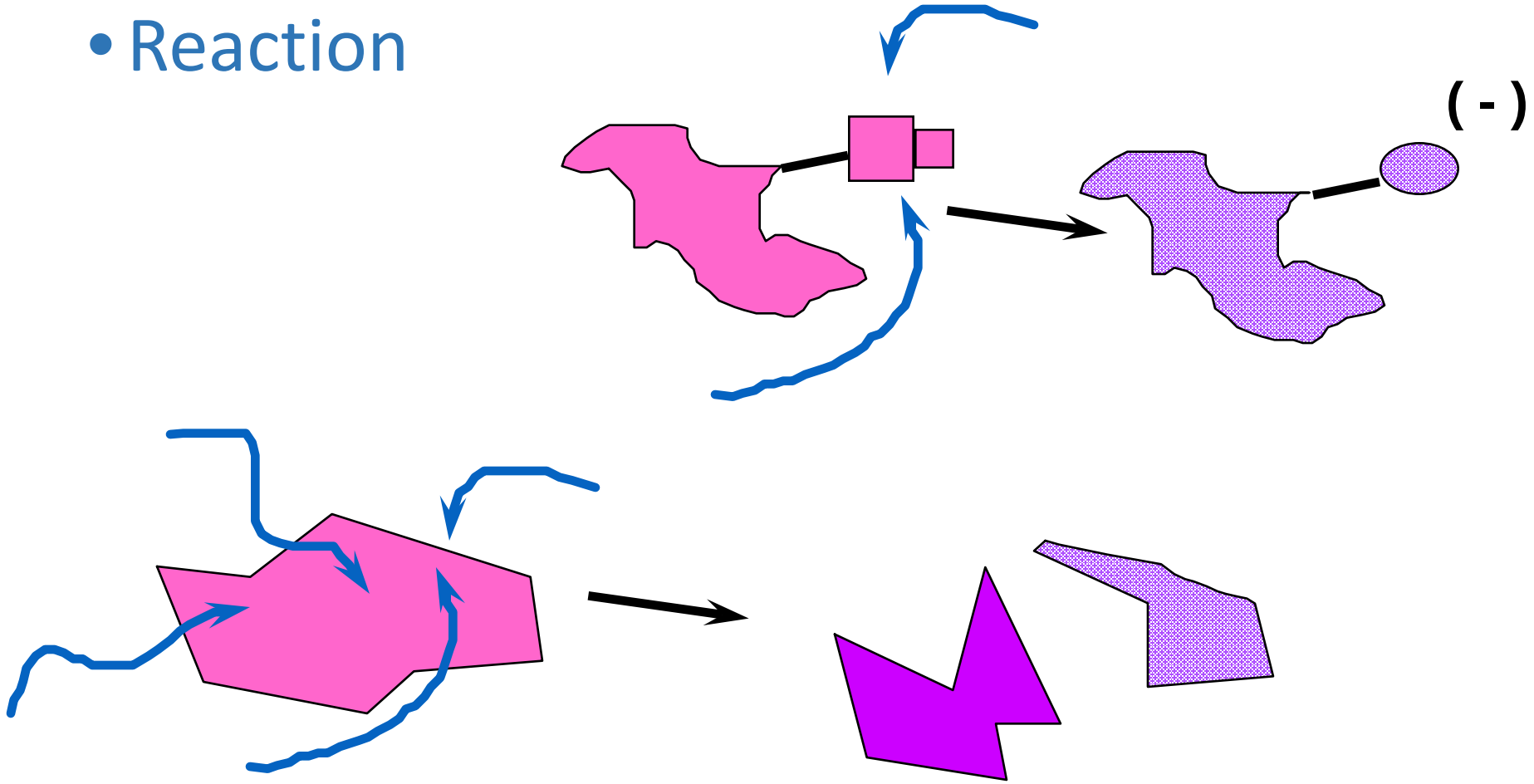
- Surfactant/emulsification



Substance intact, surface is modified

EXTRACTION

- Reaction

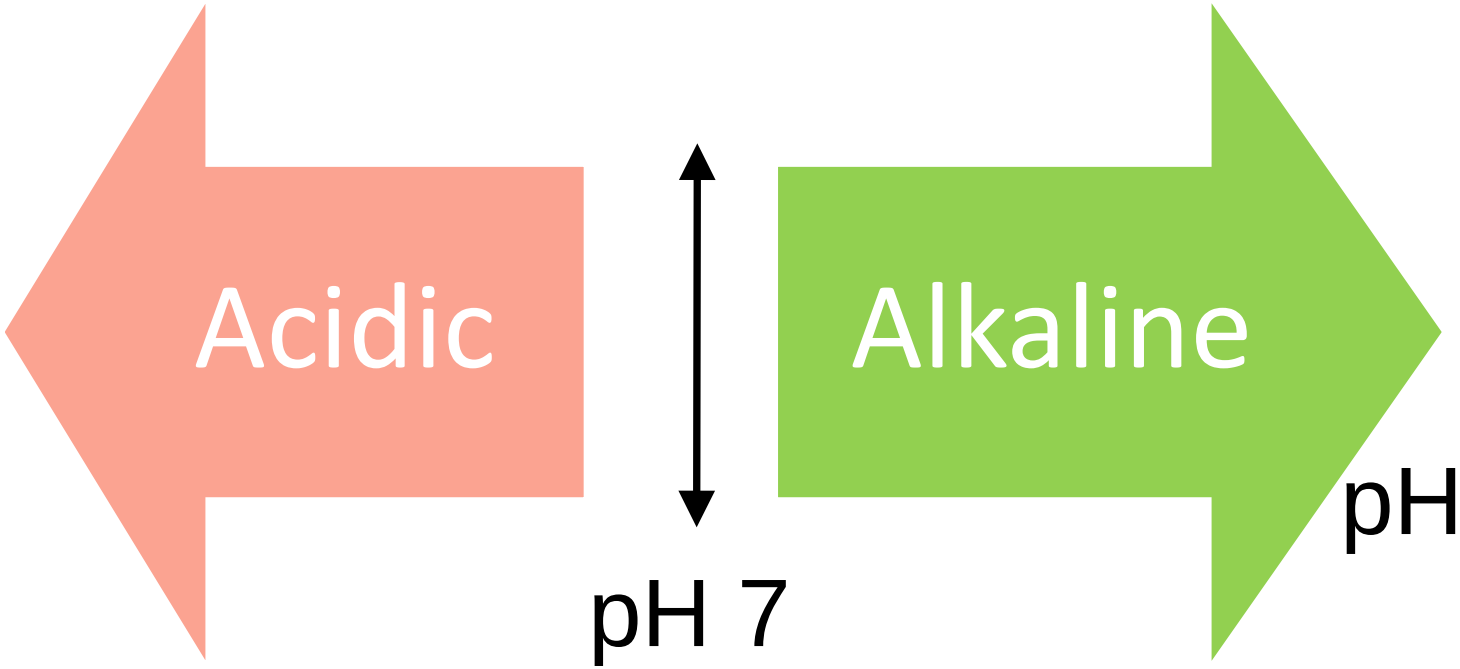


Basic Substance is altered

Cleaning Chemistry, Cleaning Agent Composition

- **Solvent**- Aqueous vs.Organic: acetone, alcohol, chlorinated organics
  - dissolve water insoluble organics
  - environmental problems
- **Alkaline**- NaOH, KOH, Carbonates, Silicates
  - Dissolution at ***high pH***
  - React/remove saponifiable organics
  - problems w/ handling, safety, corrosion, discharge
- **Acid-** Nitric, Phosphoric, Citric, Glycoloic
  - ***Low pH*** dissolution- descaling, passivation
- **Neutral**- surfactants, emulsifiers, aqueous solvents

