The use of TOC measurements to determine success of CIP methods

Joe Gecsey

Cleaning
- Regulatory Requirements

Equipment Must be Cleaned

CFR 211.67

- "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…"

**CFR = Code of Federal Regulations*

Cleaning
- Regulatory Requirements

Cleaning Processes Must be Validated

CFR 211.220

- "The manufacturer shall ***validate*** all drug product manufacturing processes… The manufacturing process includes all manufacturing steps in the creation of the finished product, including but not limited to the following procedures: ***cleaning,*** weighing, measuring, mixing…"

Cleaning
- Regulatory Requirements

Documented Validation

Establishing documented evidence which provides a high degree of assurance that a cleaning procedure consistently removes residues to pre-determined acceptable levels

cGMPs (21 CFR 211.67) - Equipment Cleaning and Maintenance

- To prevent contamination
- To prevent equipment malfunction

Life Science Industry Cleaning Issues

Industry Challenges:
Cross-contamination issues
Cleaning failures
Cleaning validation struggles
Sterility issues

Solutions so far?
Dedicated production lines
Disposable equipment
Manual cleaning
Centralized CIP
Laboratory Testing

What is Cleaning Validation?

Cleaning Validation is the methodology used to assure a cleaning procedure effectively and consistently removes residues of active ingredients to predetermined qualified levels before new product manufacturing begins.

Residuals include materials such as:

- active pharmaceutical ingredients (API)
- excipients
- cleaning agents

This is required to assure the quality of all products being manufactured using the same equipment and prevent cross-contamination

Cleaning Validation

- Involves Risked Base decisions
- Key Part of the product Life cycle
  - Cleaning in Place Procedure developed
  - SOP's for continuous Control and Verification
- Extensive Testing
  - Specific
  - Non-specific

FDA Guidance on Limits

From the FDA's guideline (same as ICH Q7A):

"The firm's rationale for the residue limits established should be logical … and be practical, achievable, and verifiable…

Some limits that have been mentioned by industry representatives include analytical detection levels such as:

- 10 ppm
- USP <643>, <645>
- activity levels such as 1/1000 of the therapeutic dose

Check the manner in which limits are established. The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable."

CIP Development

Cleaning Validation – Determines

- Verification limits – pass/fail
- Parameters to monitor in each cleaning
- Cleaning Validation often uses both methods
  - Specific
  - Non-specific

CIP Rinse Water Verification

Validation vs. Verification

Validation – Typically done once at the beginning of the product life cycle, re-checked annually or every two years

Verification – The measurement tool set used to ensure cleanliness after each batch is manufactured

CIP Cleaning-in-Place

Process set during Cleaning Validation

Cleaning of equipment using an automated cleaning system

CIP of a manufacturing vessel usually requires multiple steps.

- After draining tank, rinse with Purified Water (PW)
- Acid/caustic/acid rinse
- Detergent wash/rinse
- PW followed by WFI rinse

