Rouge Formation and Remediation

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Agenda

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- Overview of Stainless Steel
- Understand Rouge Generation
- Impact of Rouge on System
- Rouge Remediation
- Predictive maintenance for vessels with corrosive buffers
- Case Studies

Stainless Steel

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- Facts about Stainless Steel
  - Named Stainless", it is really "stain resistant"
  - Chromium oxide rich passive layer
  - Iron alloys with a minimum of 10.5% chromium.
  - Metals and non-metals are added to enhance their structure and properties:
    - Nickel
    - Molybdenum
    - Titanium
    - Copper
    - Carbon
    - Nitrogen

Types of Stainless Steel

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- Depends on Microstructure
  - Austenitic: Grades 304, 316, and 317. These have the highest corrosion resistance
  - Ferritic: Grades 430 and 434. Less ductile than Austenitic
  - Martensitic: Grades 410 and 420. Highest hardness.

Stainless steel

ASI Type	Chromium	Nickel	Carbon (max)	Iron	Silicon	Molybdenum
304	18-20	8-10.5	0.08	65-71	1.0	--
304L	18-20	8-12	0.03	65-71	1.0	--
316	16-18	10-14	0.08	62-69	1.0	2-3
316L	16-18	10-14	0.03	62-69	1.0	2-3

S = 0.03, Si = 1.0 and Mn = 2.0

Passive layer: 3 Cr + 3 O2 → 2 Cr2O3 (thin, protective, tenacious and transparent film)
Thickness of passive layer: 3 to 5 nm thick (1nm = 1 x 10^{-6} mm)

Stainless steel must contain > 10.5% Cr to allow the formation of a “passive” layer on the surface

Nature of Rouge

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- Rouge is a corrosion product on Stainless steel composed of:
  - Predominantly various forms of iron oxides
- Typical in water systems and processing equipment
- Some wipe off easily, others are tenacious and can be reddish brown to black.

Challenges of Rouge

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- Industry challenge in pharmaceutical manufacturing facilities
- Stainless steel corrosion, or rouge, is an industry-wide problem that, left untreated, can cause product contamination
- Removing rouge and maintaining passive layer of stainless steel equipment are essential preventative maintenance requirements for any manufacturing facility.

Effects of Rouge

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Types of Rouge

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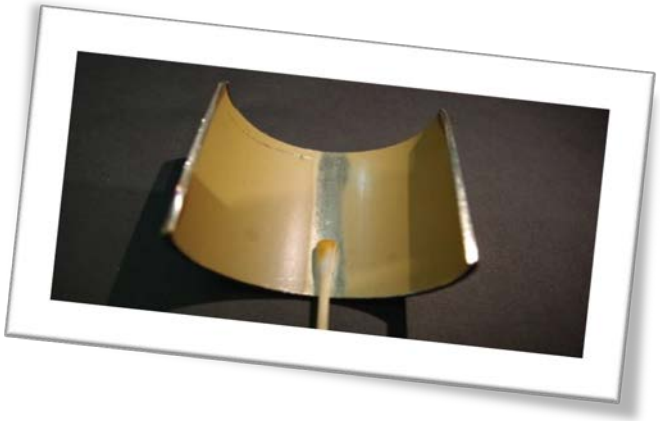
- Type I
  - Oxidized metal particles generated from external sources by erosion or cavitation of pump surfaces.
  - Easier to remove, can often be wiped off



Types of Rouge

- Type II
  - Rouge formed from in situ oxidation of stainless steel.
  - Tightly adhered, could have underlying damage.

Types of Rouge

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- Type II rouge
  - Rouged formed from in situ oxidation of stainless steel
  - Tightly adhered, corrosion driven and forms on the surface
  - Example, when chlorides or other halides are present
  - Forms in 2 stage reaction:
    - Dissolution of Cr_2O_3 layer
      - $Cr_2O_3 + 6Cl^- + 6H_2O \rightarrow 2CrCl_3(aq) + 6OH^-$
    - Oxidation of iron in the substrate
      - $2Fe + 4H2O \rightarrow 2FeO(OH) + 3H_2$

Types of Rouge

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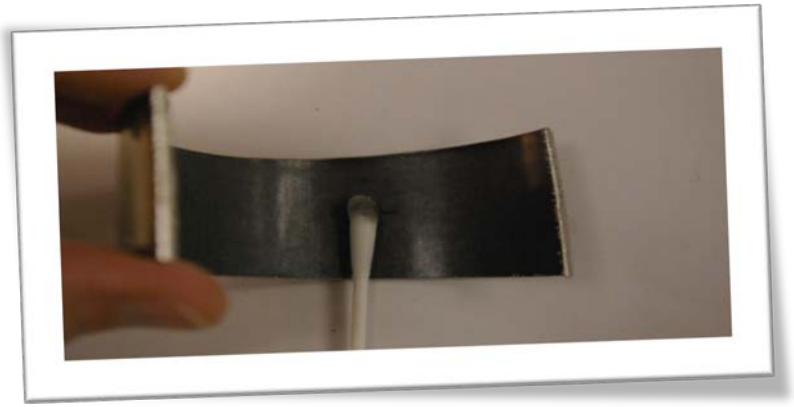
- Type III
  - Black oxide rouge generated from high temperature or steam
  - Top layer can be wiped off
  - Non-reactive, behaves like a passive layer



Formation of Rouge

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- Water system (Purified water system, Water for injection system)
- Clean steam systems
- Vessels and storage tanks
- Autoclaves
- Freeze dryers (Lyophilizers)
- After operating periods of 6 – 12 months, the inner surfaces of SS systems may show reddish-brown, rusty surface, which can be detected with a white cloth test.

Causes of Rouge

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- Destruction of the passive layer accelerated by:
- Highly corrosive environments
  - Steam
  - Chlorides, corrosive products
  - High temperature, stress, erosion
- Improper surface conditions
  - Improper welding
  - Surface defects
  - Inadequate cleaning
  - Inadequate passivation

Types of Corrosion

- Pitting corrosion :
  - Localized corrosion
  - Small pits and hole

- Stress cracking / Intergranular corrosion :
  - High temperature and corrosive environnent
  - Chromium carbide deposits along grain boundary

Types of Corrosion

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- Uniform corrosion :
  - Uniformly distributed over entire surface

- Galvanic corrosion:
  - Electrically driven process

- Crevice corrosion :
  - Shielded from full environment exposure

Warning Letter

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Maintenance of Equipment

3. Written procedures are not followed for the **maintenance of equipment** used in the manufacture, processing, packaging or holding of drug substances.

For example:

a. Internal surfaces and manual valves on the stainless steel chromatography columns used during drug substance purification are not adequately maintained. Maintenance has never been performed on the interior of columns to prevent adverse impact on cell cultures due to metal contamination. Visible rouging was observed on the exterior of the chromatography skid **(b)(4)** used in purification of ….

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm148998.htm

Warning Letter

Your firm's ISO 5 hood has an area of rust with silicone applied over it consisting of approximately ¼" x 1'.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm604131.htm

Your firm failed to establish and follow written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

For example, you did not have cleaning procedures for the manufacturing equipment you use to make **(b)(4)**patches. During the inspection, our investigator observed rust and unidentified **(b)(4)** residue on your **(b)(4)** and other manufacturing equipment.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm540251.htm

Warning Letter

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Our investigator observed rust, insects, damaged interiors, and/or drug residues in (b)(4) of (b)(4) pieces of manufacturing equipment. This equipment was identified as “clean” and was either in direct contact with API or could potentially contact API. Your deficient cleaning and maintenance practices present an unacceptable risk of introducing foreign contaminants, or cross-contamination between drugs.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm538693.htm

How to avoid / slow rouging effect ?