pH Scale



pH 0

pH 14

pH 7
Neutral

Calcium/inorganic scale,
urine & organic scales,

Organics, proteins,
oils, dirt

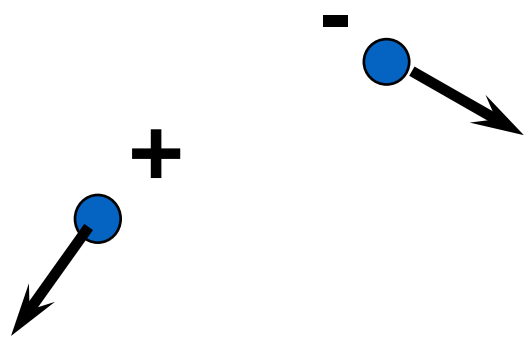
Other Components of Cleaning Agents

- Surfactants, either high or low foaming
  - anionic - negative charge

    Soap, Sodium Xylene Sulfonate
  - cationic- positive charge

    Quaternary ammonium
  - Nonionic

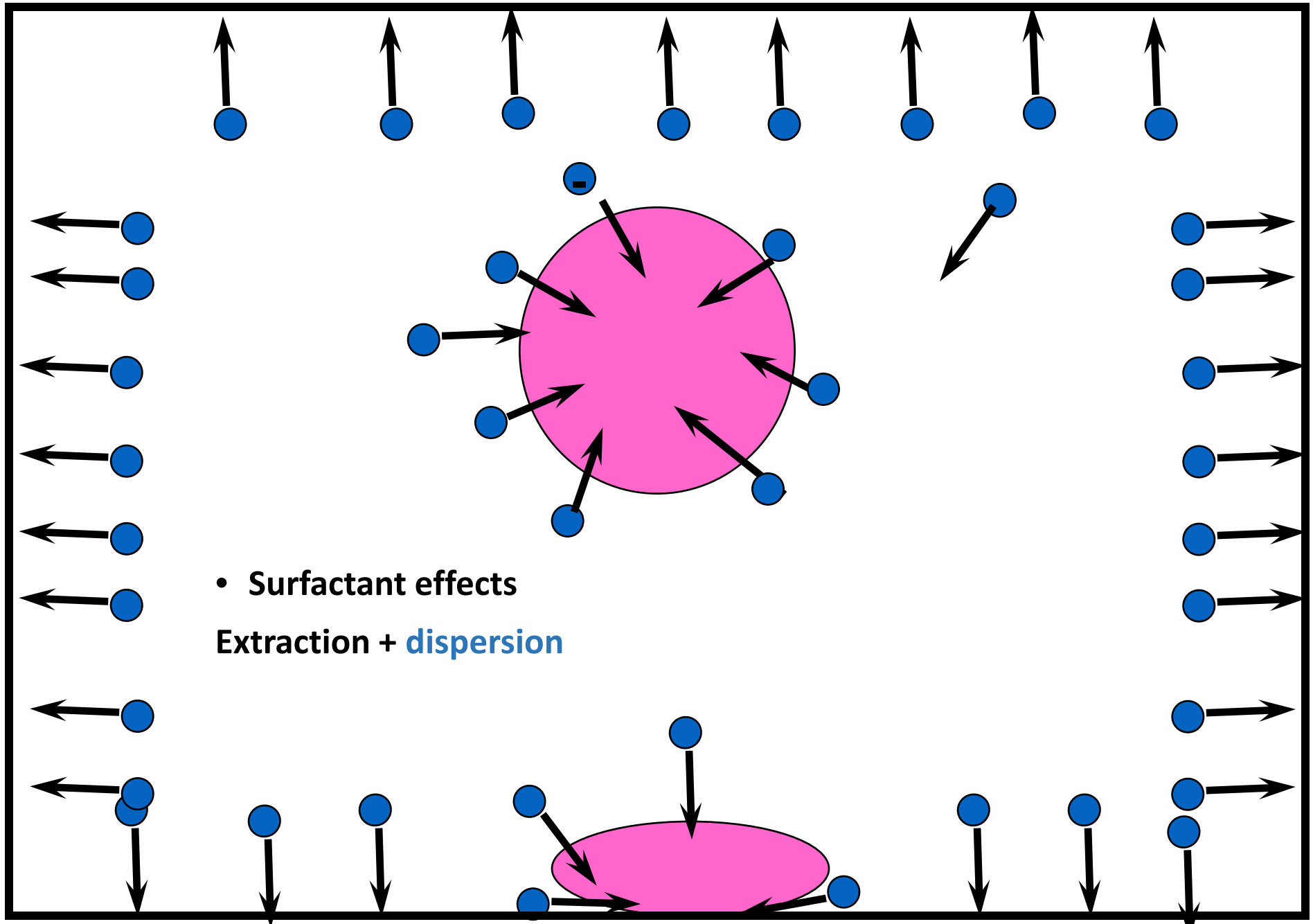
    alcohol ethoxylates



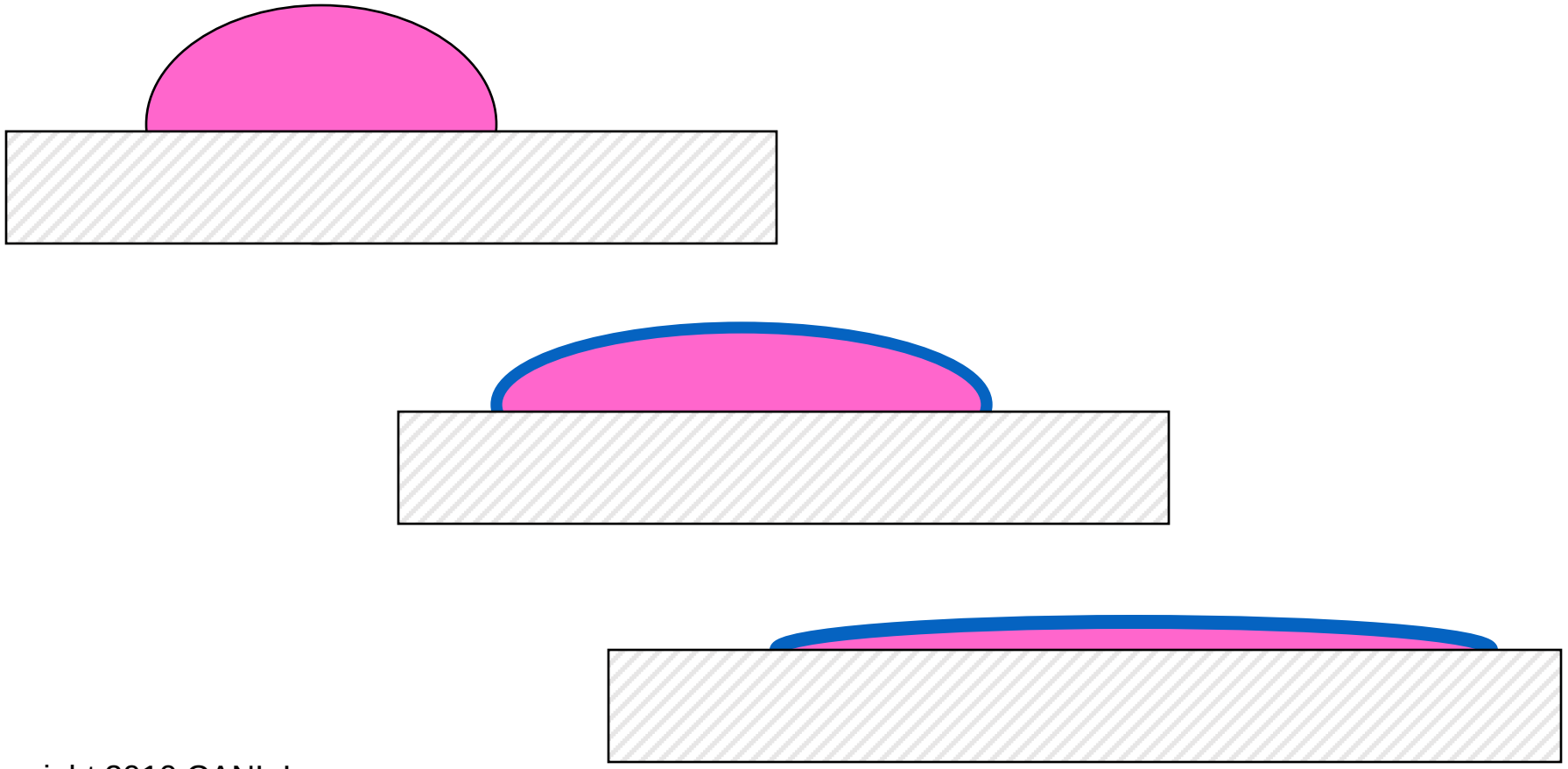
CH3-CH2-CH2-CH2-(CH2)n-O-	(CH2-CH2-O)n-CH2-CH2-OH
Hydrophobic	Hydrophilic

  - Amphoteric

    betaines



- ***Surfactant Wetting: Surface tension reduction***



Other Components of Cleaning Agents

- "Builders"
  - sequestrants/dispersants/chelants
  - lower water hardness- Ca++, Mg++,
  - Suspend and disperse residues

  Examples
  - Inorganic Phosphates
  - organic chelants (EDTA, gluconates, citrates)
  - polyacrylic acid polymers
- Enzymes
  - for medical, biologics, foods, lab equip.
  - proteases, amylases, lipases

Conventional Cleaning Agent Selection-

- **by type of chemistry/mechanism**
  - solvent
  - alkaline
  - acid
  - surfactants
  - chelants/sequestrants/dispersants
  - enzymes
  - ***multifunctional***

Water +pH Adjust + Detergents

	Solvent, Water	NaOH, KOH Acid	+ Surfactants	+ Builders
Penetration	X		X	
Dissolution	X	X High/low pH		
Emulsification	X	X	X	
Reaction				
Suspension			X	X

…..matched to residue type. What chemistry will remove what residues?

Residue	Chemistry
organics	solvents, alkaline+surfactant
proteins/biologics	alkaline+surfactant
inorganics/scales	acid, chelants
oils/fats/wax	solvents, alkaline+surfactant
silicones	solvents+alkaline+ surfactant
particulate	chelant+surfactant

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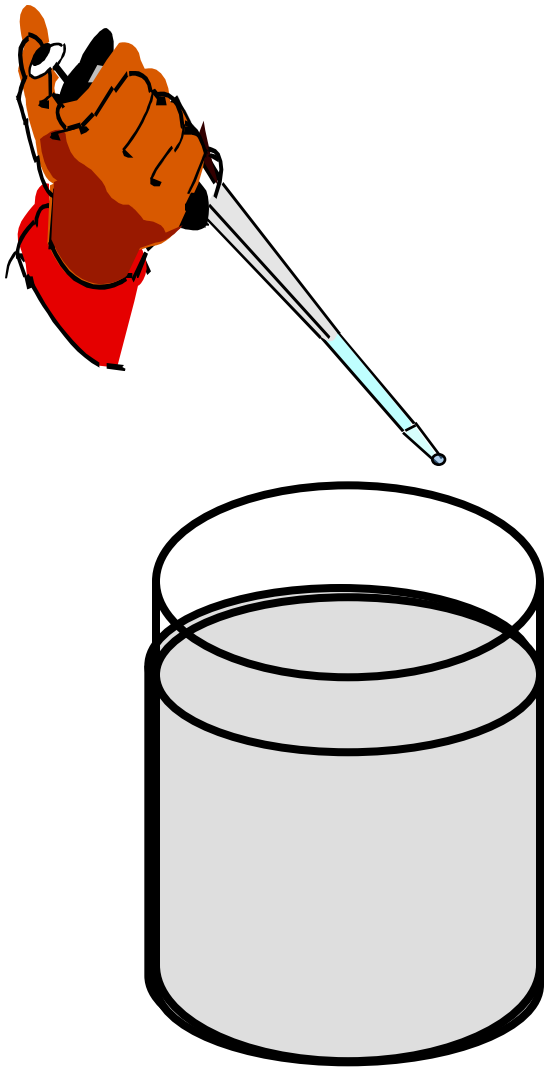
6.6.5.2 The chemistry and potential interactions between process residues and chemicals used as part of cleaning processes should also be understood, for example, the solubility of process residues in cleaning agents or rinsing agents should be considered to avoid situations in which process residues are not removed or whether degradation products may be formed that may be harder to clean or more toxic than the original process residue.

Solubility does not always predict “cleanability”

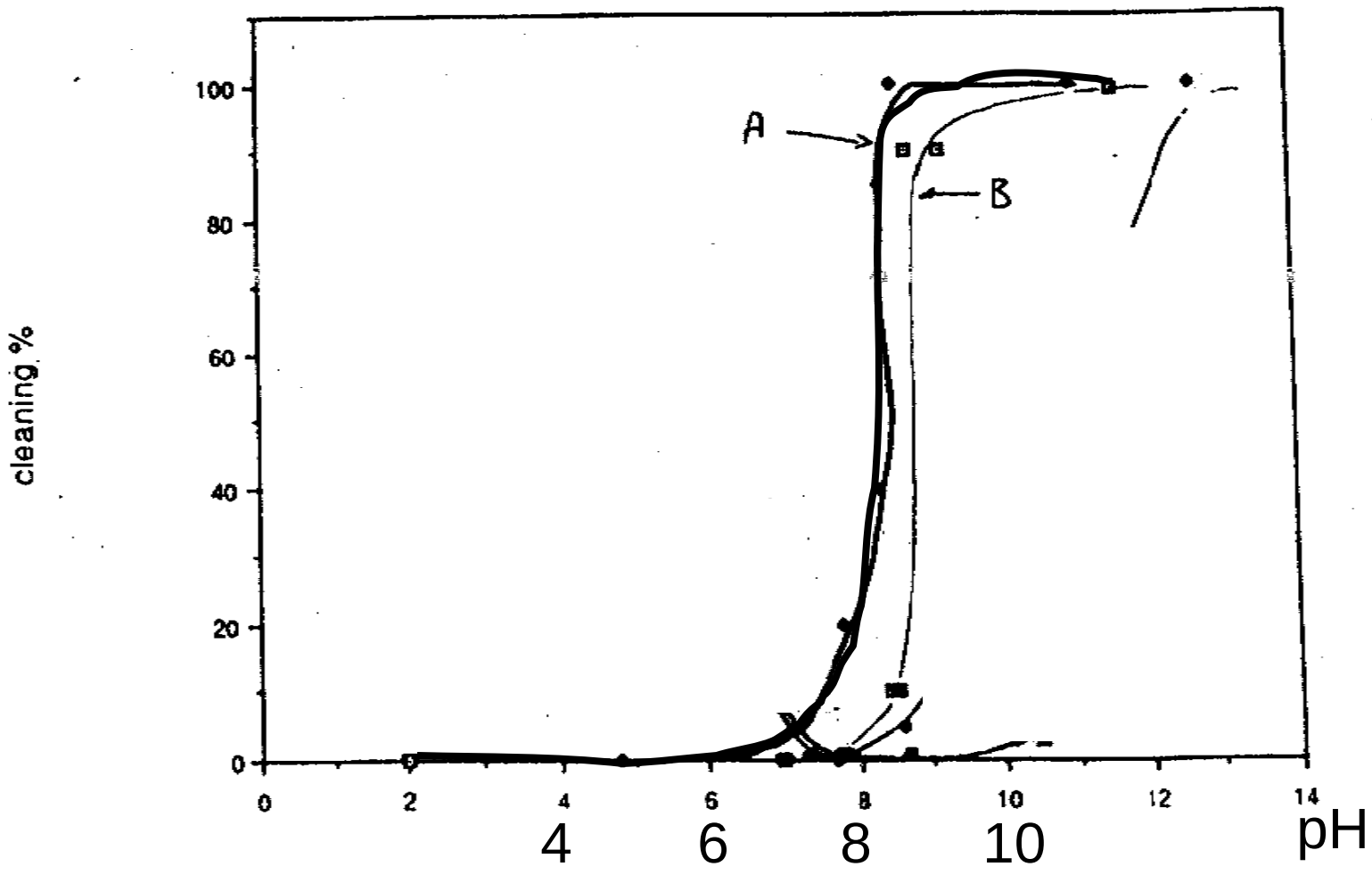
- Solubility is saturation level in solvent (mg/L solvent)
- Other factors affect dissolution RATE
- Other surface mechanisms or chemistry may overcome inherent solubility



Organic Residue Adhesion and Removal Parameters

- Substrate composition/energy
  - surface oxides
  - Surface hydrophobicity
- Residue interaction / bonding
  - acid-base, electron donor-acceptor reactions
- Residue physical & chemical
  - solubilities, pKa, melt point, viscosity
  - reactivity, structure, functional groups