CIP = Clean In Place

Parts/equipment used for sterile drug production

Prevent batch-to-batch carry-over

- Drug product
- Cleaning fluids

Production in cleanroom

CIP Terms

CIP = Clean In Place

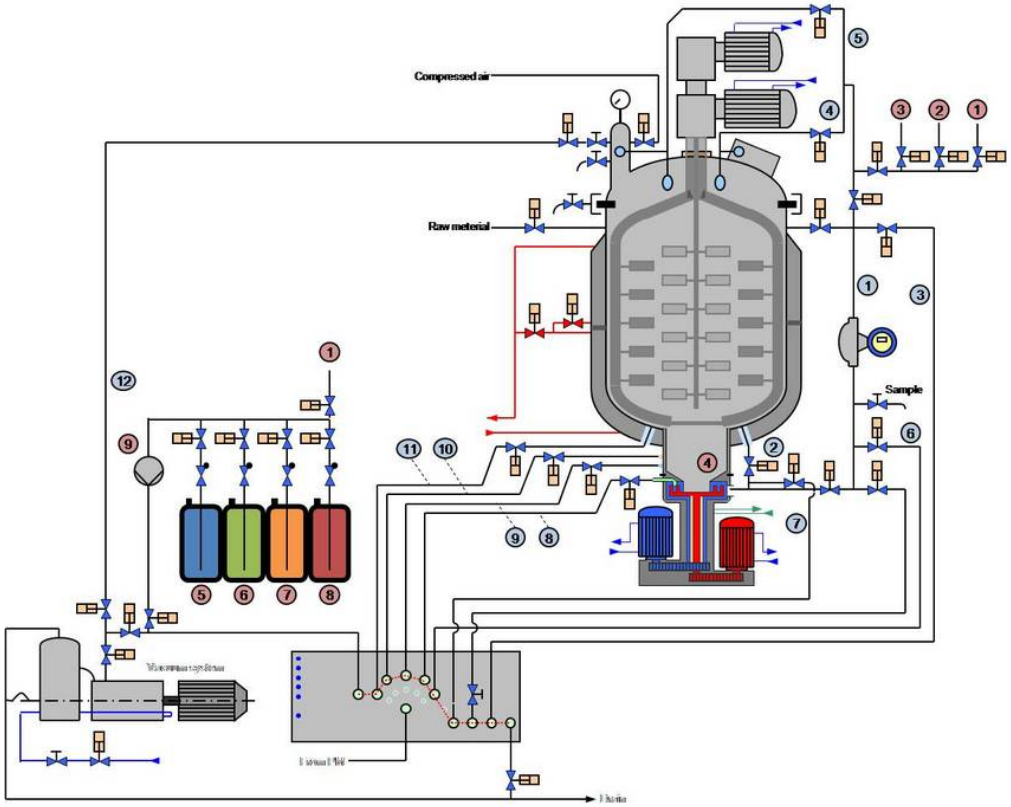
COP = Clean Out of Place

SIP = Sterilize In Place

Dedicated CIP

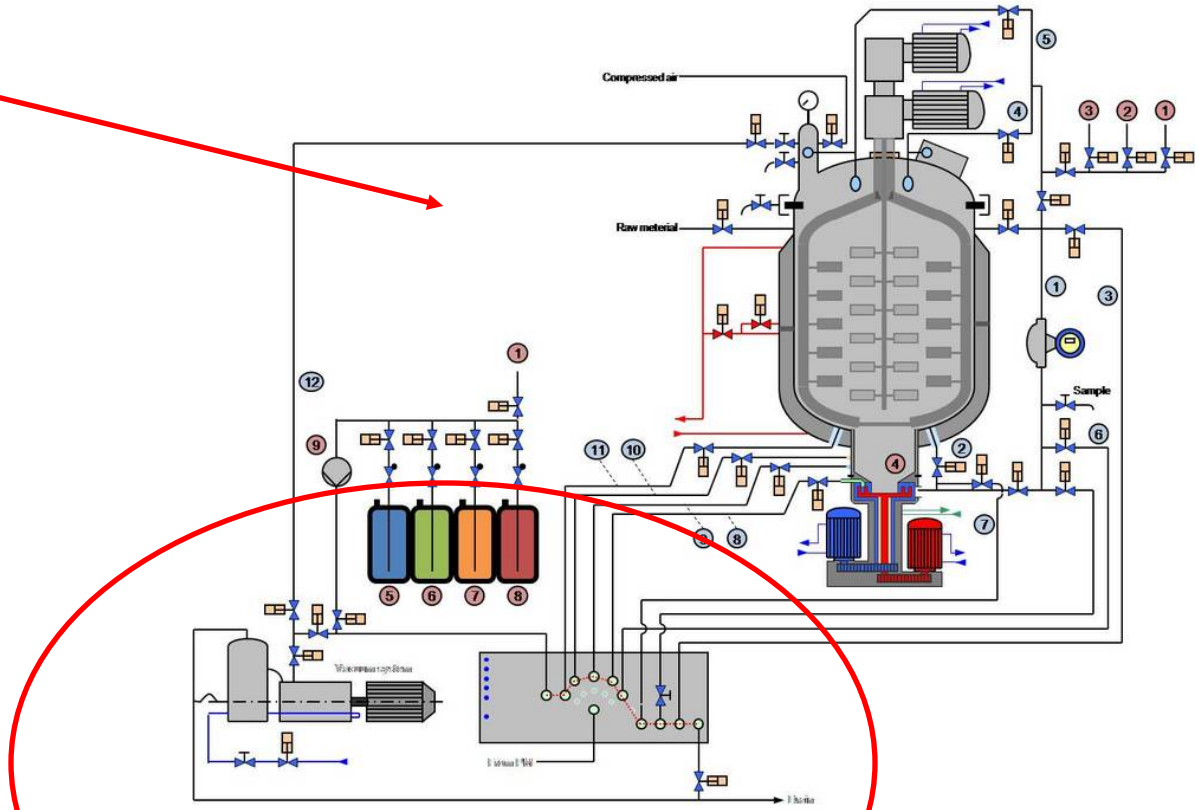
Dedicated to one vessel

Only periodic use



Dedicated CIP

Process Vessel



Cleaning System

Mobile CIP

Vessel 1

Vessel 2

Vessel 3

Vessel 4

Mobile CIP

- Mobile CIP skids because used to clean multiple vessels:
- Frequent use
- Costly re-qualification
- Alternative manual QC analysis costly

COP

COP
Station

Process Vessel 1

Process Vessel 2

Process Vessel 3

Process Vessel 4

COP

Central COP cleaning station because:

Frequent use

Costly re-qualification

Alternative manual QC analysis costly

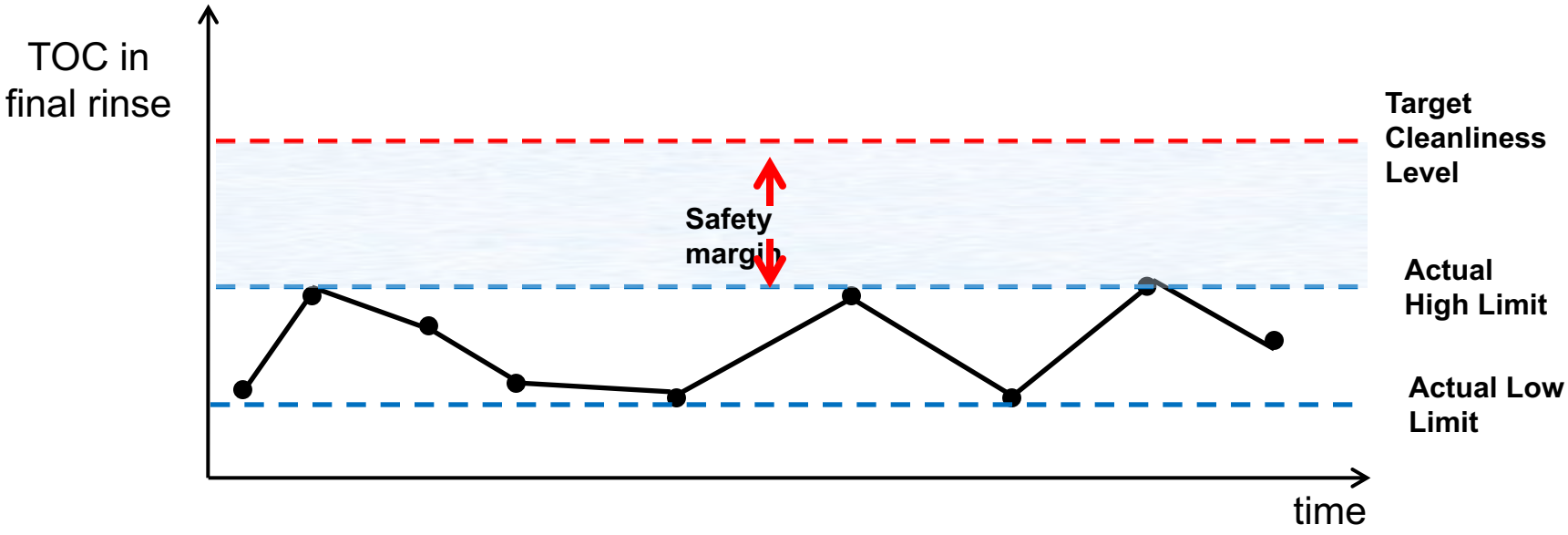
COP Station

Parts Washers

Used where CIP or COP is not practical

Cleaning Program Development

1. Establish target cleanliness level
2. Establish efficient cleaning chemicals
3. Define CIP program steps
4. Validate new CIP program efficacy



Methods to collect sample

1. Swab

2. Rinse sample

3. Visual

(Note: determine % recovery, limit of detection, limit of quantitation, accuracy of method, reproducibility...etc.)