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- Stainless steel composition – 316L is the best option
  - ✓ Ni improve the stability of the passive layer
  - ✓ Mo improve micro pitting resistance
  - ✓ Low carbon
- Surface finishing
- Avoid corrosive contaminant / environment:
  - ✓Chloride , Sulfide
  - ✓ Steam
  - ✓High temperature
  - ✓ Residue
- Cleaning procedure:
  - ✓Remove effeciently residues
  - ✓Optimal frequency of sanitization
- Periodic Maintenance

Derouging and Passivation Considerations

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- Effective removal of any visible rouge
- Process constraints (e.g., temperatures, flow rates, etc.)
- Avoiding damage to surface finish caused by excessively aggressive chemistries
- Operator safety when handling hazardous chemicals

Derouging and Passivation Considerations

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- Environmental concerns (e.g. phosphates, volatile compounds, etc.)
- Adherence to industry standards (e.g., ASTM A 967)
- Use of chemicals that are not part of the validated process cleaning operations

Derouging

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- No single “recipe” for performing a successful derouging operation.
- Example of model operating procedure:
  - A laboratory-based assessment to establish effective derouging parameters
  - A robust alkaline cleaning to remove organic residues
  - An acid treatment to remove iron oxides
  - Process monitoring to assess the effectiveness of the treatment.

Derouging

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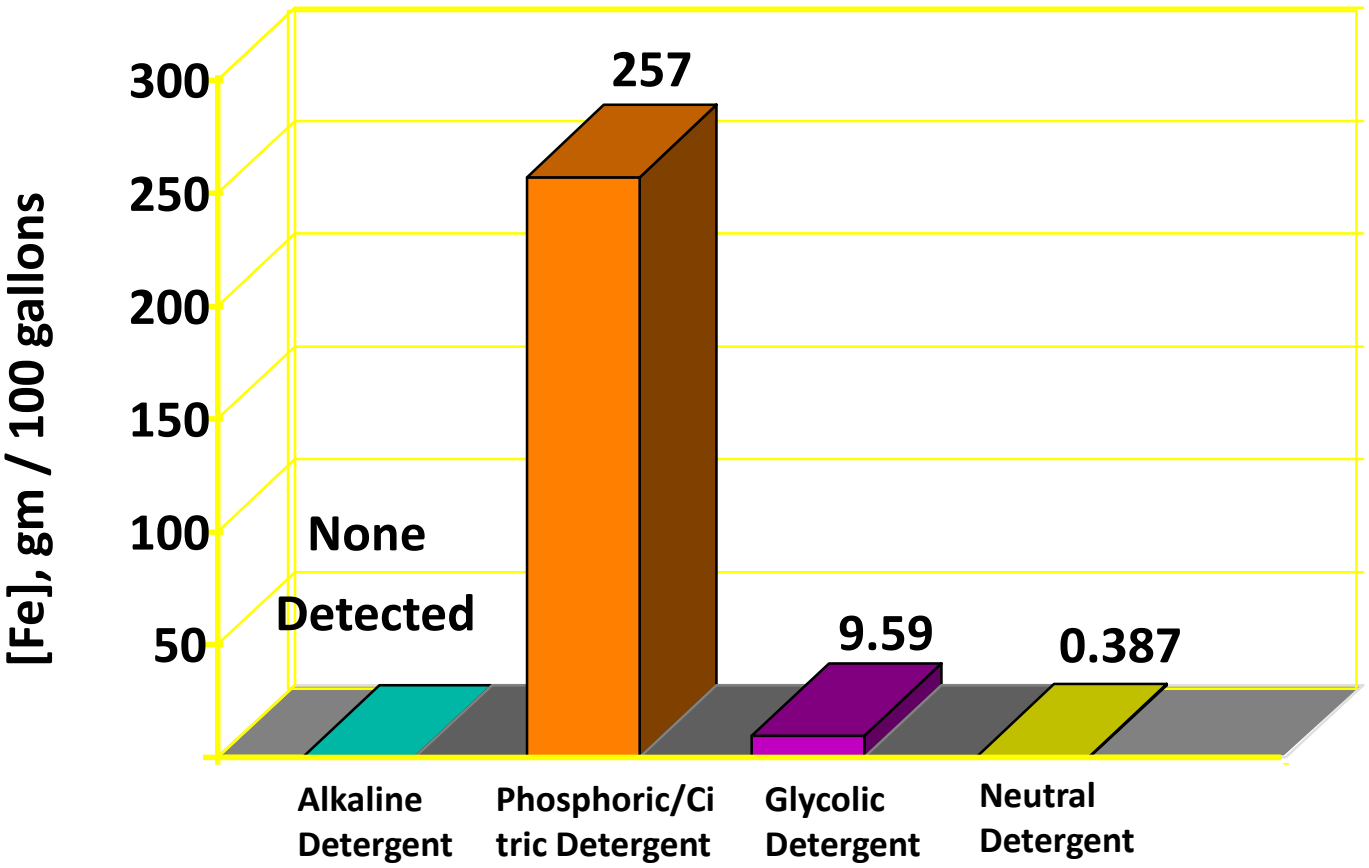
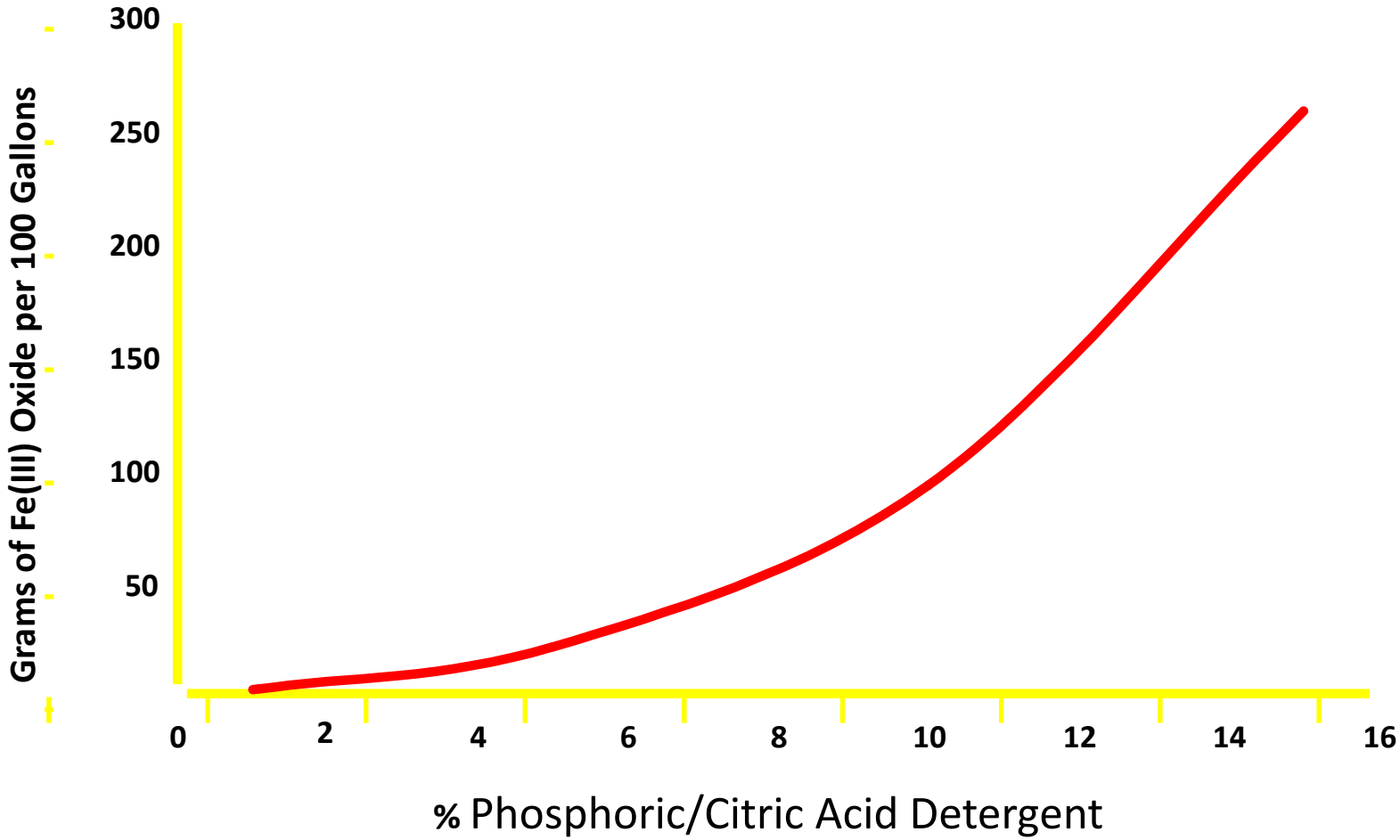
- Removal of metal oxides by solubilization
- Depends on concentration and temperature
- Concentration of dissolved Fe increases initially in the derouging solution
- Critical to remove any organic residue before the derouging step
- HACH test kit – Field tool to measure level of Iron