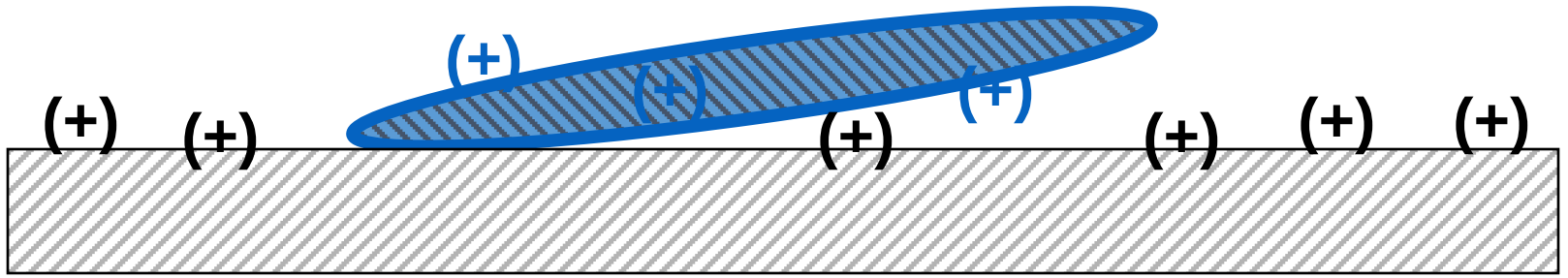
A & B: Stearic acid at two different conditions (Organic acid, insoluble in water)

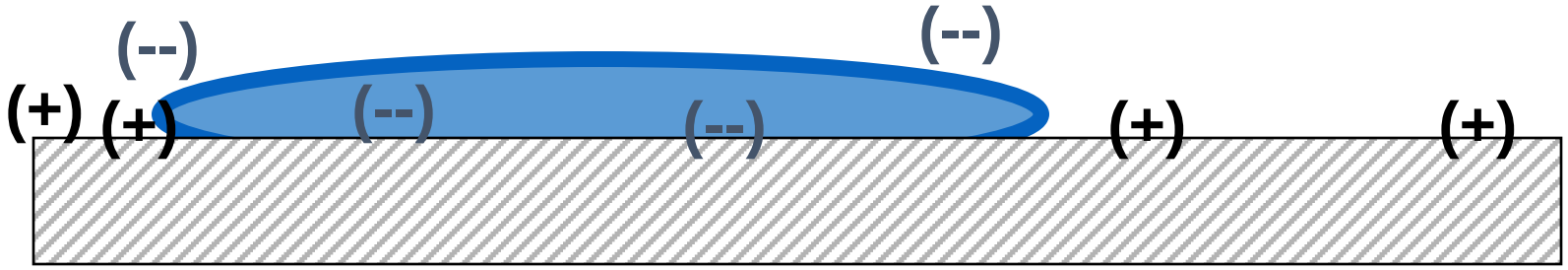


Isoelectric points of select materials- in water at 25°C

Solid Surface	Active Components	Isoelectric Point
Steel	Fe_2O_3, Fe_3O_4, Cr_2O_3	8.5
Glass	SiO_2	2.5
Molybdenum	MoO_3	3.7
Aluminium	Al_2O_3	9.0
Titanium	TiO, TiO_2, TiO_3	6.0
Tantalum	$Ta2O_5$	5.2

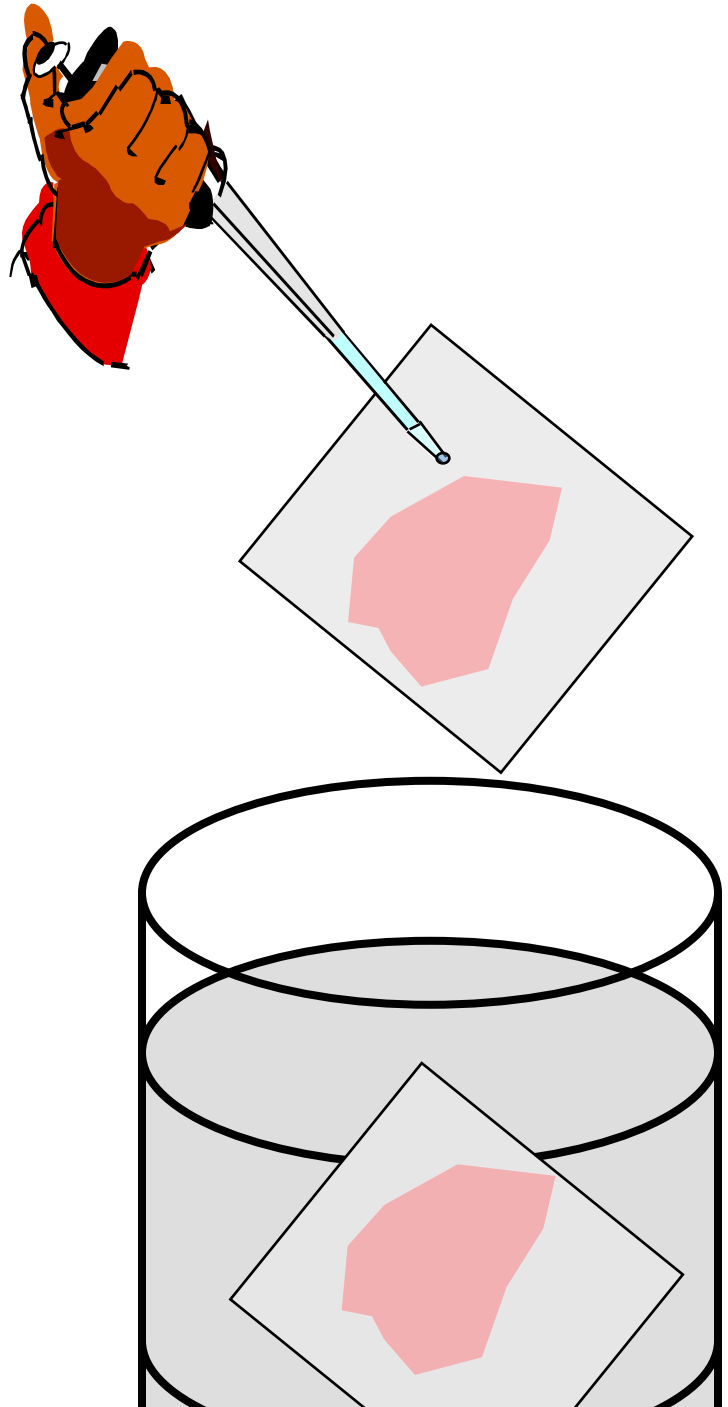
Surface Charge





Cleanability method

- Known qty of challenge residue solution is spiked on a specified test surface and dried
- Immersion extraction with cleaning agent , rinse fluid, or with spray, wipe or simulation of actual procedure
- Compare extracted amount with known amount; or visually compare remaining residue at given time.



Standard Cleanability Method

- Specified surfaces, test panels
- Standard surface preparation
- Consistent coupon spiking and sample prep (spiking qty., area)
- Controlled, repeatable drying, heat, simulation
- Consistent extraction
  - Agent prep and volume
  - Agitation, hydrodynamics- minimal stirred immersion
  - Temperature control
- Removal criteria
  - Visual, Water-break free,Gravimetric, Analytical

Residue Removal Study,“Cleanability” Study

Relative ranking only…

- better than solubility ranking
- IS a way to evaluate cleaning thermodynamics
- IS NOT a way to determine actual process cleaning time and kinetics
- Is NOT intended to clean to an analytical end point

Cleaning process Evaluation/Selection

- Agent-Cleaning chemistry/thermodynamic requirements
- Method- fluid, hydrodynamics, coverage
- Procedure:
  - Sequence, duration, interval, technique
  - manual; automatic
- Measurement:
  - sampling, analytical

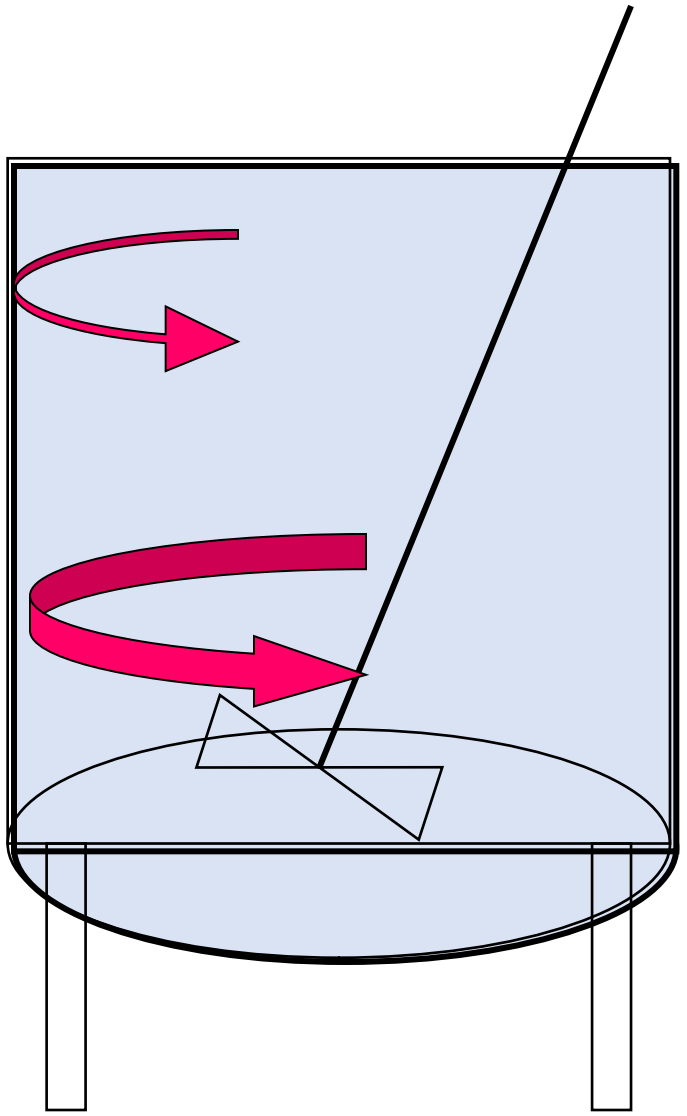
Process parameters & variables

- Access & Coverage
- Exposure/Intensity
  - Temperature
  - Action/Hydrodynamic/physical= METHOD
    - Flow, pressure, spray impingement,
    - Brush, mop, wipe
  - Chemical/Thermodynamic
  - Time/Procedural

System	As Qualified	Test
Equipment	Tank Y	IQ
Challenge	Drug A	Lab extraction
Process	SOP X	
Method	Stirred Immersion	OQ- *coverage*, mixer rpm
Agent	Water	Specs.,QC, EM
Temp.	40 °C	OQ, calibrations
Procedure	Automatic CIP , 3 X 10 min	OQ- Timer, SOP, fill & drain rate
Measurement		
Samples	3 swab, 1 rinse	Visual Observations
Analysis Acceptance	Active A, <10 ppm, <1ppm	Limits policy, recovery study
Qualified by	IQ, OQ,3 PQ runs	PQ Protocol