Methods for Analyzing Cleaning Samples

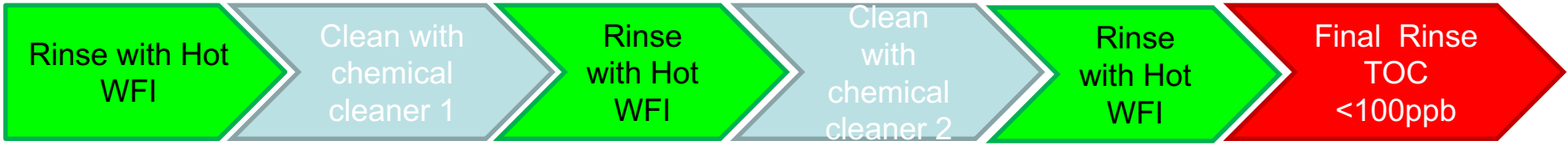
- Specific Methods
  - Sensitive to a single compound or product
  - May need several methods
    - One for each compound
  - Requires costly reagents
  - Time consuming
  - Highly trained technician
- Typical Specific Methods
  - HPLC: High-Pressure Liquid Chromatography
  - Spectrophotometric
- Non-Specific Methods
  - TOC
  - Conductivity
- Non-Specific Methods
  - Overall measurement, not product specific
  - Can be reagentless
  - Can give fast analysis
  - Can be automated

Advantage of measuring final rinse

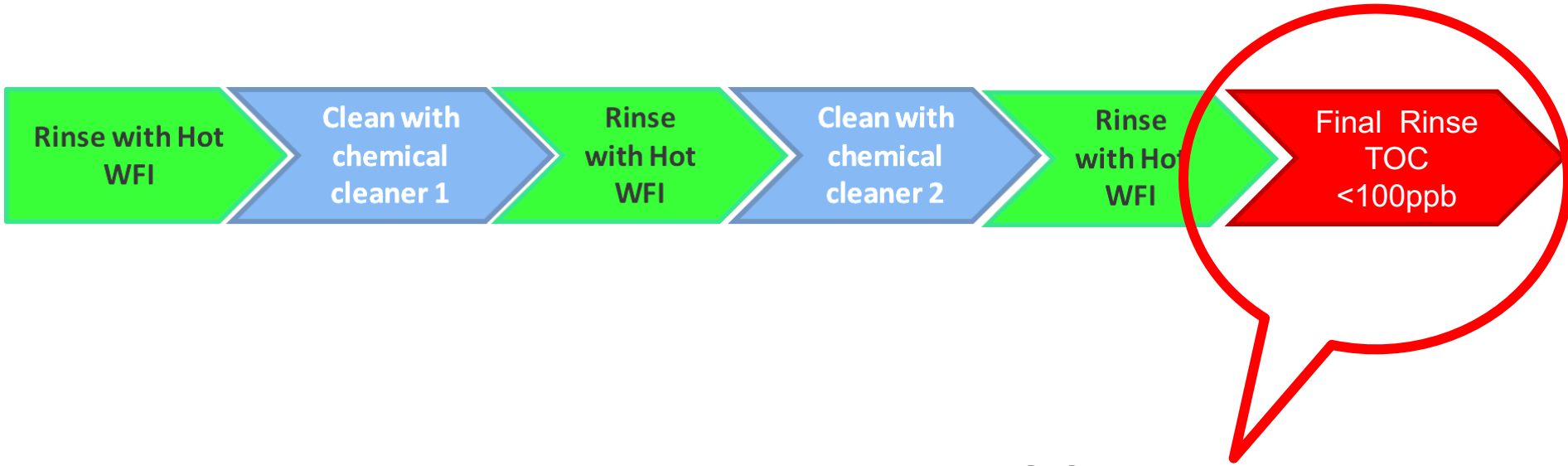
The rinse occurs after cleaning has been completed, so:

- not as direct as swabbing but will cover the entire surface area (and parts inaccessible to swabs)
- much greater ease of sampling than swabbing
- reduced number of samples are required to calculate a ‘carryover’ figure compared to swabbing

Typical CIP Process

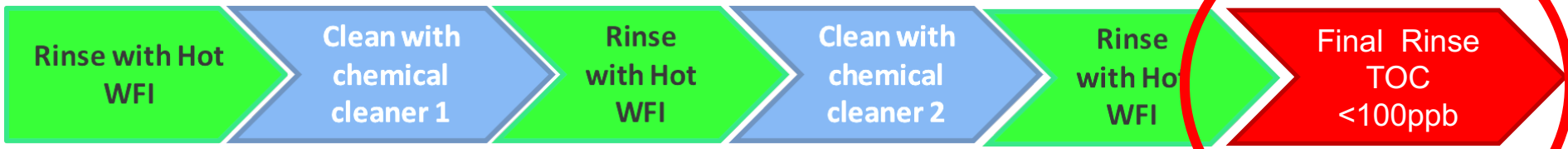


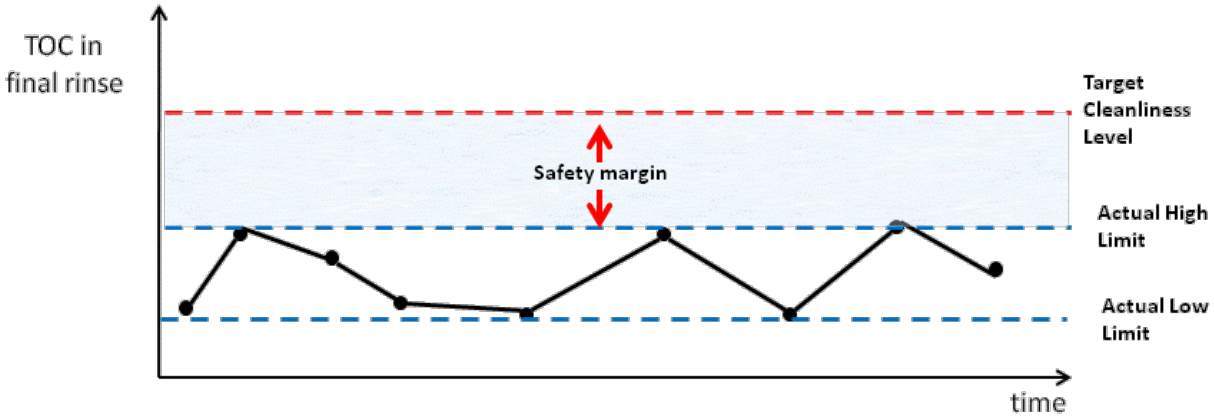
Verifying CIP Process



TOC sample taken here verifies the CIP cycle was effective

Verifying CIP Process





Industry expects <10ppm.
Target is usually <1ppm.
Typical results <100ppb (0.1ppm)