Tech Tip #3016 – Rouge and Derouging
Tech Tip #3017 – General Procedure for Derouging Stainless Steel Surfaces

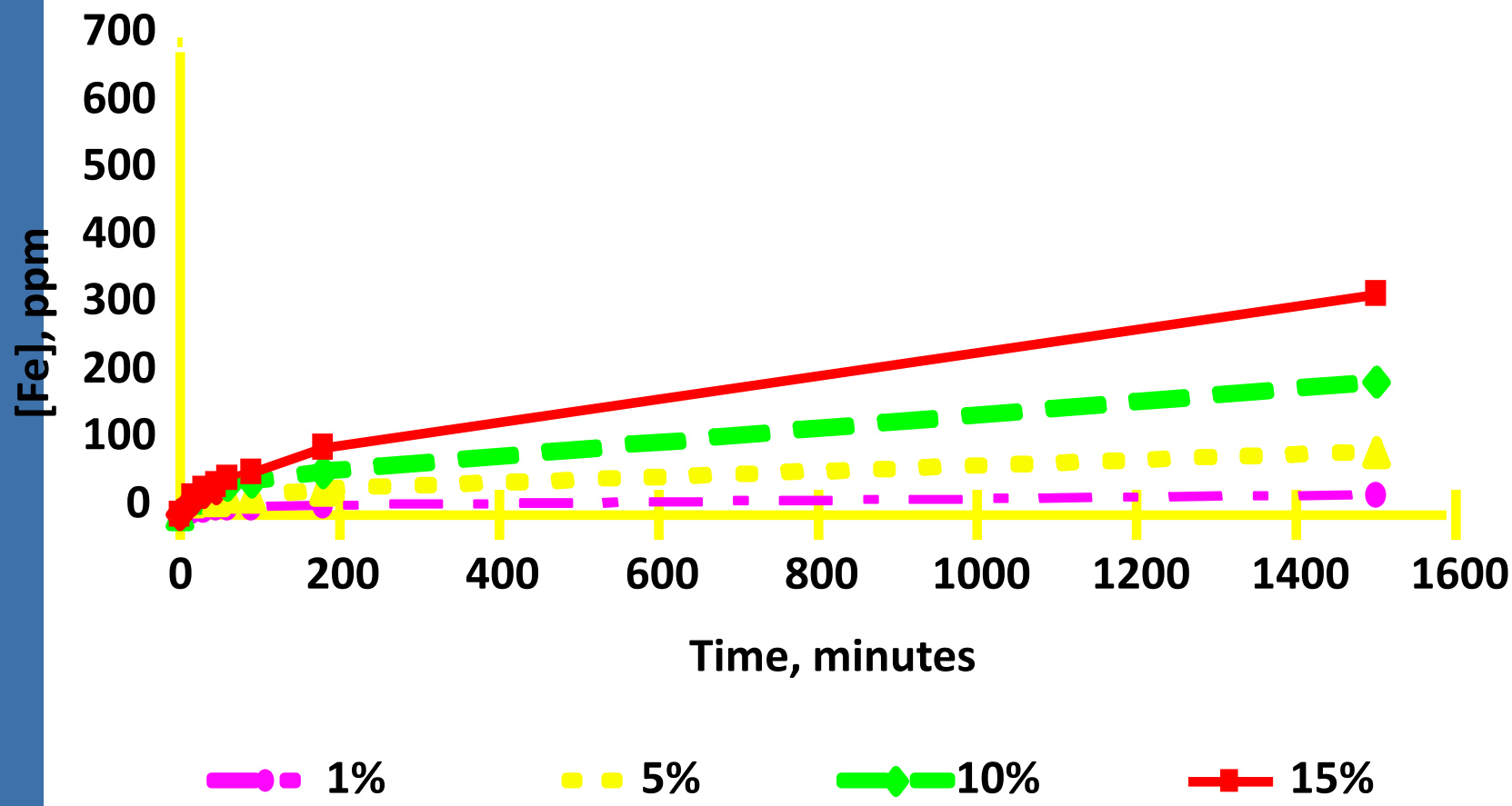
Solubility of Fe(III) Oxide in Various 15% Solutions



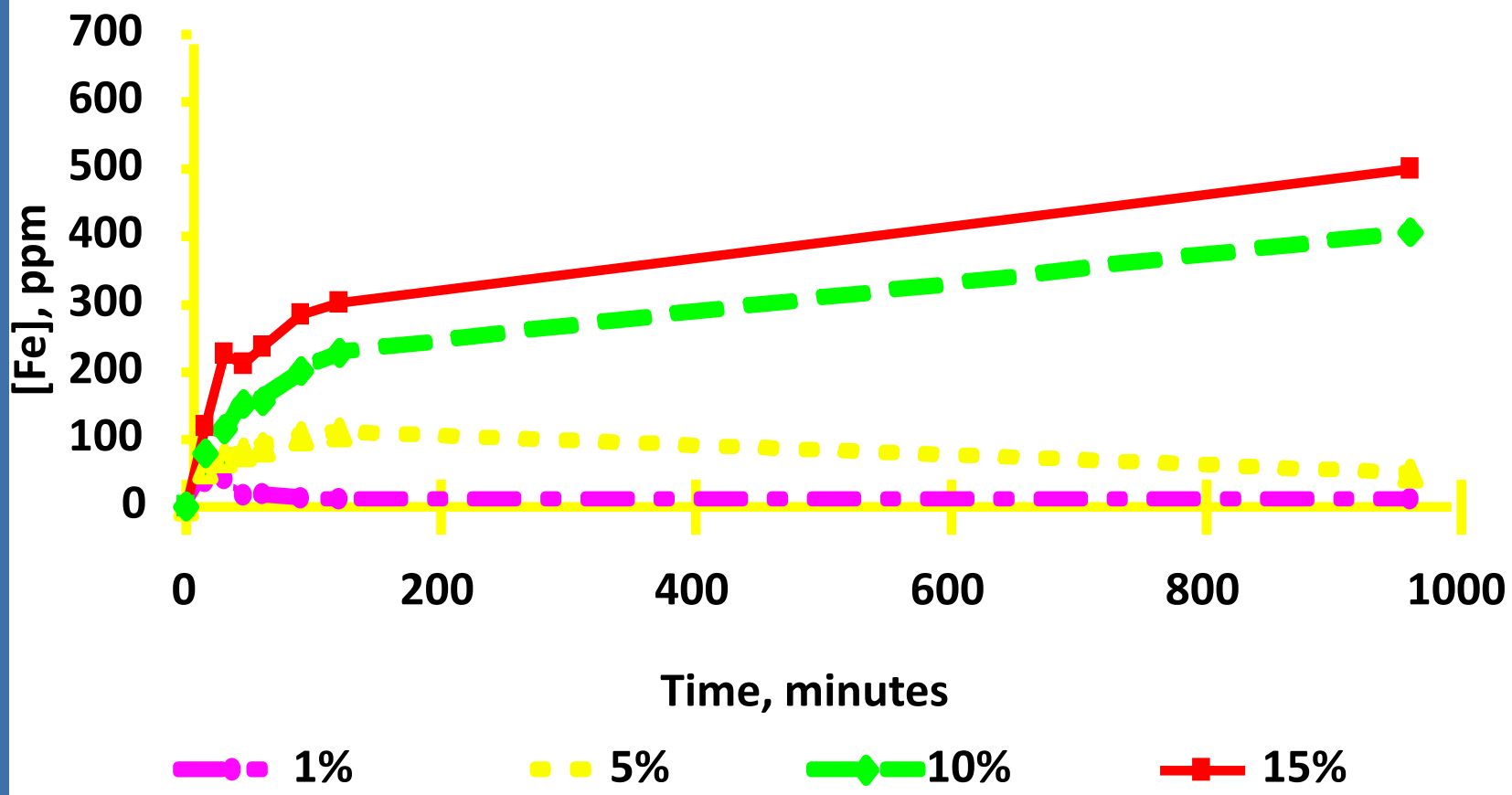
Solubility of Fe(III) Oxide in the Phosphoric/Citric Acid Detergent