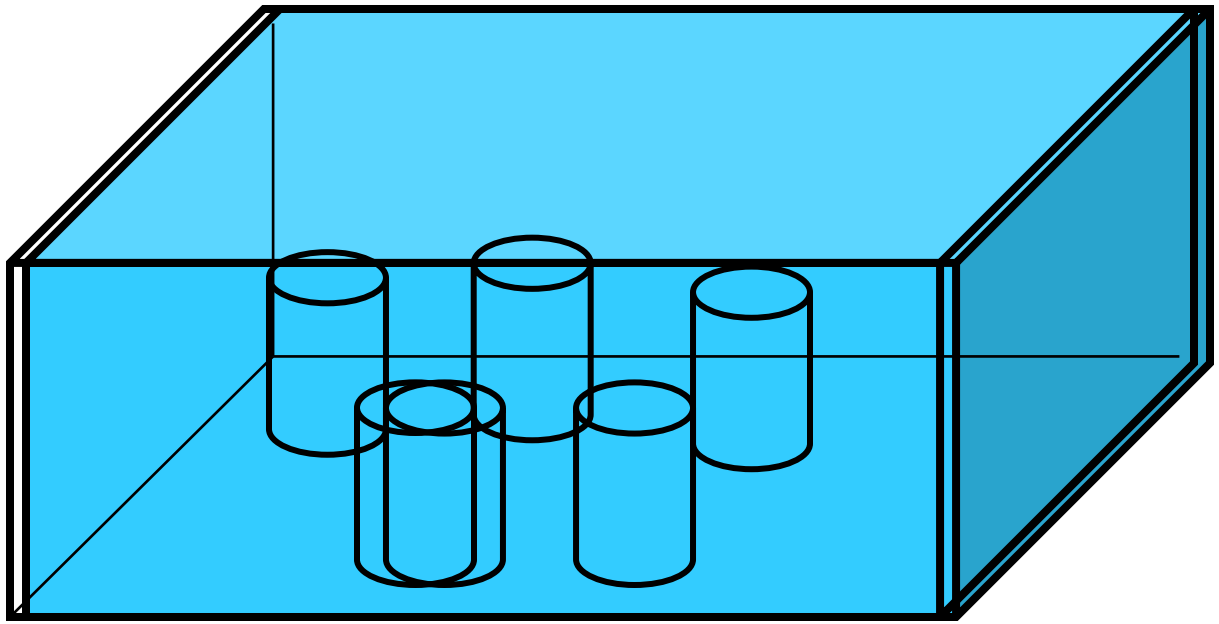
Immersion CIP

- Temperature
- Hydrodynamics
- Chemistry
- Time
- + Coverage



Immersion COP Washer

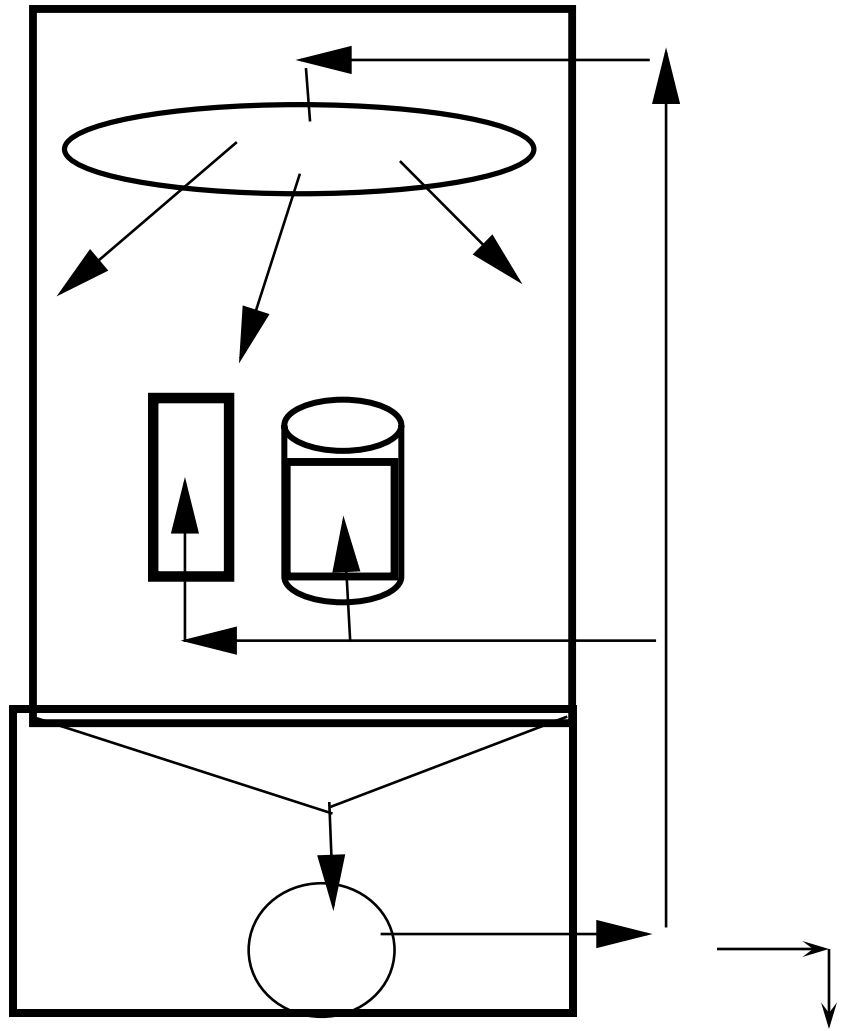
- Temperature
- Hydrodynamics
- Chemistry
- Time
- + Coverage



System	As Qualified	Parameter
Equipment	**LOAD Y**	**QTY Parts, orientation, position**
Challenge	Drug A, Lube Oil	
Process	**SOP X**	
Method	**Immersion** ***Ultrasonic***	-Fill level, volume -Residual water *-Sonication Settings*
Agent	Water	-Water quality
Temp.	40 °C	-Water Temp -Inlet Water temp -Heating capacity
Procedure	Automatic COP, 3 X 10 min	-fill & drain rate -timers

Spray Method- COP machines

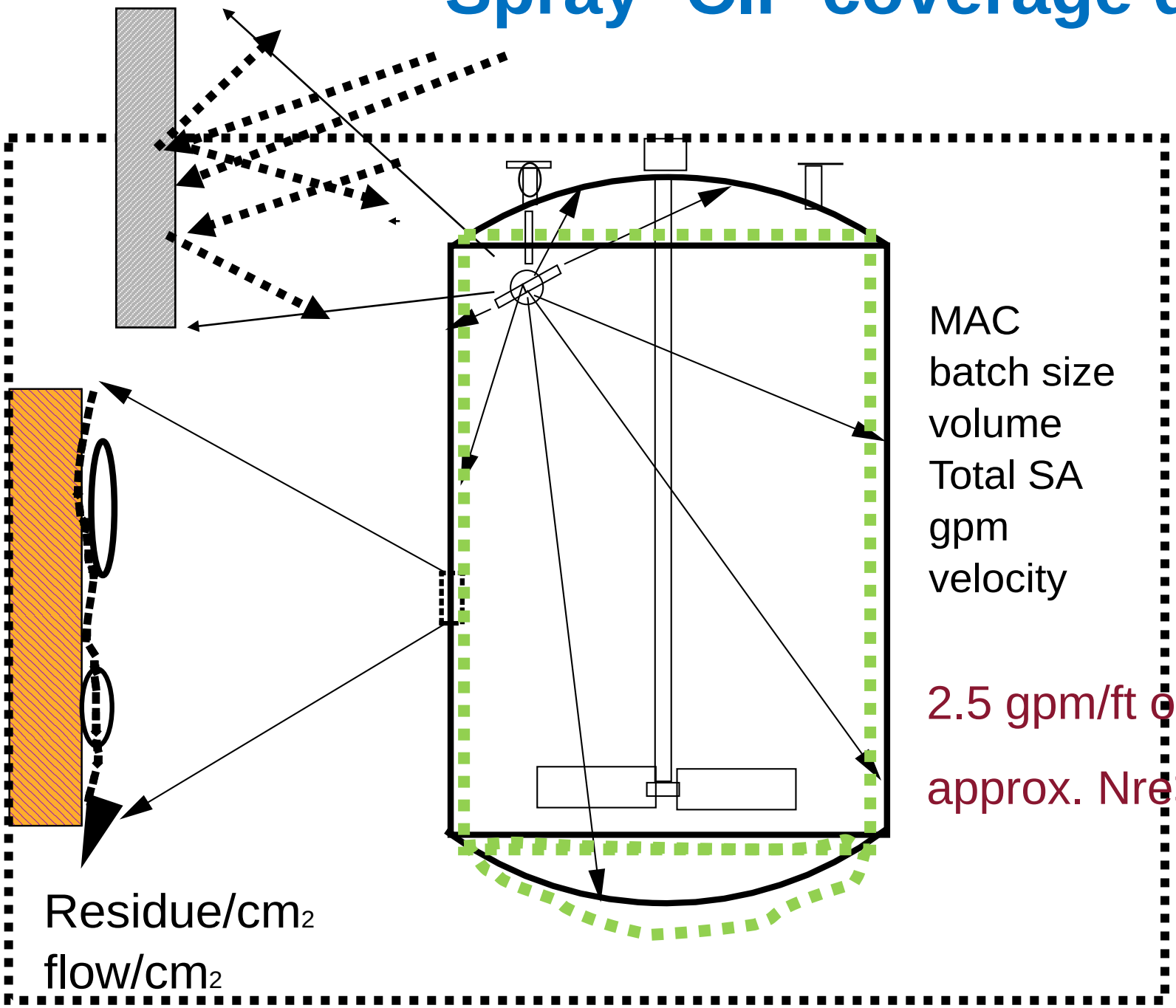
- Batch cycles
  - Pre-rinse
  - Detergent
  - rinse/sanitize
  - final rinse
- Fixed and moving spray nozzles



New Constraint is Foam

System	As Qualified	Parameter
Equipment	LOAD Y	QTY Parts, orientation, position
Challenge	Drug A, Lube Oil	
Process	SOP X	
Method	Spray Washer	-Wash tank volume -Spray Manifold -Pump pressure, flow
Agent	Water	-Water quality
Temp.	40 °C	-Water Temp -Inlet Water temp -Heating capacity
Procedure	Automatic COP Cycle	-fill & drain rate -Cycle steps & timers

Spray- CIP coverage devices



MAC
batch size
volume
Total SA
gpm
velocity

2.5 gpm/ft or 30 LPM per m circum.

approx. Nre>2000 , 1 ft/sec velocity

Residue/cm$_2$
flow/cm$_2$

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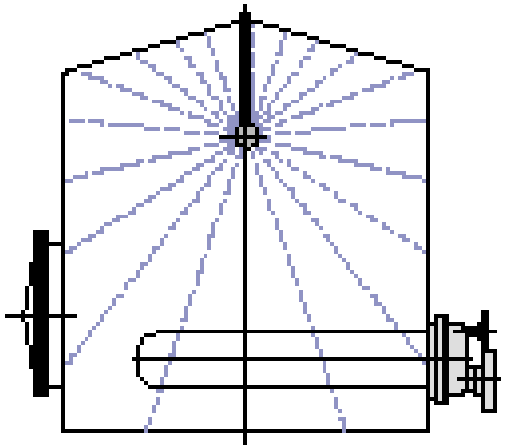
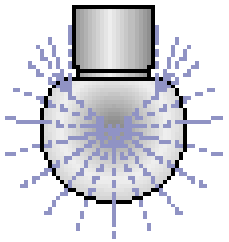
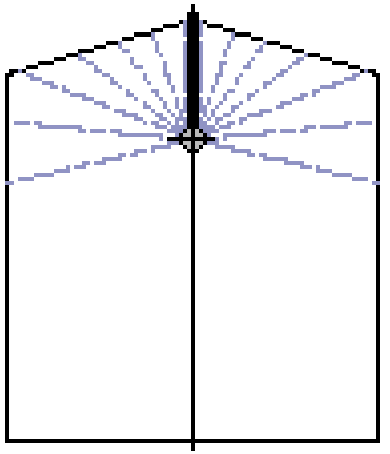
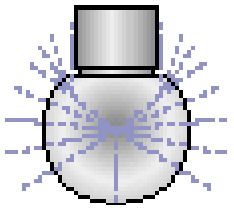


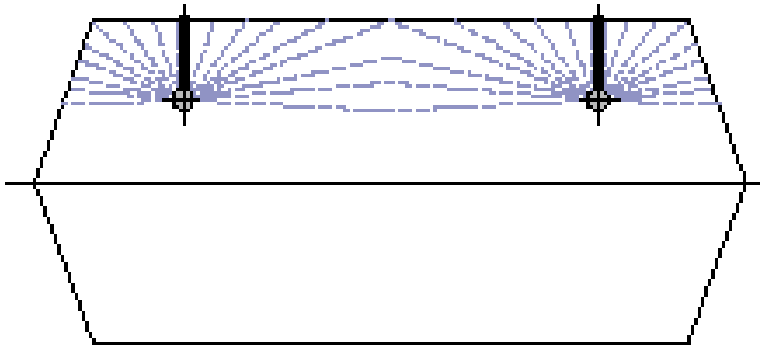


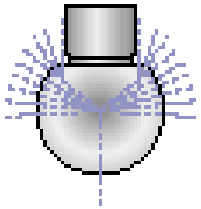
Spray pattern A
for vertical tanks with
tank internals