Current Methods

Clean In Place monitoring

- Time
  - Determined during Cleaning Validation
  - Extra time typically added to ensure cleanliness

- Conductivity – most common method
  - Only checks Ionic contamination
  - Non-specific

- Lab TOC - Grab Samples of Final Rinse water
  - Verifies removal of organic contamination
  - Wide range of TOC
  - Most products and cleaners organic based
  - Non-specific

Comparison CIP verification techniques

Laboratory Grab Sample

+Verifies every time

–Cost of labor

–Restricts production

–Cost of laboratory instrument reagents

–Additional laboratory workload

On-line TOC & Conductivity

+Verifies every time

+Automated – no labor cost

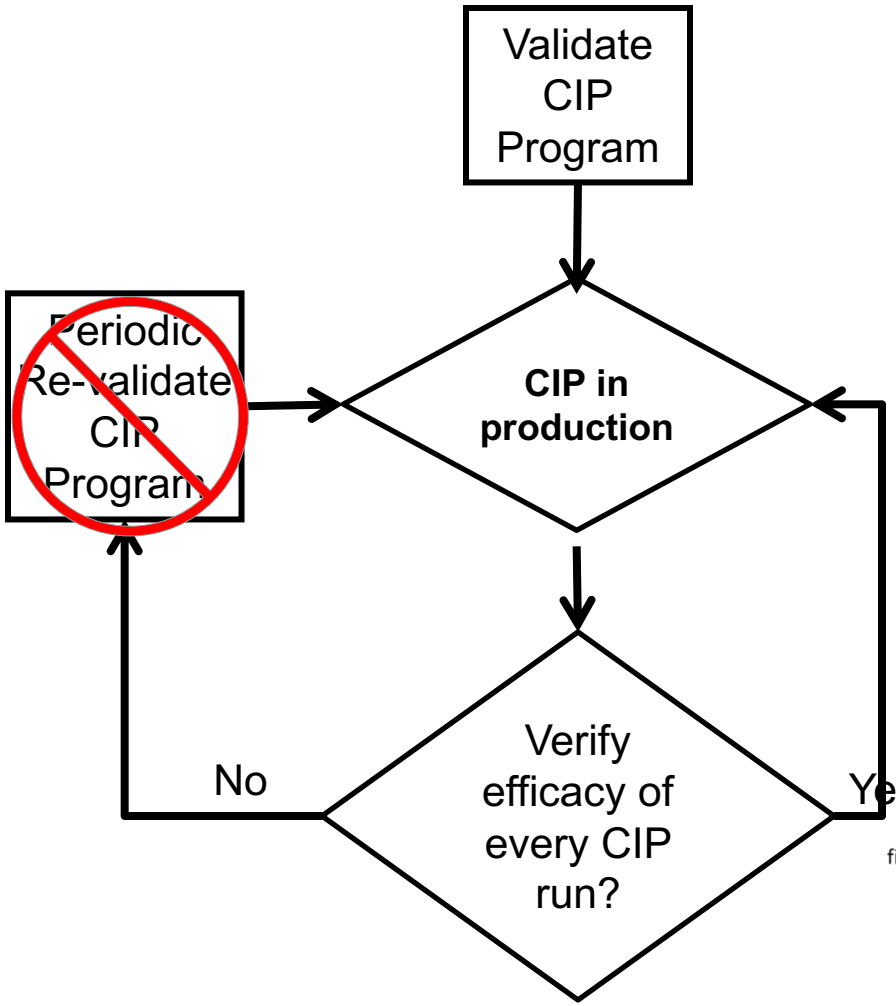
+Speeds up production

+No reagents cost

+No additional laboratory workload

–Cost of on-line instrumentation

Advantage of verifying every CIP run

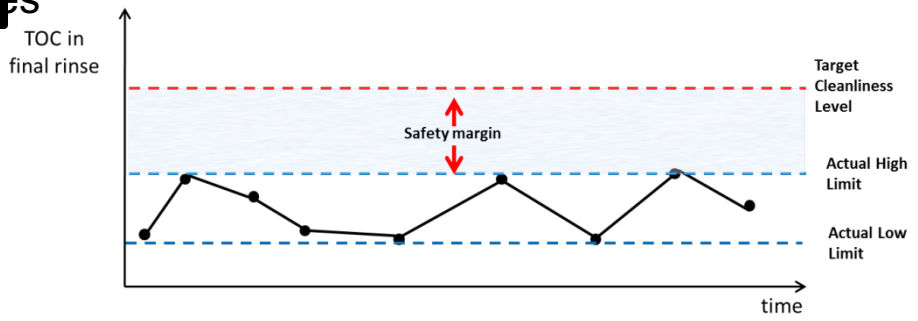


Advantages:

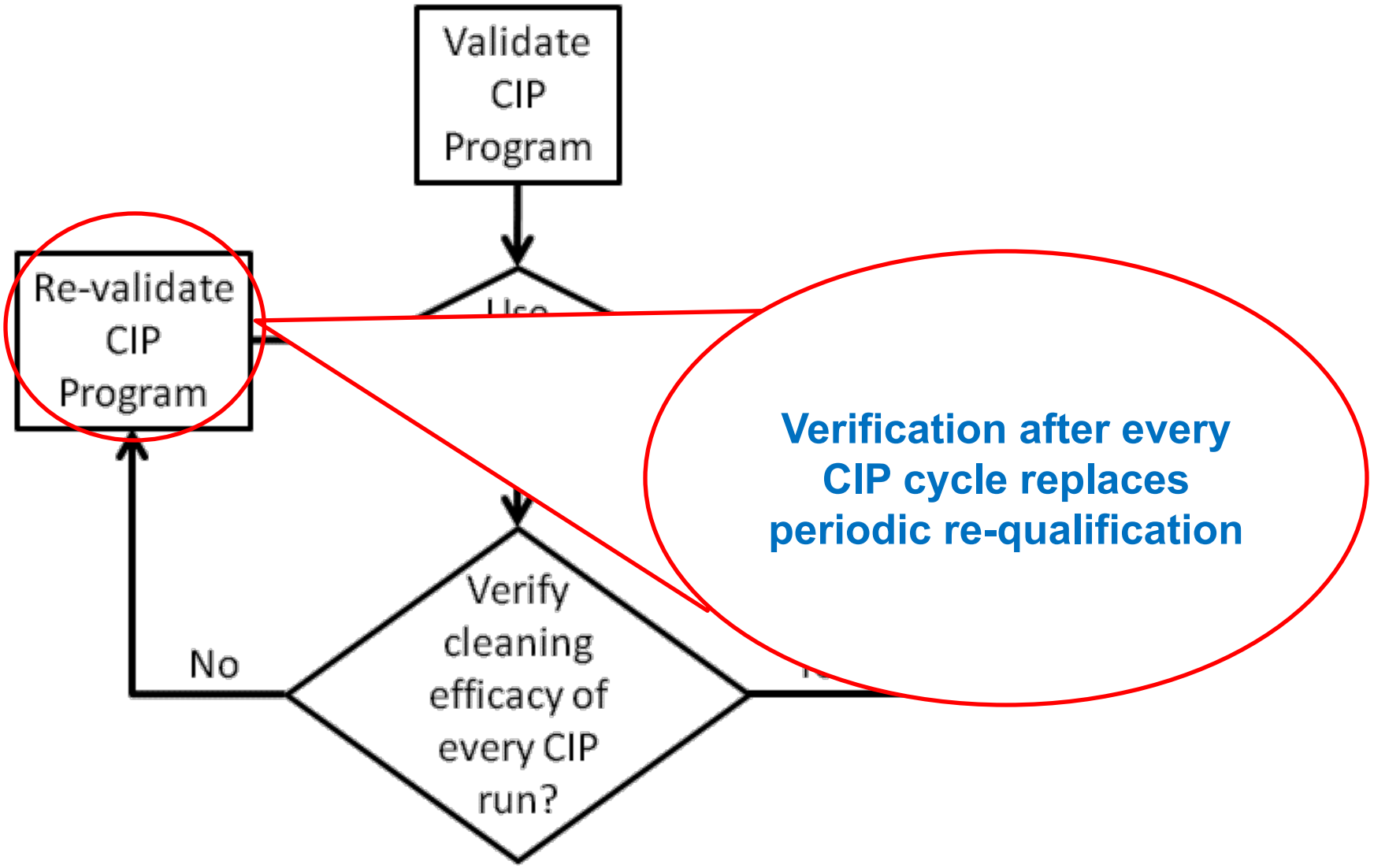
Improved compliance

Eliminates requirement for CIP re-validation = **$ 150K** saving over 2 years

Increases productivity

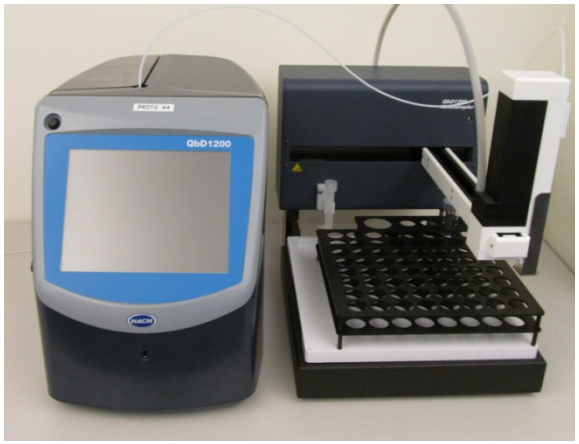


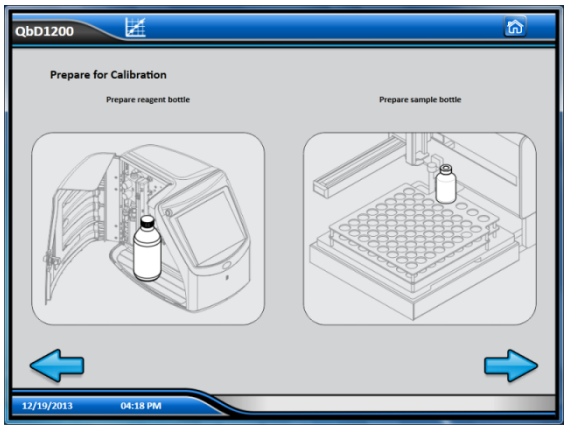
Techniques to verify CIP run

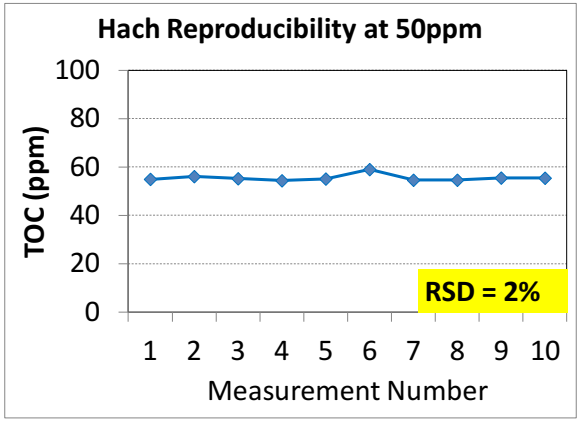


At-Line Verification

- Grab Sample Based Testing
- Multiple Grab Samples
- Wide Range for Validation and Verification process
- Swabs/Coupons