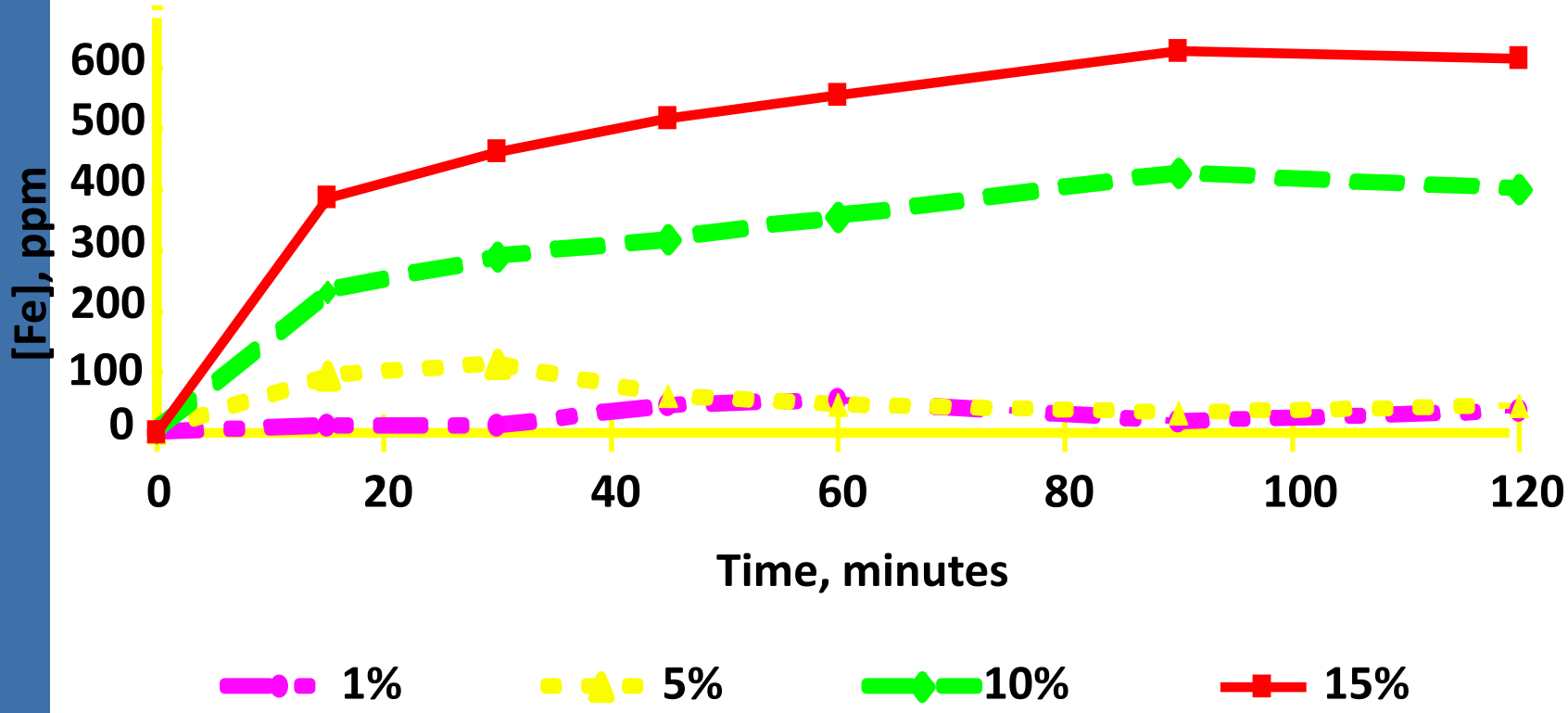
Solubility of Fe(III) Oxide in Phosphoric/Citric Acid Detergent @ 25°C



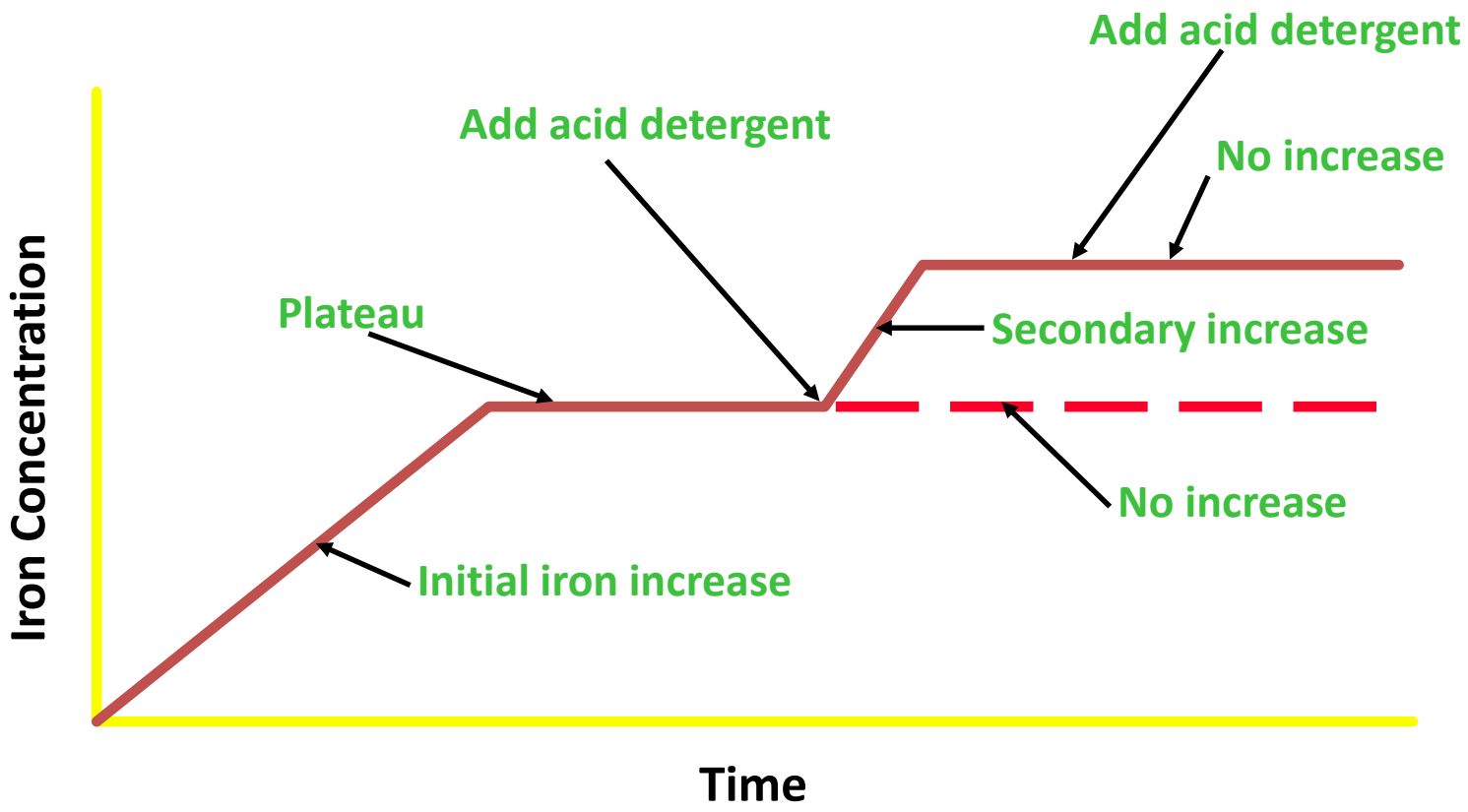
Solubility of Fe(III) Oxide in Phosphoric/Citric Acid Detergent @ 60°C