Spray pattern G
for vertical tanks





Spray pattern L
for horizontal tanks

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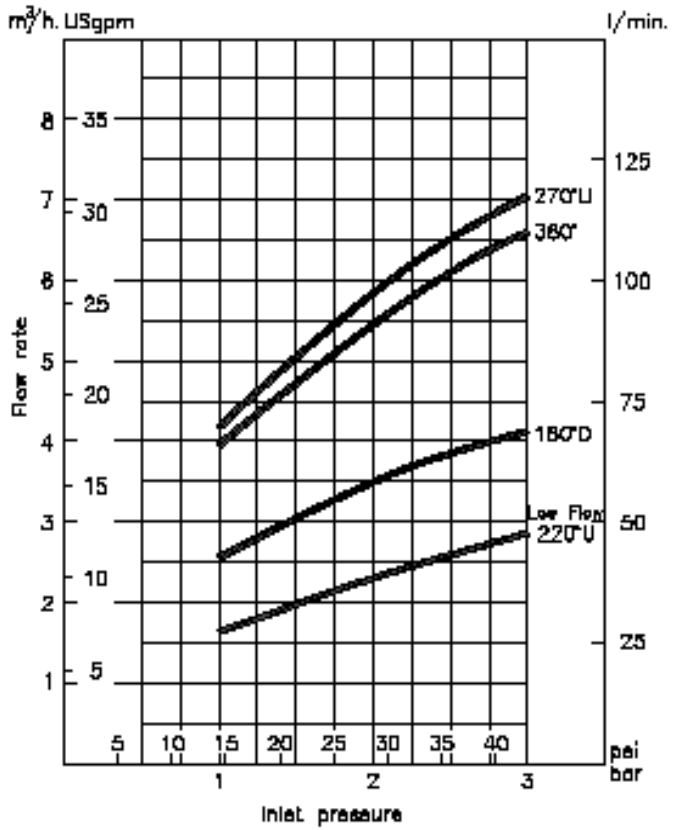
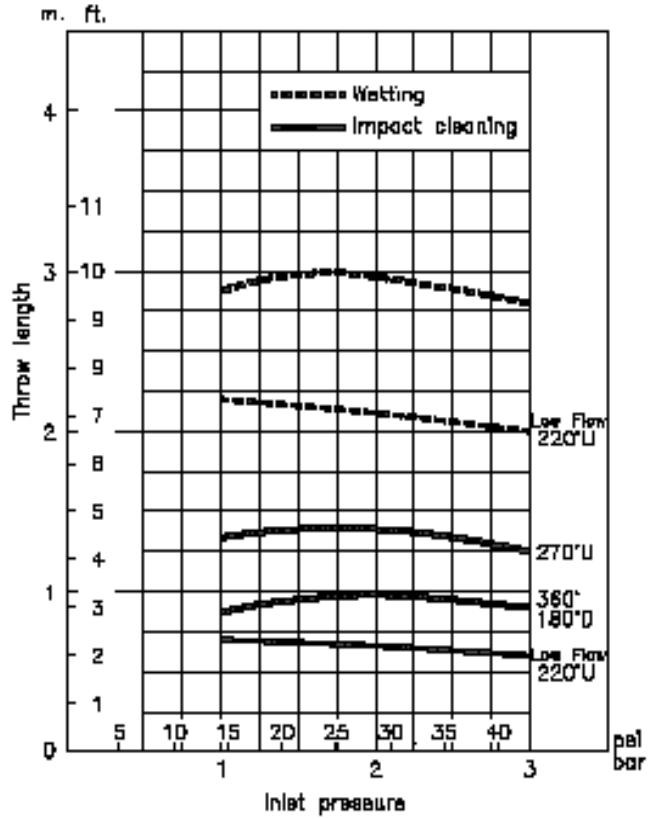
Tank Cleaning Systems

Type **SaniMidget**

Flow Rate



Cleaning Radius



Toftejorg

TANK CLEANING SYSTEMS

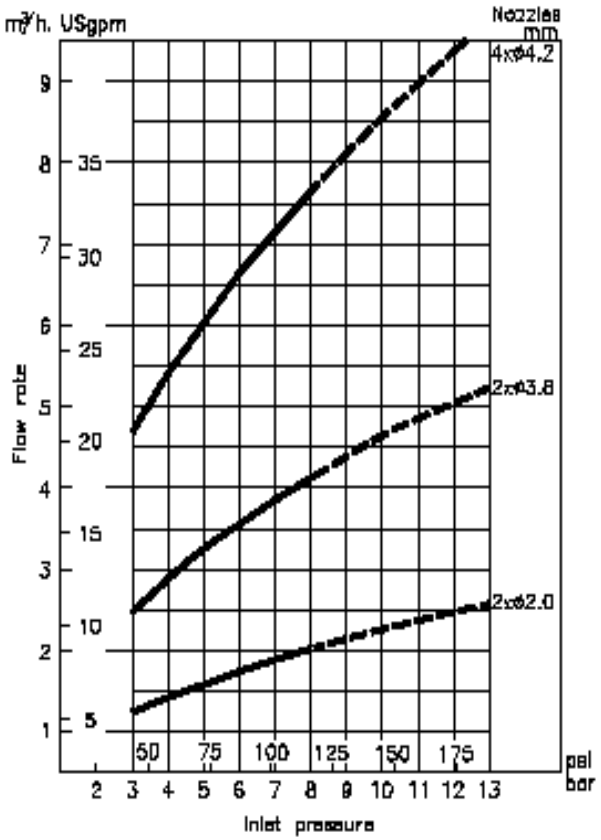
TYPE

SaniJet 20

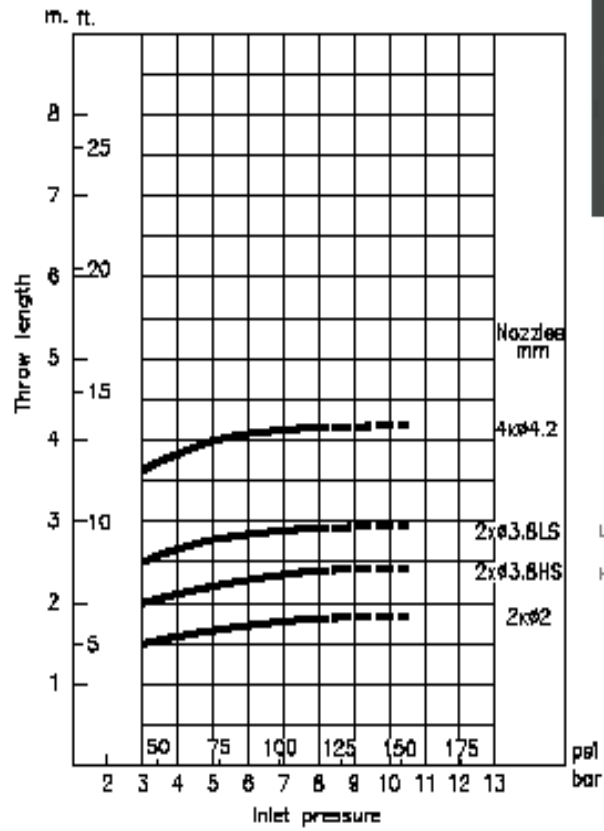
Media driven

Performance data:

Flow rate



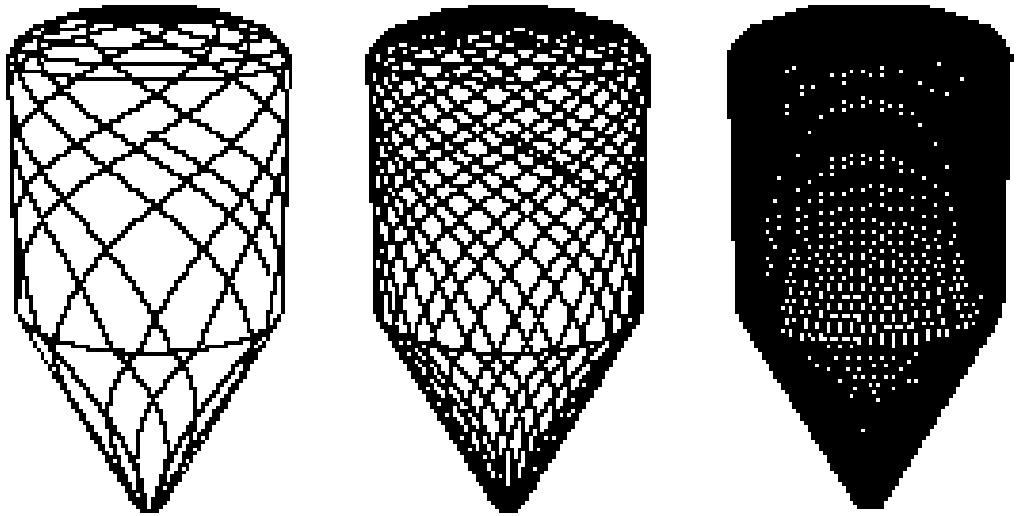
Effective Throw Length
Media driven



LS = Low Speed

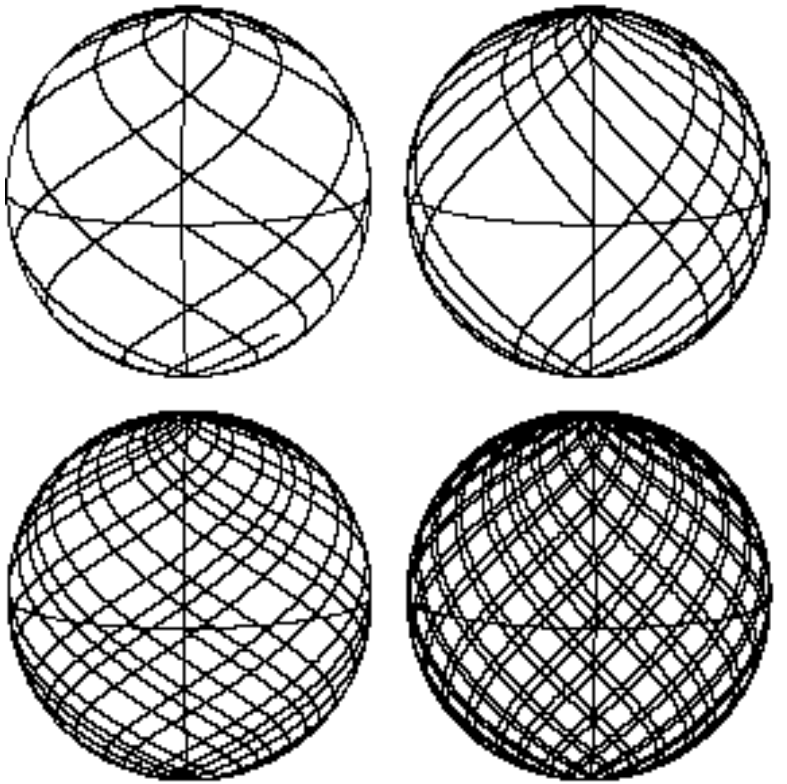
HS = High Speed

Example - 2 nozzle machine



0.8 min. 2.3 min. 6 min.

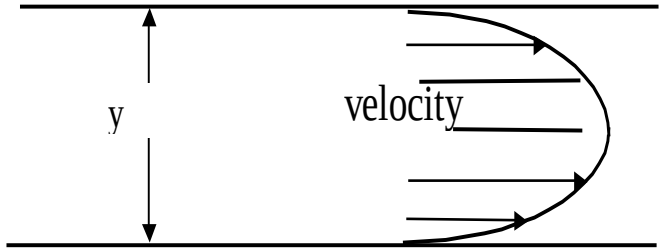
Golden Section Traditional
cleaning pattern cleaning pattern



CIP Spray Design Issues & Requirements:

- location and coverage of spray nozzles
- no blind spots, no shadows
- no wrinkles, seams, in flexible materials
- cleanable surfaces- drainable surfaces
- no horizontal ledges