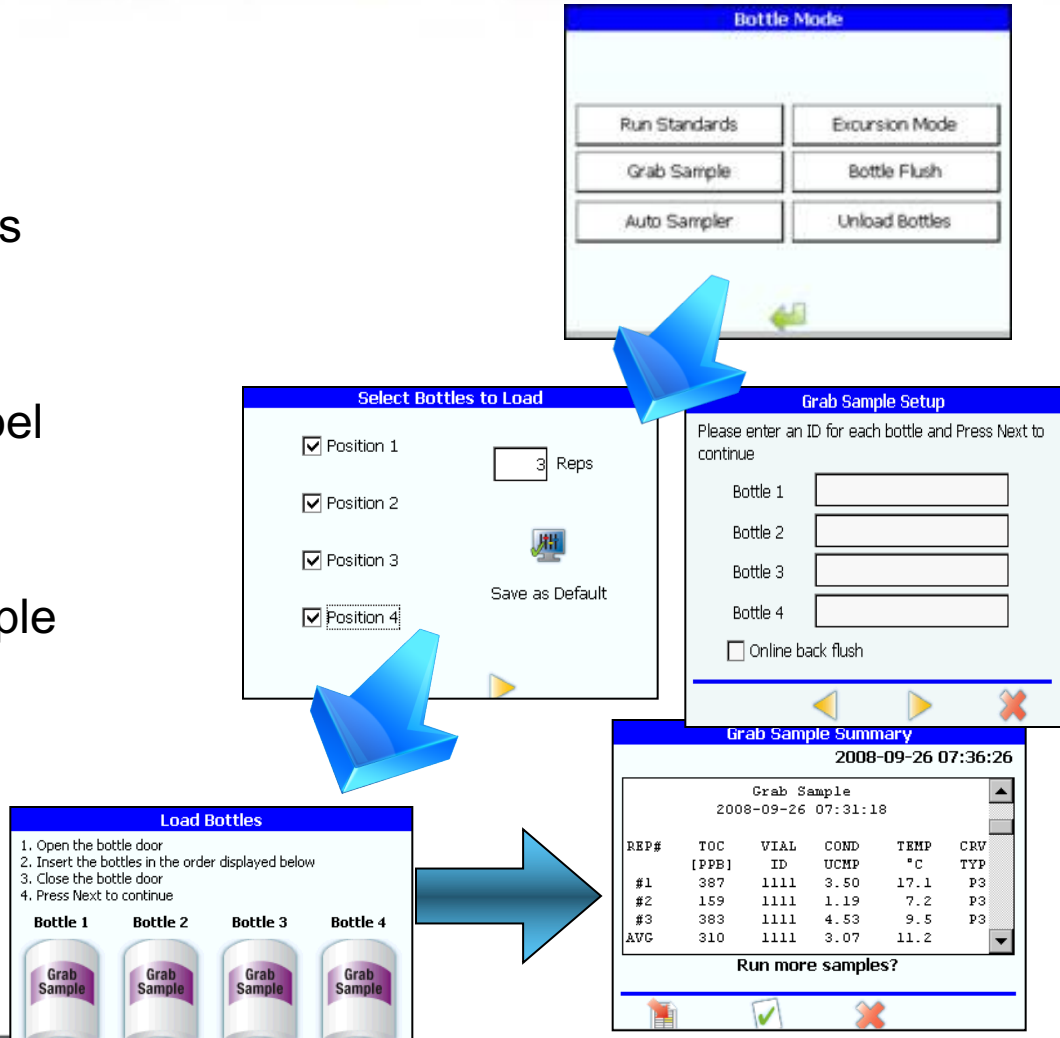




Grab Sample Analysis at the Line

CIP Grab Sample Testing

- Easy to run multiple grab samples
- Ideal for applications with small number of grab samples
- Nine character alpha-numeric label
- Facilitates conversion from lab to on-line TOC
- Brings lab analysis close to multiple sample points

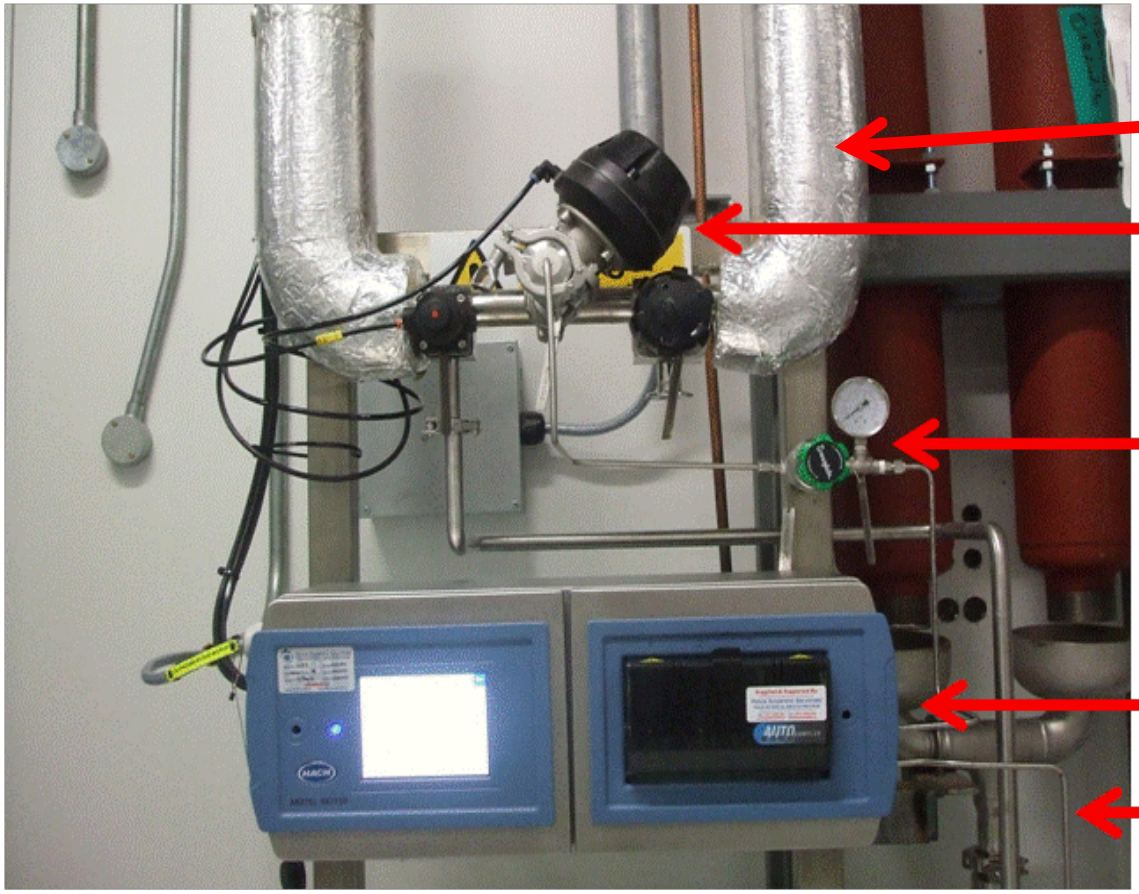


On-Line TOC Option

Automated Clean In Place monitoring

- On-line TOC Monitoring
  - Final Rinse water
  - Verifies removal of organic contamination
  - Most by products and cleaners organic based
  - Non-specific
  - Reduce frequency of re-validation of process

On-line TOC for CIP Rinse water



Portable CIP with on Board Conductivity and TOC

Cleaning of equipment using an automated cleaning system

CIP of a manufacturing vessel usually requires multiple steps.