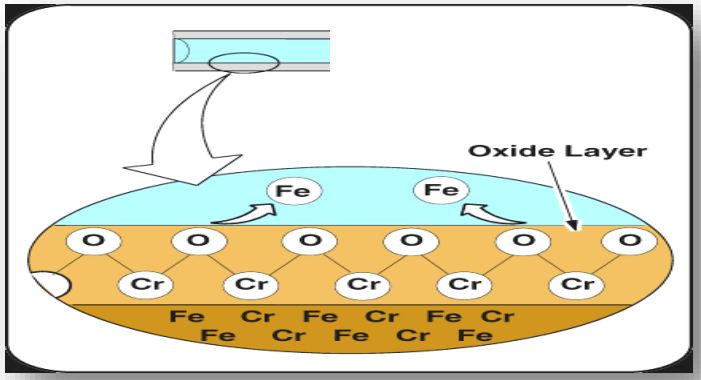
Solubility of Fe(III) Oxide in Phosphoric/Citric Acid Detergent @ 80 °C



Suggested Approach



Passivation



- Stainless steel has the ability to resist corrosion by forming a relatively unreactive Cr enriched passive film in the presence of oxygen
- Clean surface is a critical prerequisite to the formation of this film

Passivation

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- Passivation can be enhanced with the use of chemical treatments.
- Analytical techniques like x-ray photoelectron spectroscopy (XPS) are commonly used to quantify the depth and quality of this passive layer by measuring the chromium-to-iron ratio (Cr/Fe).

Passivation

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- Chemical methods can be used to enhance the nature of this passive layer
  - Nitric acid, phosphoric acid, citric acid, other proprietary chelant formulations are typically used.
  - Nitric acid and citric acid are ASTM referenced
- Passivation goal:
  - ✓ dissolve the free iron
  - ✓ acceleration Cr_2O_3 formation
  - ✓ smooth surface
  - ➔ Regenerate the passive layer

INDUSTRY STANDARDS
ASTM A 380 : Standard practice for cleaning, descaling and passivation of SS parts, equipment, and systems
ASTM A 967 : Standard specification for chemical passivation treatments for stainless steel parts

Passivation Processes

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Process	Reference	Conditions
Nitric acid	ASTM A380/A967	10-40%, 30-90 min
Phosphoric acid	ASME BPE 2009	5-25%, 1-4 hrs
Phosphoric acid blends	ASME BPE 2009	5-25%, 1-4 hrs
Citric acid	ASTM A967	10%, 1-4 hrs
Chelant systems	ASTM A967	3-10%, 1-4 hrs

Test matrix for evaluation

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Water-wetting and drying
High humidity
Salt spray
Copper sulfate
Potassium ferricyanide-nitric acid
Cyclic polarization
Koslow test kit
Electrochemical pen
Augar electron spectroscopy (AES)
Glow-discharge optical emission spectroscopy (GD-OES)
X-ray photoelectron spectroscopy (XPS) or Electron spectroscopy for chemical analysis (ESCA)

Reference:
ASTM Designation: A 967-01 Standard Specification for Chemical Passivation Treatments for Stainless Steel Parts
ASME BPE-2012, Table E-3, Non Mandatory Appendix E Passivation Procedure Qualification

Type of Derouging & Passivation

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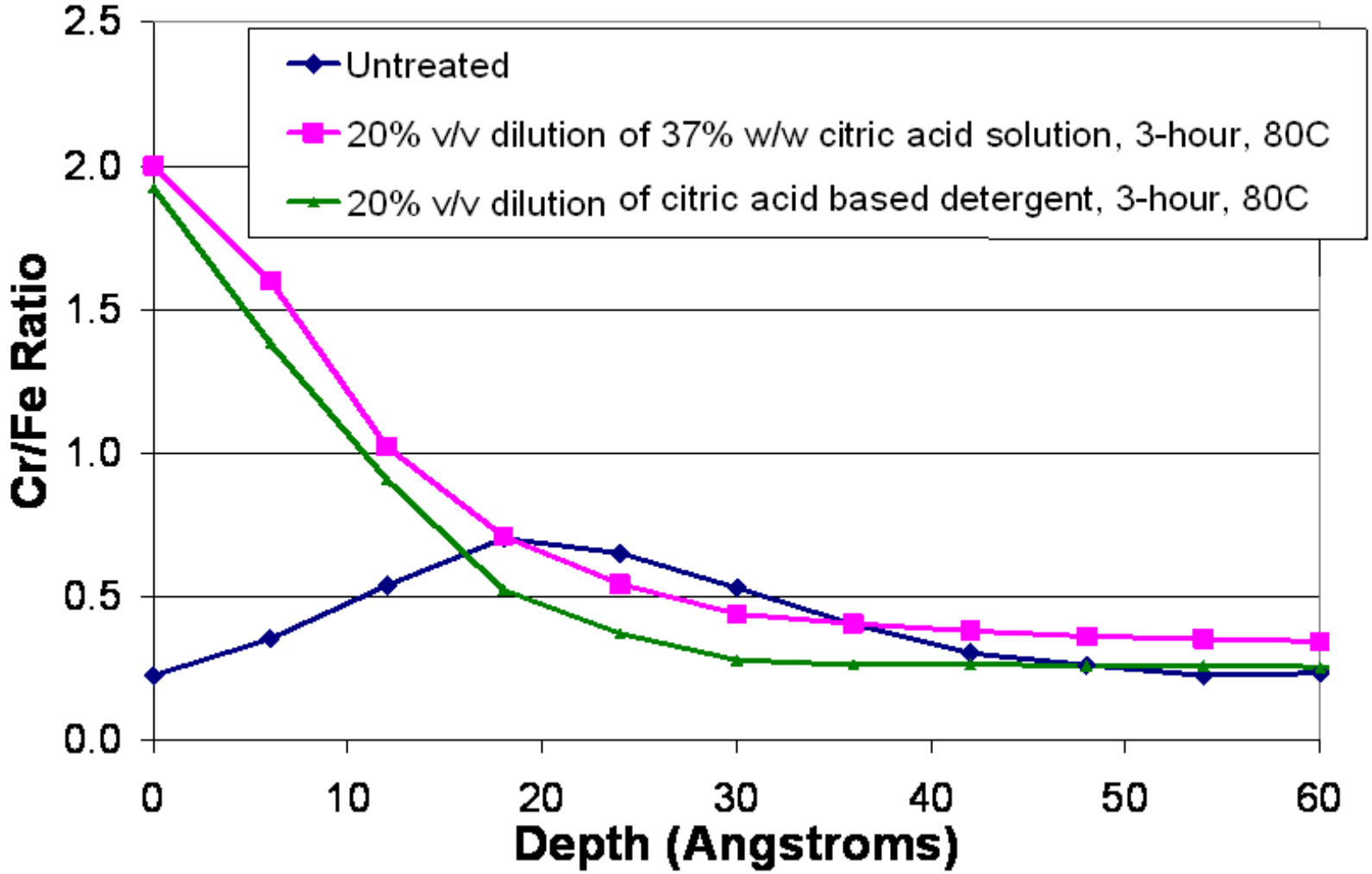
- Mechanical :
  - Electropolishing (ASTM A 380): Electrochemical process. Metal ions are removed from surface
  - Manually polished
- Chemical (ASTM A 967):
  - Nitric acid
  - Phosphoric acid
  - Citric acid
  - Oxalic acid