Pipe Flow



volume
Total SA
gpm
velocity

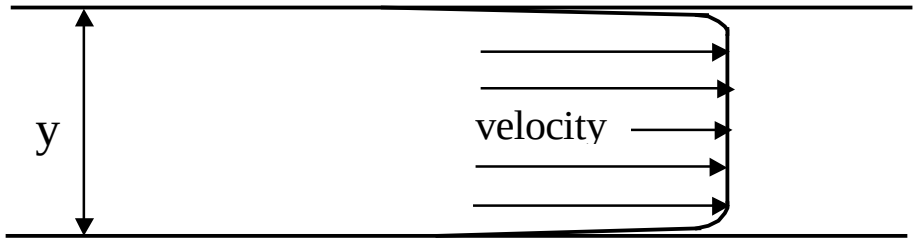
Target velocity = 1.5 m/sec.,

2.5cm OD 35 lpm

5 cm OD 162 lpm

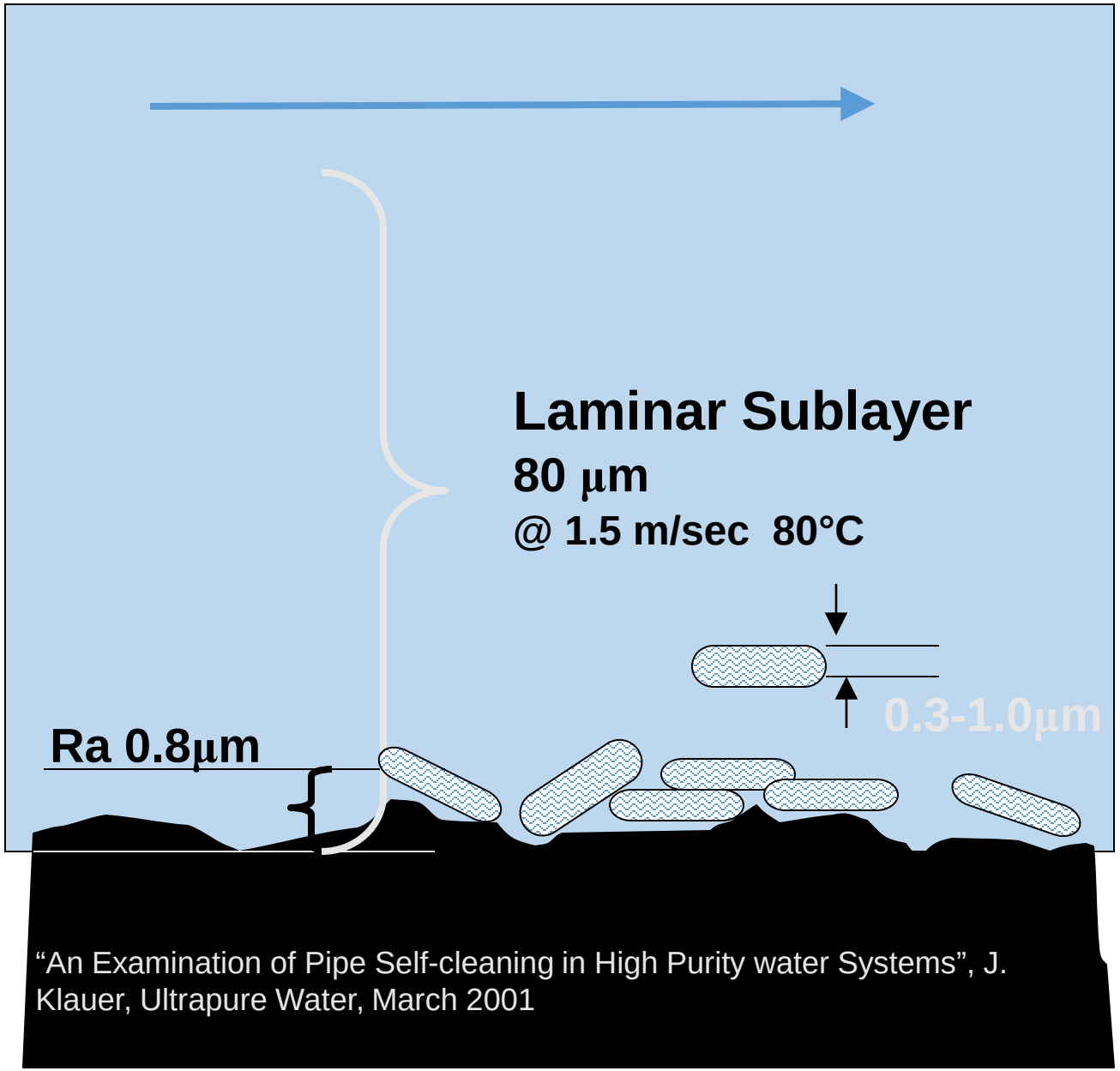
7.6 cmOD 380 lpm

Residue/cm$_2$
flow/cm$_2$



“An Examination of Pipe Self-cleaning in High Purity water Systems”, J. Klauer, Ultrapure Water, March 2001

- Fluid-mechanical cleaning of wall will not happen even at high velocities.
- Wall shear stress too low even in turbulent flow
- Laminar sublayer is 0.06-0.12mm for hot water, much thicker than residue layers
- *Any residue thickness less than static layer is removed by chemical extraction, not physical removal*



"An Examination of Pipe Self-cleaning in High Purity water Systems", J. Klauer, Ultrapure Water, March 2001

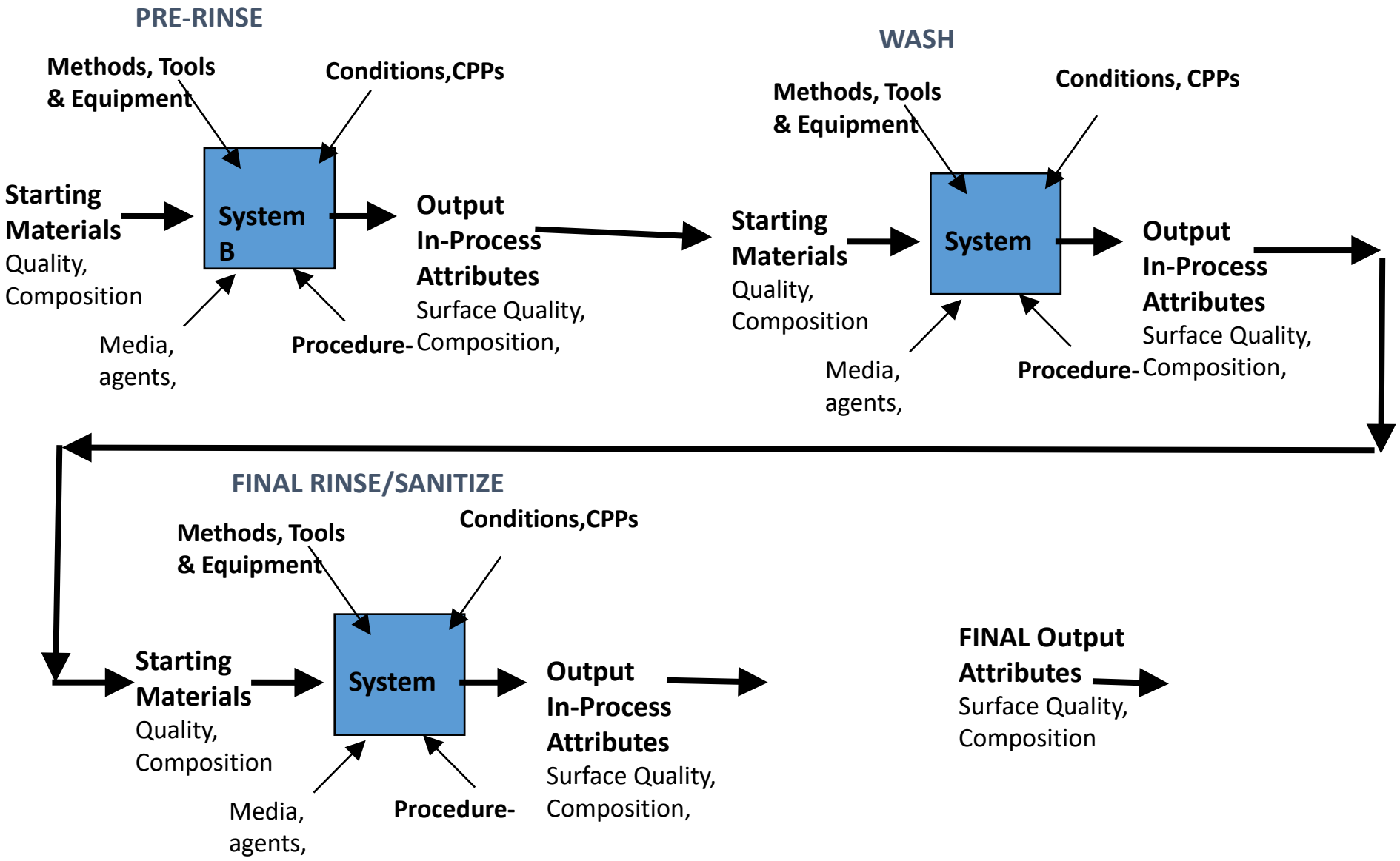
Cleaning process Evaluation/Selection

- Agent-Cleaning chemistry/thermodynamic requirements
- Method- fluid, hydrodynamics, coverage
- **Procedure:**
  - **Sequence, duration, interval, technique**
  - **manual; automatic**
- Measurement:
  - sampling, analytical

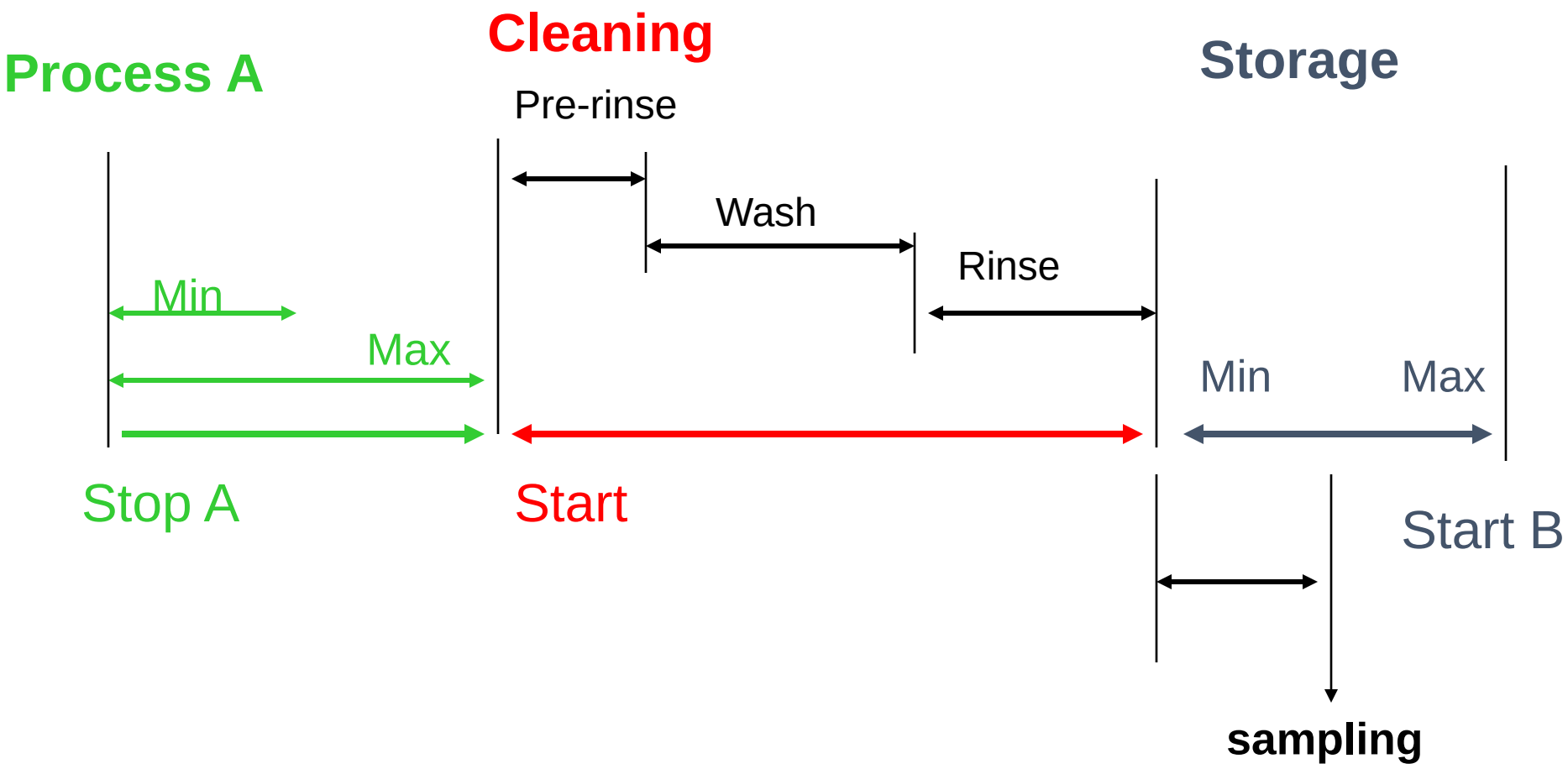
Cleaning Process Control-Sources of variation? Procedural parameters & variables

- Time factors-Sequence, Duration, Interval
  - Other Time Concepts- dirty hold time (DHT) and clean hold time (CHT)
- Technique/time-pattern, direction, speed, flow path
- Type of Procedure and Process Control
  - Manual vs. Automated
  - Clean-In-Place (CIP) vs. disassembly and transport to washer (COP)
  - Recirculation vs. single pass
- Process Measurement