- After draining tank, rinse with Purified Water (PW)
- Acid/caustic/acid rinse
- Detergent wash/rinse
- PW Rinse
- WFI Final rinse

LIFE SCIENCES LSUG USERS GROUP

Automated TOC Results

CIP with Onboard Conductivity and TOC

Conductivity

- Two channels
- Instantaneous measurement
  - Cleaning solution
  - Rinse water levels

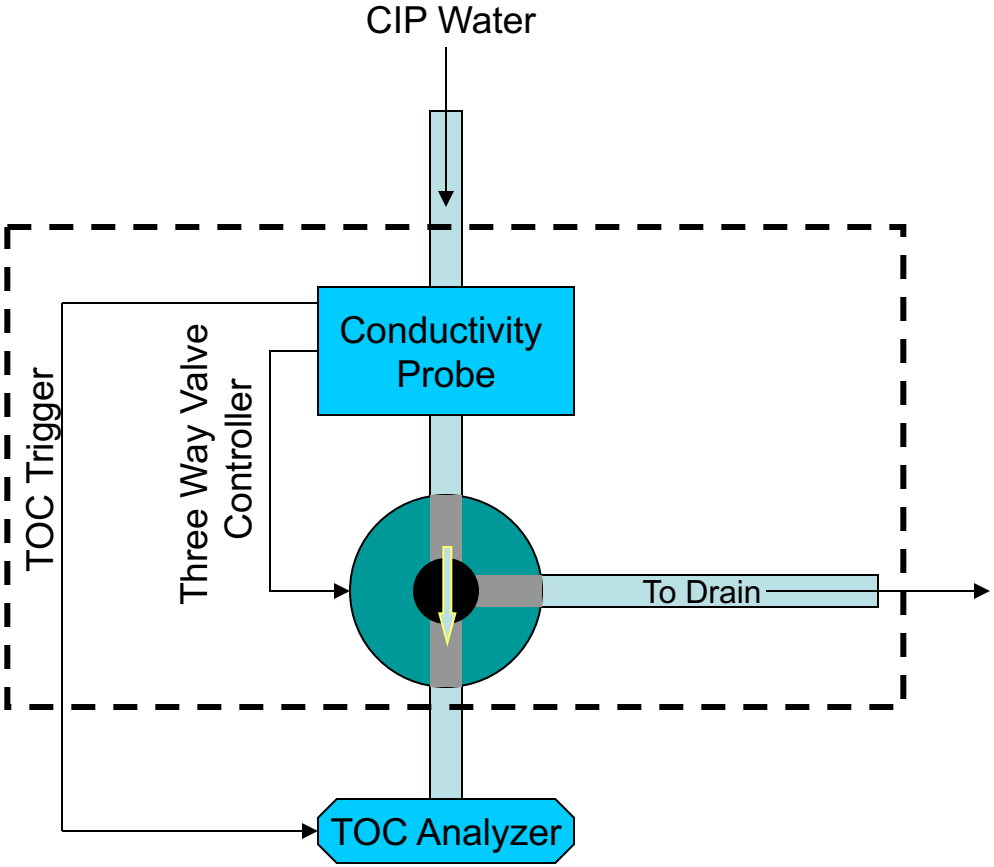
TOC

- Digital control capability
- USP <645> and <643>
- On-line TOC using system pressure
- Results 4-6 Minutes
- Ability to sit dry without constant flow