XPS Depth Profile

(X-ray Photoelectron Spectroscopy)



Koslow test kit – Field tool

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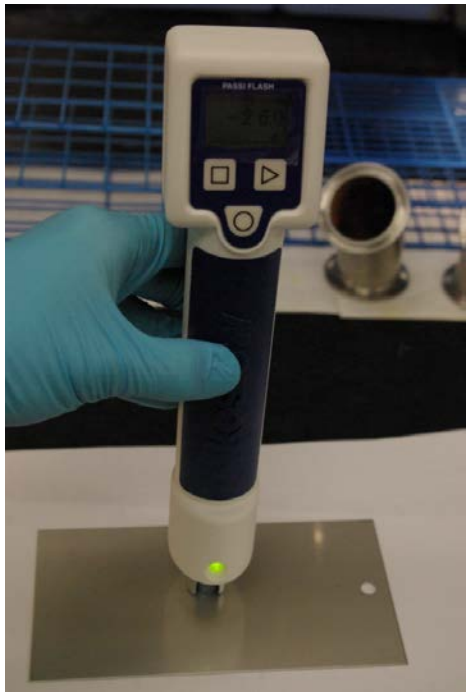

Millivolts	Indication (Light Color)
+1000 to -199	High Non-Passive Range (RED)
-200 to -400	Passive Range (GREEN)
-401 to -1000	Low Non-Passive Range (RED)

Process Equipment – Suggested Approach

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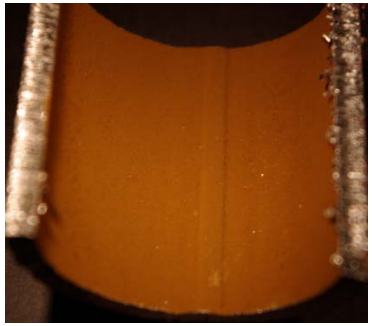
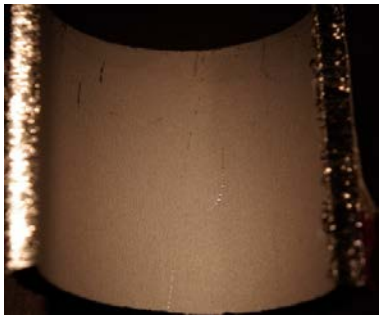
Step 1: Thorough pre-cleaning

- Formulated alkaline detergent at 5% +/- additive
- 60 to 80ºC for 1 to 2 hours
- Rinse with water

Step 2: Acid cleaning and passivation

- Formulated phosphoric or citric acid based detergent at 15% concentration
- 80ºC for 3-5 hours
- Rinse with water



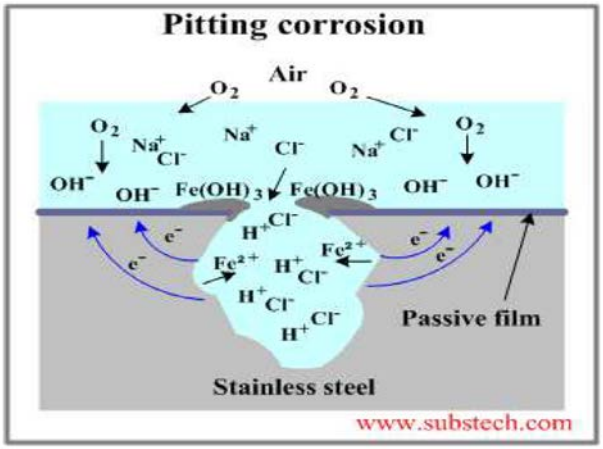


Example (pre cleaning critical)

Pipe section cleaned with 1% v/v Alkaline detergent plus detergent additive at 60°C for 60 minutes by agitated immersion

Micro-pitting

- 300 Series Stainless Steel alloys are prone to corrosion in the presence of chlorides
- Pitting corrosion is an electrochemical oxidation-reduction process, which occurs in the **absence of the passive layer**



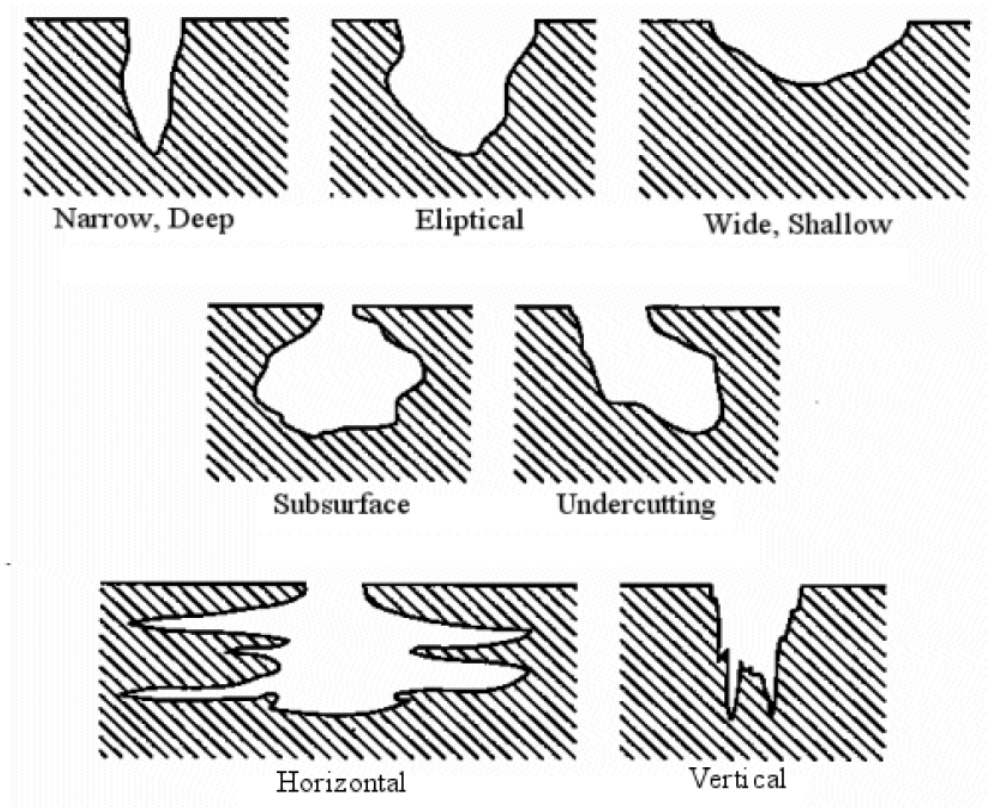
Micro-pitting

- Micro pitting is a type of local corrosion
- Causes damage in the form of pits or spots
- Can be due to presence of corrosive buffers