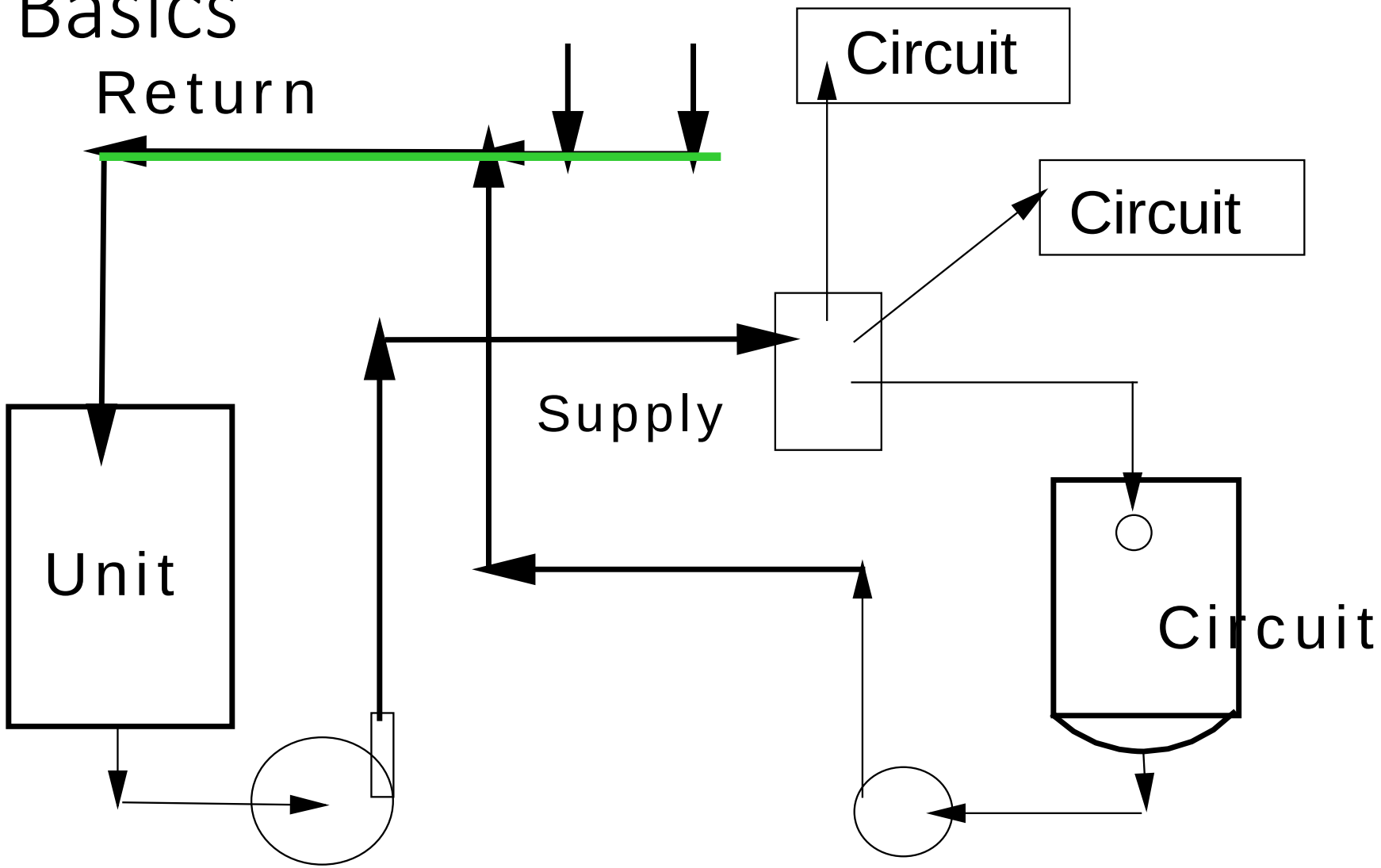
Process Validation Compliance

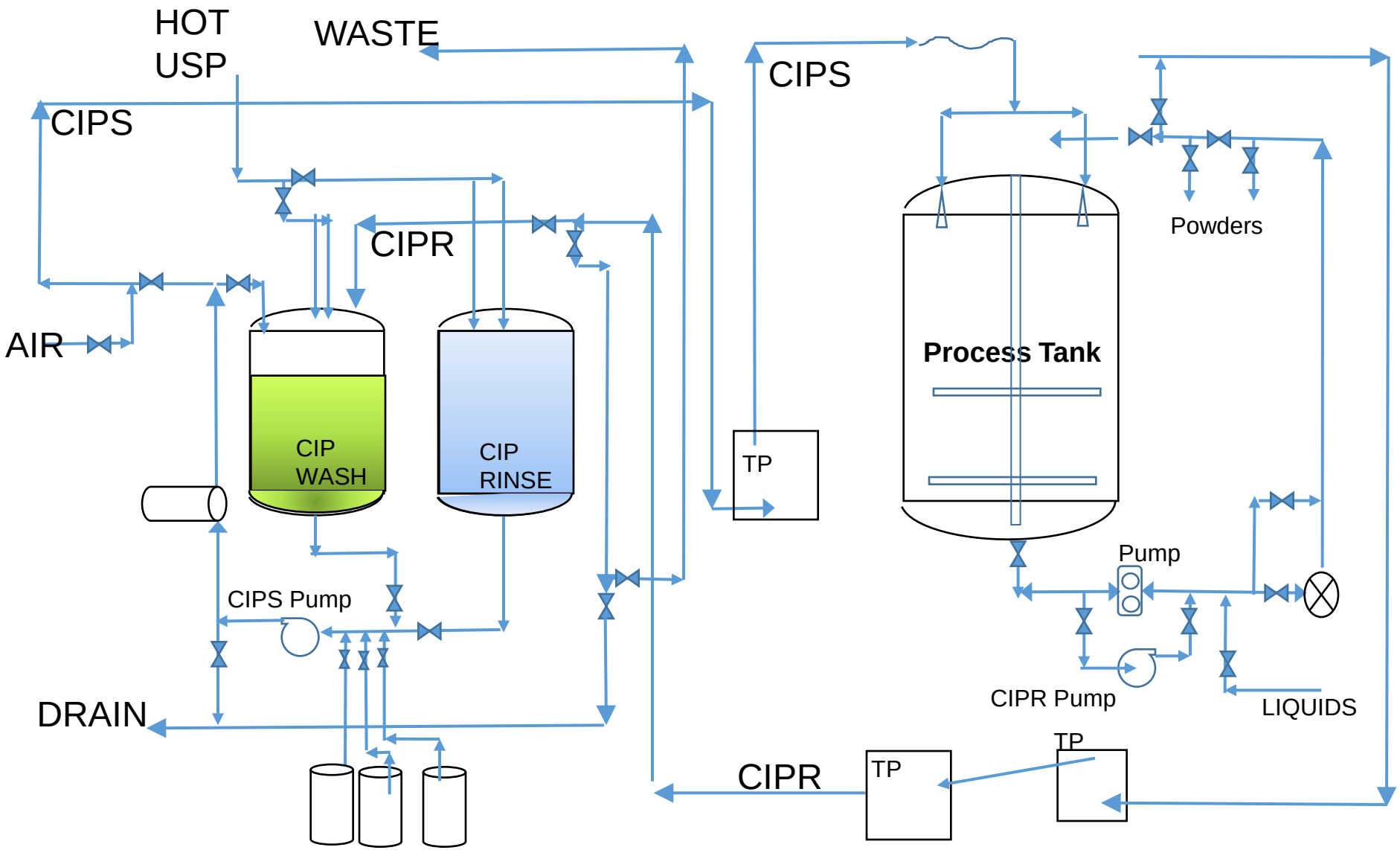


Time frames


Process A
Cleaning
Storage
Pre-rinse
Wash
Rinse
Min
Max
Min
Max
Stop A
Start
Start B
sampling

CIP Basics

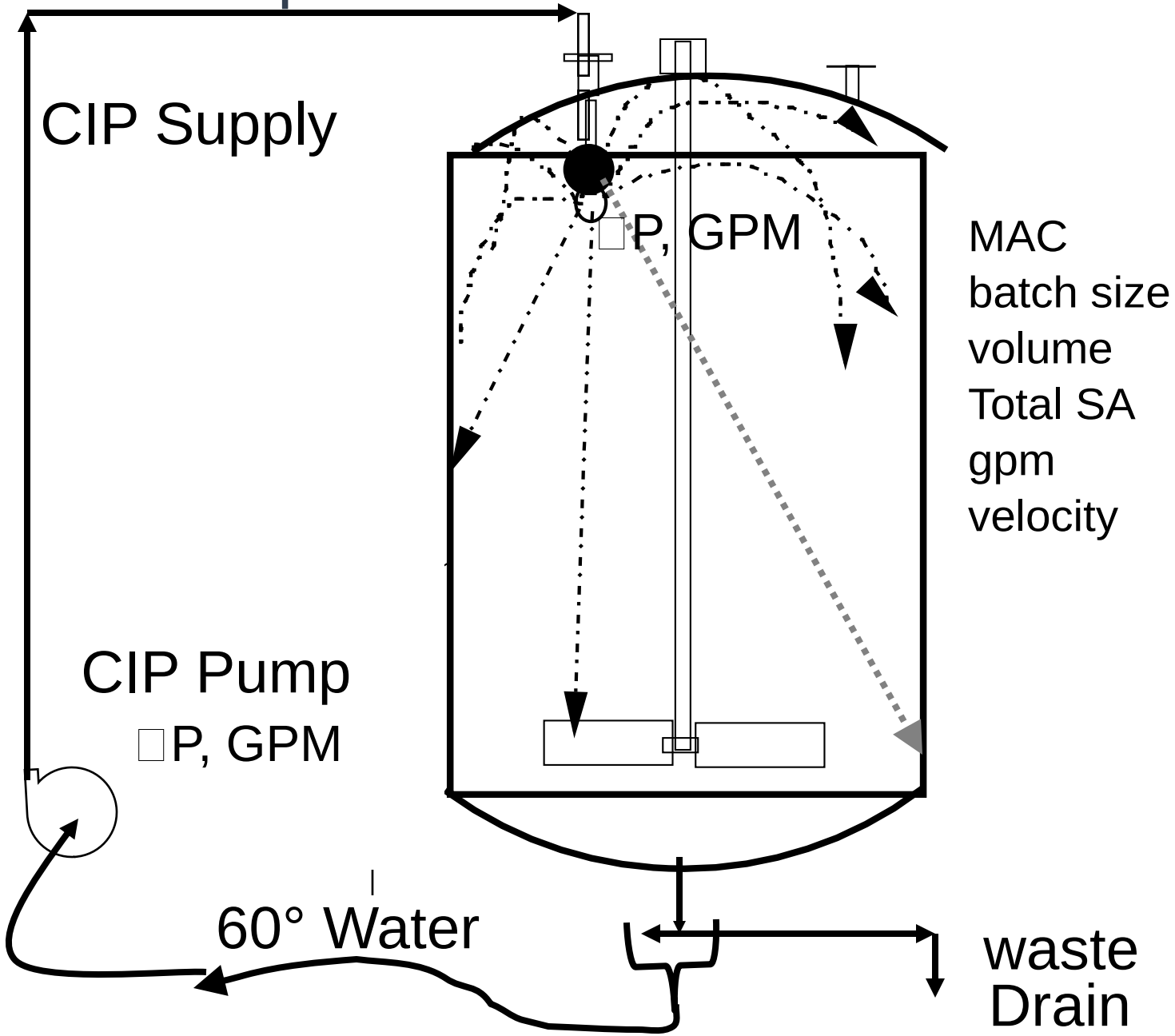



HOT
USP
WASTE
CIPS
CIPS
CIPR
AIR
CIP
WASH
CIP
RINSE
TP
Process Tank
Powders
Pump
CIPS Pump
DRAIN
CIPR Pump
LIQUIDS
TP
CIPR
TP
TP

CIP strategies/options

- Single pass or “once through”
- recirculation
- reuse
  - final rinse from A used as pre-wash for B

LRCIP Concept



Cleaning process Evaluation/Selection

- Agent- Determined by nature of residues
    - Also nature of cleaning method, waste disposal, personnel safety, materials compatibility !!
- Method- Determined by nature and design of equipment
- Procedure- Determined by you to meet process requirements

Cleanability of Pharmaceutical Soils from Different Materials of Construction

The authors look at the cleanability of pharmaceutical soils from a variety of materials of construction to determine the relative ease of cleaning and explore potential grouping strategies as part of a comprehensive cleaning validation program.