Conductivity and TOC testing determine key levels

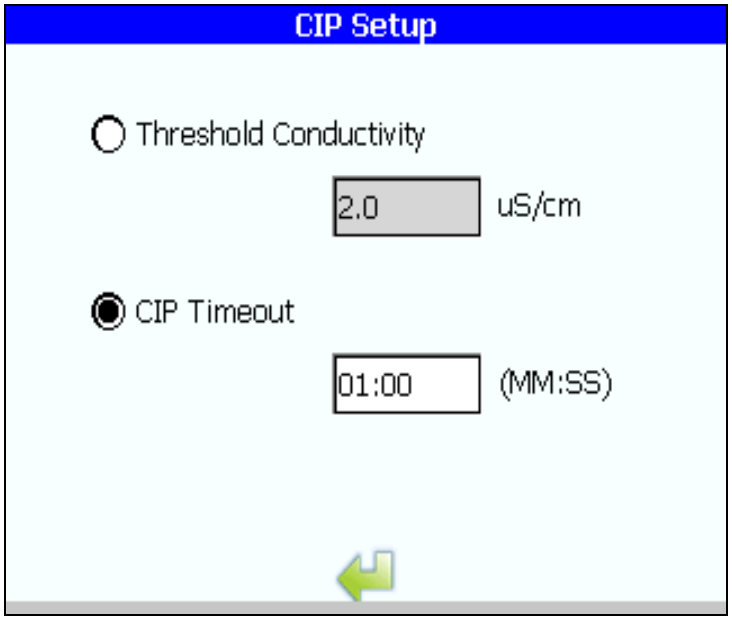
Module Schematic: Three Way valve

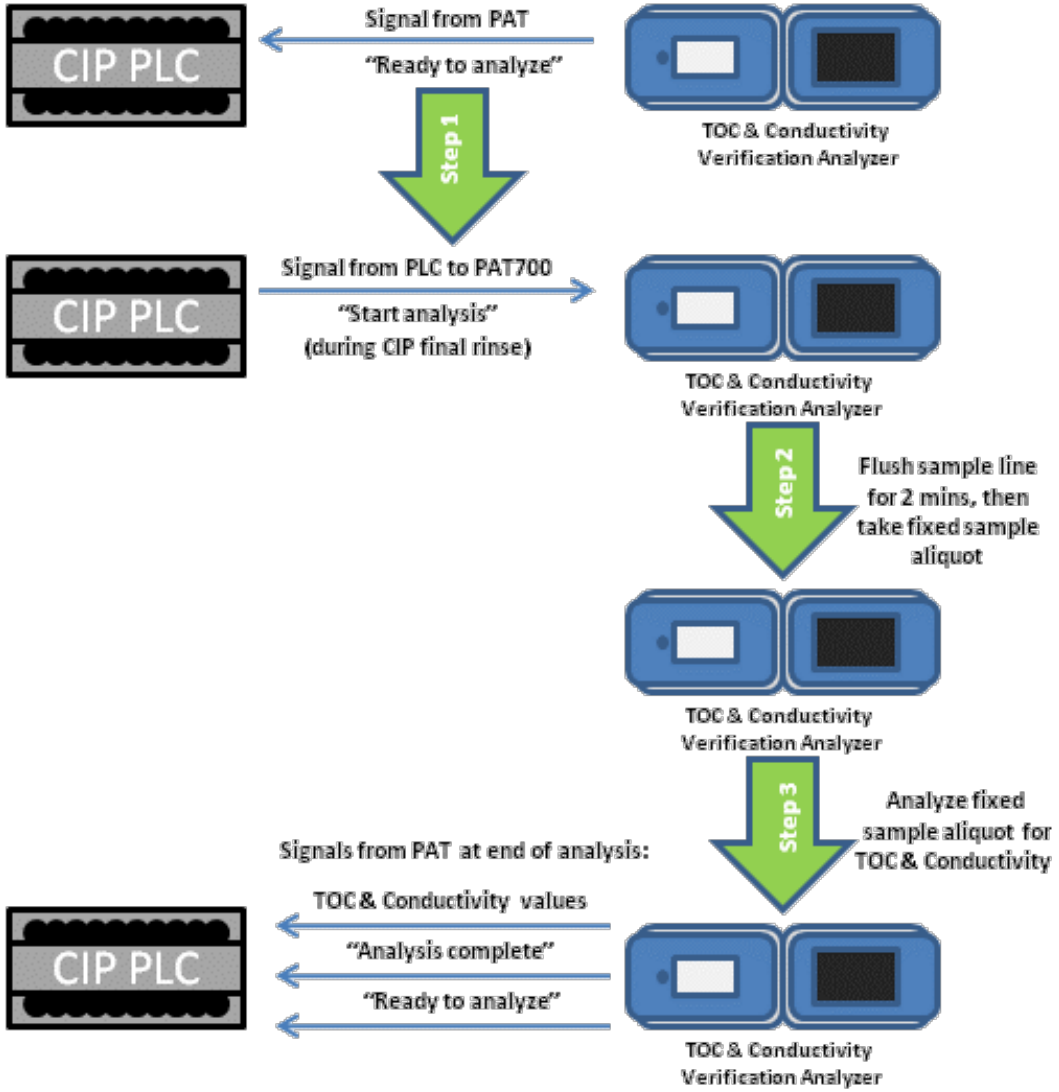
- CIP return or drain water passes through conductivity probe
- Conductivity decreases to a predetermined value
- Controller will switch the valve to flush through the TOC analyzer



Automating the CIP Process

Signal to PLC
- Time
- Internal or external Conductivity





Operational Results

Start 12.Dec.2008 - 14:05

End 12.Dec.2008 - 15:45

CIP Test Report #1	Pre rinse 1		Pre rinse 2		Wash 1		Post rinse		Wash 2		Post rinse 2		Final Rinse	
	SP	PV	SP	PV	SP	PV	SP	PV	SP	PV	SP	PV	SP	PV
Number of repetition	2	2	-	-	1	1	1	1	1	1	1	1	1	1
High	6	-	-	-	6	-	6	-	6	-	6	-	6	
Pressure (bar g)		4.7	-	-		4.8		4.9		5		4.9		4.8
Low	4	-	-	-	4	-	4	-	4	-	4	-	4	
Level, vessel (liters)	150	151	-	-	200	202	125	124	200	198	125	126	225	227
Duration time (sec)	55	55			360	360	45	40	240	240	45	46	100	105
Temperature (°C)	45	46	-	-	65	66	60	62	60	59	80	82	25	26.7
Cleaning agent 1 (kg)	-	-	-	-	0.75	0.78	-	-	0.55	0.57	-	-	-	-
Cleaning agent 2 (kg)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TOC (ppb)	-	-	-	-	-	-	-	-	-	-	-	-	-	**73**
High	-	-	-	-	5	-	-	-	5	-	-	-	0.85	
Conductivity (µS/cm)	-	-			-	3.75	-	-	-	2.5	-			**0.72**
Low	-	-	-	-	2	-	-	-	2	-	-	-	-	-
Flow (lpm)	-	65				63	-	66		63	-	64	-	-
Drain CIP internal	30	30	-	-	30	30	30	30	30	30	30	30	60	60
Drain Supply (sec)	30	30	-	-	30	30	30	30	30	30	30	30	60	60
Drain w/pump	20	20	-	-	20	20	20	20	20	20	20	20	30	30

Benefits of On-line Monitoring

- Reduced time and cost
  - Faster knowledge and response
- Eliminate bad results due to grab sampling error
- Results in minutes instead of hour or days
- Cost of manufacturing down time
  - $4,000 to $6,000
  - *One day = > $100,000 lost production
- Continued Process Verification

Benefits of Automation

Consistent Verifiable Process

- Real time control

Improved Product Quality

- Repeatable manufacturing
- Confirmed Product Safety

Cost Effective Production

- Reduced water usage
- Reduced waste
- Reduced downtime

Benefits of Automation

- Why companies feel they no-longer need to re-qualify if they measure every CIP final rinse

- The FDA PAT Guide states "*In a PAT framework, validation can be demonstrated through continuous quality assurance where a process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process end points*."

Thank you!!!!

Contact:

Joe Gecsey

jgecseyjr@Beckman.com

Cell: (541) 210-1094