White stains

Pitting

Micro-pitting



Buffer Storage

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- Stainless steel maintenance of buffer tanks
- Verify the parameters and frequency of an acid detergent to maintain a passive layer on the 316L stainless steel coupons
- Buffer (HEPES Free Acid, Sodium Chloride, pH 5 Acetate)

Test Procedure (Case Study)

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- Preparation of passivated SS coupons
  - Clean 316L, stainless steel coupons were passivated with 11 % v/v acid detergent at 70 °C for 120 minutes to passivate the surface
  - After exposure, the coupons were rinsed with DI water and left to dry for 60 minutes
- Coupons were tested to confirm passive condition (Per Koslow test kit);

Test Procedure (Case Study)

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- SS coupons were exposed to solution of buffer (Hepes free acid and sodium chloride) and agitated in the shaker for 7 days or 14 days prior to exposing coupons to more low concentration acid detergent rinse as indicated below:
    - 0.4 % v/v acid detergent at 60 °C for 10 min every 14 days
    - 2.1 % v/v acid detergent at 60 °C for 10 min every 14 days
    - 0.4 % v/v acid detergent at 45 °C for 10 min every 7 days
    - 2.1 % v/v acid detergent at 45 °C for 10 min every 7 days

Test Procedure (Case Study)

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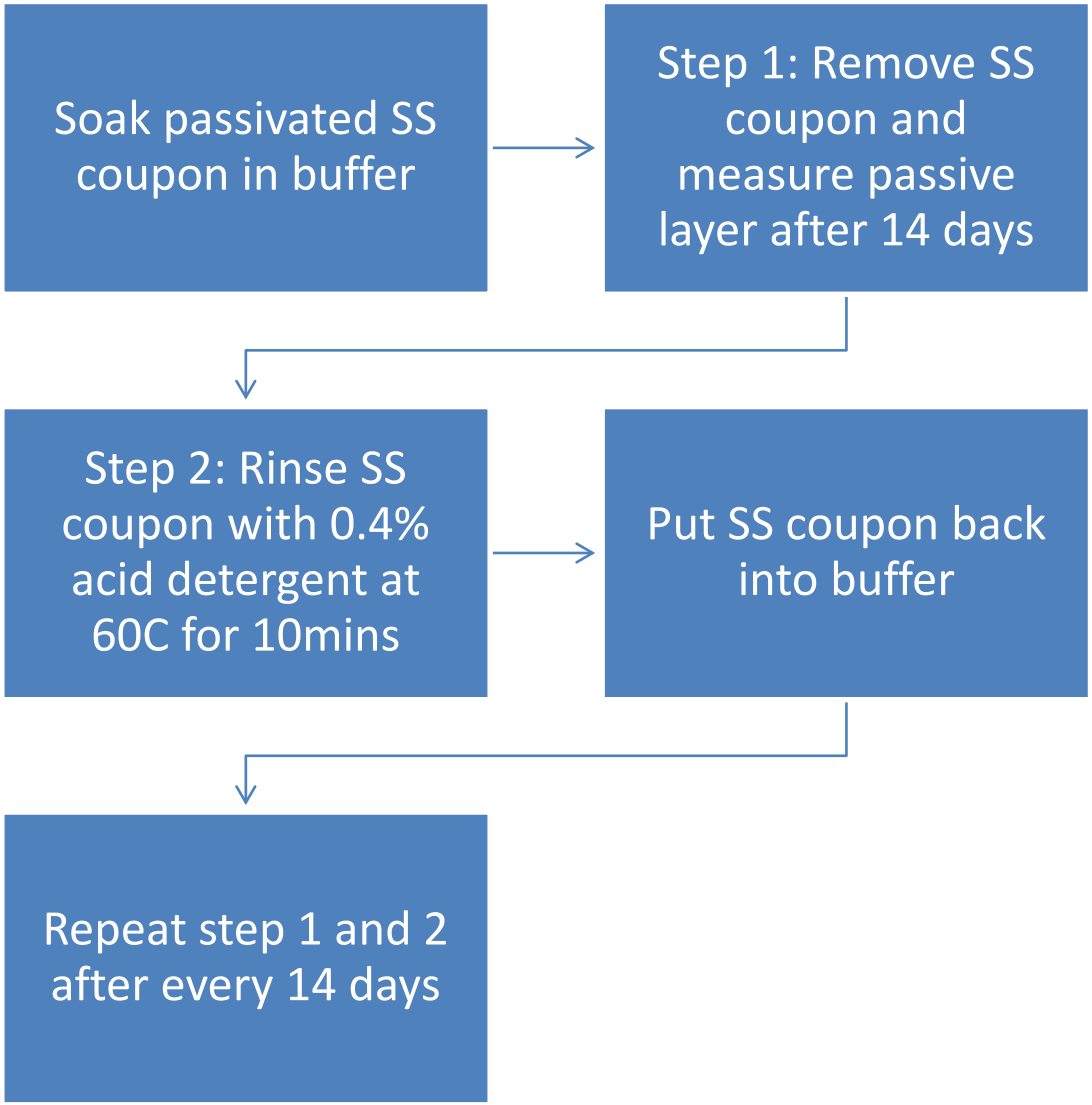

Controls

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- Control coupons are washed with 11 % v/v acid detergent at 70 °C for 120 minutes and is not exposed to periodic acid rinse with above listed conditions
- **Negative control** - Stored in buffer while mixing at ambient temperature. – **FAILED after 21 days**
- **Positive control** - Stored dry at rest in sample container at ambient temperature – remained **PASSIVE after 42 days** per Koslow Test Kit.

Results at 45 °C:

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Cleaner	Koslow Test kit results after agitating with buffer (days)	Results
0.4 % v/v acid detergent at 45 °C for 10 min every 7 days	7	Pass
	14	Pass
	21	Fail
	28	Fail
2.1 % v/v acid detergent at 45 °C for 10 min every 7 days	7	Pass
	14	Pass
	21	Fail
	28	Fail

Negative control - Stored in buffer while mixing at ambient temperature. – FAILED after 21 days

Results at 60 °C

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Cleaner	Koslow Test kit results after agitating with buffer (days)	Results
0.4 % v/v acid detergent at 60 °C for 10 min every 14 days	14	Pass
	28	Pass
	42	Pass
2.1 % v/v acid detergent at 60 °C for 10 min every 14 days	14	Pass
	28	Pass
	42	Pass

Negative control - Stored in buffer while mixing at ambient temperature. – FAILED after 21 days

Recommendation: Perform 0.4% acid detergent rinse at 60°C for 10 min every 14 days.