Pharmaceutical Technology,Volume 38, Issue 7, Jul 02, 2014;By Kelly Jordan, Richard J. Forsyth, Keith Bader

Prep: Each individual coupon was spotted with 1 ml of the soil. The soil dried for at least 4 hours, or until visually dry, but no longer than 3 days DHT. Dried coupons were reweighed and the coupon weight was subtracted to determine the net weight of the residue.

Exposure: The coupons immersed in a 600-ml beaker containing 400 ml of room-temp.purified water. 400 ml was the minimal volume necessary to completely cover the coupons. The water was agitated on a magnetic stirrer at a fixed rotation w/o vortex.

Cleanability endpoint: visibly clean to the observer under defined conditions: distance 18 inches, optimal viewing angle dependent on the material-of-construction coupon type, and 700 lux light intensity. The coupons were removed from the beaker immediately after the visual endpoint was determined.

Table II. Time to visual cleanliness (min).

Materials of construction	Growth media 10% serum - A	Regeneration buffer	Zinc buffer	Growth media 10% serum - B	Phosphate buffered saline	Growth media 10% serum with phenol red
316 stainless steel	7:18	0:09	0:10	4:09	3:11	5:43
Acrylic	4:33	N/A	N/A	5:49	0:58	4:20
Ethylene propylene diene monomer (EPDM)	0:46	N/A	N/A	0:32	0:13	0:39
Glass	5:33	N/A	N/A	0:22	0:10	7:16
Nickel-steel alloy (Hastelloy)	6:22	N/A	N/A	6:17	1:19	4:37
Polyether ether ketone (PEEK)	0:28	N/A	N/A	0:22	0:20	4:17
Polypropylene	3:17	N/A	N/A	0:25	0:17	1:16
Silicone	0:28	N/A	N/A	0:29	0:32	0:33
Polytetrafluoroethylene (Teflon)	0:33	N/A	N/A	0:35	0:11	0:40
Synthetic fluoropolymer rubber (Viton)	0:25	N/A	N/A	0:22	0:10	0:26

N/A – these two soils did not dry. Times on stainless steel are representative of all material-of-construction coupons.

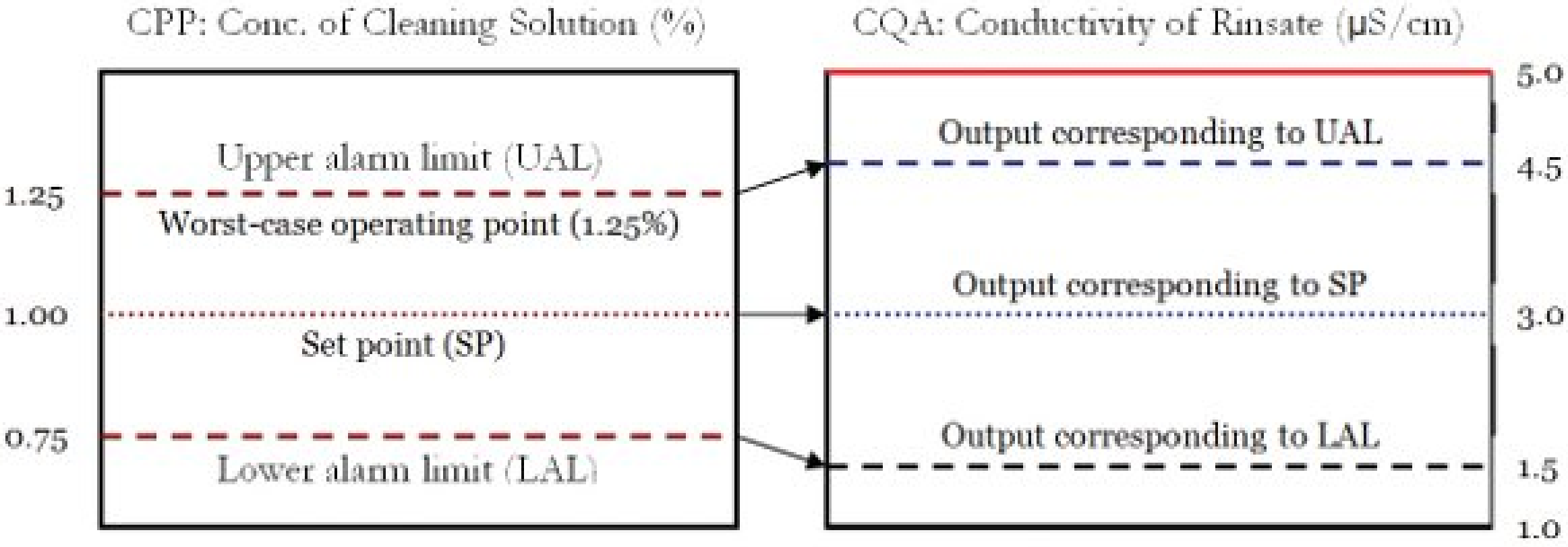
Table V. Total organic carbon (TOC) results (% removed).

Materials of construction	Growth media 10% serum - A	Regeneration buffer	Zinc buffer	Growth media 10% serum - B	Phosphate buffered saline	Growth media 10% serum with phenol red
316 stainless steel	116%	80%**	89%	83%	*	88%
Acrylic	113%	N/A	N/A	83%	*	88%
Ethylene propylene diene monomer (EPDM)	113%	N/A	N/A	83%	*	89%
Glass	117%	N/A	N/A	82%	*	89%
Hastalloy	***	N/A	N/A	***	*	***
polyether ether ketone (PEEK)	***	N/A	N/A	***	*	***
Polypropylene	117%	N/A	N/A	83%	*	90%
Silicone	***	N/A	N/A	***	*	
Polytetrafluoroethylene (Teflon)	115%	N/A	N/A	94%	*	89%
Synthetic fluoropolymer rubber (Viton)	113%	N/A	N/A	82%	*	89%
Positive Control Data						
TOC (ppm)	10120	125440	120640	7440	*	11184

N/A – these two soils did not dry. TOC data on stainless steel are representative of all MOC coupons.
* Phosphate buffered saline contains no TOC.
** Soil contained 20% ethanol, which evaporated during drying.
*** Data not generated. Samples expired due to instrument malfunction.

Strategies for Developing a Robust Cleaning Process Part I: Application of Quality by Design to Cleaning; *American Pharmacetical Review,* July 1, 2010; R. Sharnez

DOE Case study: Consider a cleaning cycle that consists of an alkaline wash followed by successive rinses with water. The traditional and QbD approaches to cleaning characterization are compared in Figure 2,



In these studies, the relative cleanability of the process soil is evaluated by subjecting soiled coupons to simulated cleaning conditions [7-13]. The CPPs for these experiments are listed in Table 1

Strategies for Developing a Robust Cleaning Process Part I: Application of Quality by Design to Cleaning; *American Pharmacetical Review,* July 1, 2010; R. Sharnez

Critical Process Parameter	Operating Range (Control Space)		Characterization Strategy	
	Lower Acceptable Limit (LAL)	Upper Acceptable Limit (UAL)	Traditional Approach: Characterize with CPPs at set point or typical operating conditions	QbD Approach: Characterize with CPPs at their respective worst-case operating points
Hold Time (days)	1	7	4	5
Concentration of cleaning solution (%)	0.75	1.25	1.0	0.75 (for wash) 1.25 (for rinse)a
Temperature of cleaning solution (°C)	60	80	70	60
Flow rate (gpm) or Pressure [b] (psig) of cleaning solution or rinse water	12 10	18 14	15 12	12 10

[a] Rinse out studies may not be required if the equipment is cleaned with process solvents (i.e. formulated cleaning agents are not used)
[b] At sprayball or other suitable location where pressure can be correlated to flow rate

Wash time as a function of hold time (Stage I data).

Run	Hold Time (days)	Cleaning Time (normalized)
R_1	1	1.0
R_2	3	1.4
R_3	5	1.8
R_4	7	1.4

Wash time as a function of temperature (Stage II data). The hold time is set to the worst-case operating value of 5 days (Table 2), and the concentration of the cleaning solution is controlled at the worst-case operating point of 0.75% (Table 1).

Run	Temp. deg. C	Cleaning Time (normalized)
R_5	80	2.0
R_6	70	2.2
R_7	60	2.4

The above seven-run experimental strategy can provide a reasonable estimate of the worst-case operating point within the design space

Setting the average fluid velocity under experimental conditions (V_{avg}) to the worst-case operating value for the equipment (V_{MIN}) provides assurance that if the soil can be cleaned by the simulated wash at small-scale, then it can also be cleaned by the actual wash at full scale. This condition is valid only if, for the duration of the wash, there is adequate contact between the cleaning solution and the surface being cleaned. For CIP circuits, this condition is generally satisfied if the system is qualified to provide adequate spray coverage to the surfaces that need to be cleaned.

The worst-case operating conditions for the wash (5-day hold time, 60°C and 0.75%) and the rinse (60°C and 1.25%) based on the above seven-run experimental strategy are summarized in Table 4.

Process step	CPPs and their worst-case operating points		
	Hold Time (days)	Temperature (°C)	Concentration (%)
Wash	~ 5	60	0.75
Rinse	NA	60	1.25

BLENDER Cleaning Plan

Cleaning/extraction grouping study:

- Water Solubility
  - A Soluble
  - B Soluble
  - C Slightly Sol.
  - D Insoluble
  - E Insoluble

- Water Extraction
  - A 12 min.
  - B 14 min.
  - C 25 min.
  - D >60 min.
  - E >60 min.

Evaluation per Q7A

	A	B	C	D	E
Product Type					
Solubility					
“Cleanability”					
Potency					
Toxicity					
Stability					

Does Solubility Index predict relative residue removal rate?

BLENDER Cleaning Plan

Cleaning/extraction grouping study:

- Water
  - A 12 min.
  - B 14 min.
  - C 25 min.
  - D >60 min.
  - E >60 min.
- **Alkaline Detergent**
  - A 2 min.
  - B 4 min.
  - C 12 min.
  - D >60 min.
  - *E 8 min.*

Batches/Year

- ◆40
- ◆40
- ◆2
- ◆20
- ◆20

Case: Blender Cleaning Plan

Equipment	Residues	Method	Procedure
Blender	**A,B,C,E** **Test w/C**	**Immersion** **Agitation** **Alk. Det.** **CP-700**	**CIP** **Automatic**
	D, **Test w/D**	**Immersion** **Agitation** ***WATER??***	**CIP** **Automatic**

Case: Blender Cleaning Plan

Cleaning/extraction grouping study:

- Current Cleaning Agent CP-700
  - A 2 min.
  - B 4 min.
  - C 12 min.
  - D >60min.
  - E 8 min.
- Alternate Agent CP-400 Acid
  - A 12 min.
  - B 15 min.
  - C 25 min.
  - D 15 min.
  - E >60 min.

Case: Blender Cleaning Plan

Equipment	Residues	Method	Procedure
Blender	**A,B,C,E** **Test w/C**	**Immersion** **Agitation** **CP-700**	**CIP** **Automatic**
	D, **Test w/D**	**Immersion** **Agitation** ***CP-400 Acid***	**CIP** **Automatic**

For “how to clean?”,”what to test?” decisions….

- All products of all cleanability have to be cleaned from all equipment of every difficulty of cleaning to a level that protects against cross contamination of any and all next products below the health based exposure limit.
- Cleanability design issues ***of equipment*** should not be used in a consumer risk score. All equipment of all design must be cleaned to residue levels that protect every product made in the equipment.
- Cleanability of ***product related residues*** is not used to estimate a consumer risk score, it is the basis for determining cleaning chemistry, process groupings and process endpoint/capability
- Cleanability ratings are used to select and justify “worst case” residue for testing for a process group

TABLE 1 Examples of Risk Reduction

Risk Reduction Elements	Examples of Risk Reduction Steps
Reduce severity	Hazard removal Hazard replacement (for example, move to safer cleaning agents) Equipment dedication
Reduce likelihood	Cleaning process improvements Cleaning optimization (DoE) Operator training SOP improvements (for example, poka-yoke) Equipment dedication Modifications of equipment design Improvements in equipment storage practices Selection of new equipment Product campaigning
Increase detectability	Analytical method improvement (lower DL) Sampling method improvement (increased recovery) Cleaning process monitoring Statistical process control Introduction of PAT (for example, at-line release)