Case Study #1:

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PH 5 Acetate

1) Evaluate cleaning with de-ionized water
2) Evaluate passive layer during wet storage of buffers (192 hours)
3) Use of a low concentration acid cleaner to maintain passive surface

H 5 Acetate

Results: pH 5 Acetate

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PACE #4E018 – PH5 Acetate
Air-dried at ambient temperature for 72 hours

Agitated Immersion

CLEANER	CONC.	TIME/ TEMPERATURE	VISUAL OBSERVATION	WATER BREAK-FREE
DI water	----	5 min / amb	Visually Clean	YES


PACE #4E018

Passivate coupons with 15% v/v acid detergent for 180 minutes at 80°C

Expose passive coupon to buffer and periodically test passive condition

TIME (Hours)	RESULTS
24	PASS
48	PASS
72	PASS
96	FAIL
120	FAIL
192	FAIL

Results: pH 5 Acetate

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- Washed and rinsed 316L stainless steel coupons
- Passivated with 10% v/v acid detergent at 80°C for 40 minutes
- Rinsed with DI water and dried at RT for 60 min.

Exposed to pH 5 Acetate solution and agitated for 3 to 4 days then wash coupon with a low concentration of acid detergent (0.5% v/v, 80°C for 10 minutes)

Time (days)	Results
3	PASS
7	PASS
10	PASS
14	PASS
17	PASS
21	PASS
24	PASS
28	PASS
31	PASS

Caste study #2 : Initial Observation (1/3)

Caste study #2 : PACE Testing (2/3)

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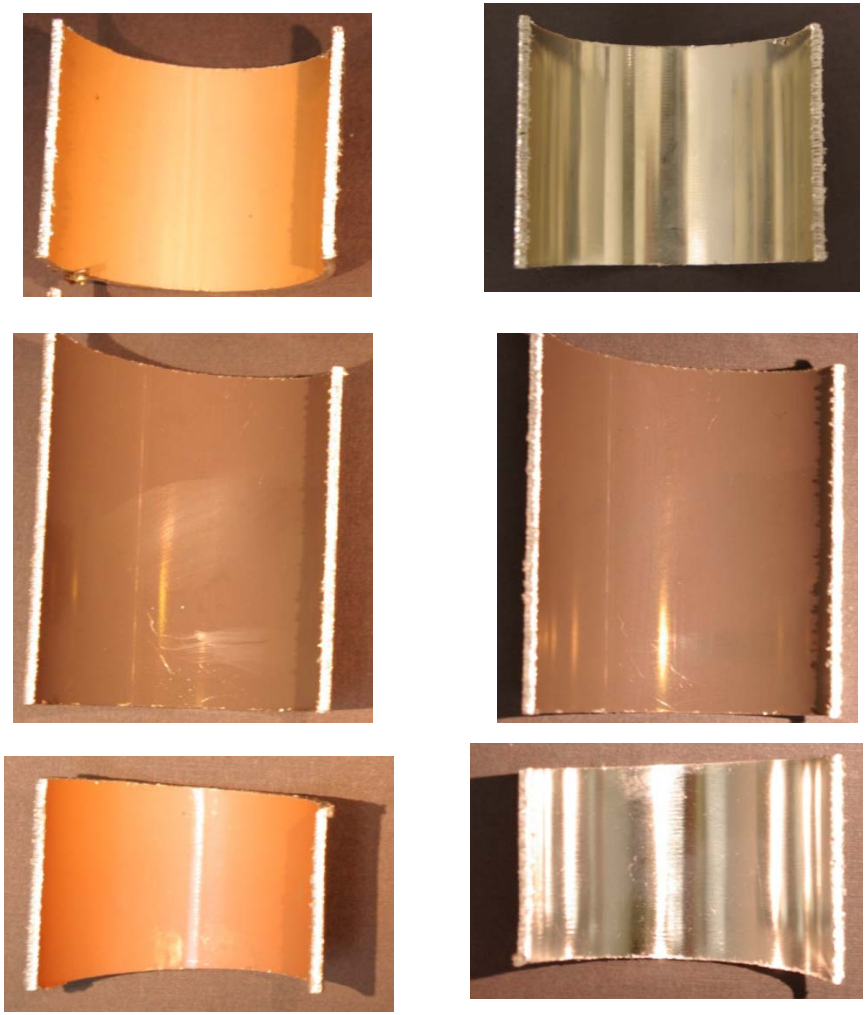

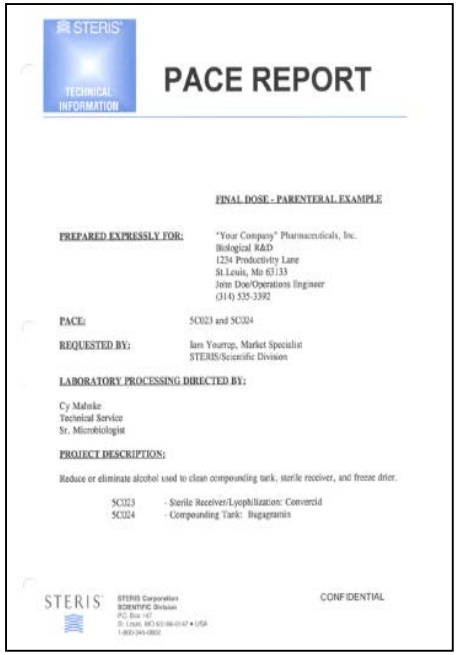

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TECHNICAL INFORMATION

PACE REPORT

FINAL DOSE - PARENTERAL EXAMPLE

PREPARED EXPRESSLY FOR: "Your Company" Pharmaceuticals, Inc.
Biological R&D
1234 Productivity Lane
St.Louis, Mo 63133
John Doe/Operations Engineer
(314) 535-3392

PACE: 5C023 and 5C024

REQUESTED BY: Iam Yourrop, Market Specialist
STERIS/Scientific Division

LABORATORY PROCESSING DIRECTED BY:

Cy Malnke
Technical Service
Sr. Microbiologist

PROJECT DESCRIPTION:

Reduce or eliminate alcohol used to clean compounding tank, sterile receiver, and freeze drier.

5C023 - Sterile Receiver/Lyophilization: Convercid
5C024 - Compounding Tank: Bugagramin

STERIS
STERIS Corporation
SCIENTIFIC Division
P.O. Box 147
St. Louis, MO 63166-0147 • USA
1-800-245-0802

CONFIDENTIAL

5% v/v CIP 100 at 60°C for 2 hours followed by 20% v/v CIP 200 at 75°C for 4 hours then 25% v/v CIP 200 at 75°C for 2 hours

Caste study #2 : Field Trials (3/3)

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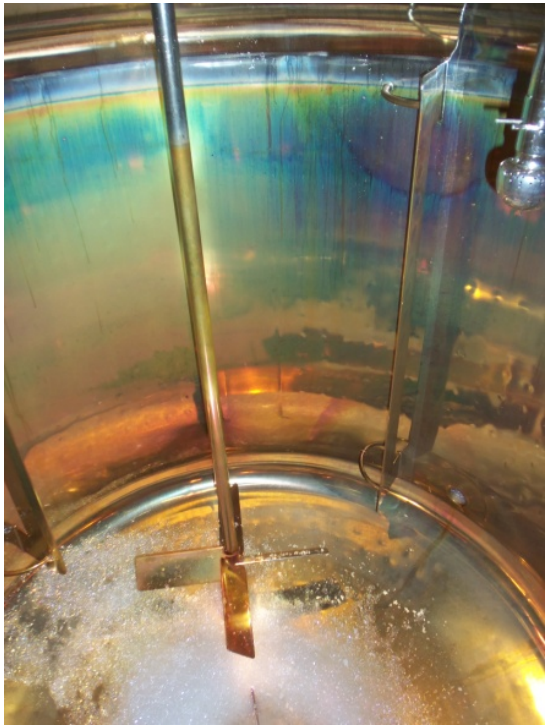

5% CIP 100® Alkaline Process and Research Cleaner at 60°C for 2 hours then
25% v/v CIP 200 re-circulating in the process vessels and piping circuits for approximately 9.5 hours while periodically measuring iron oxide levels in the solution

Case Study #3

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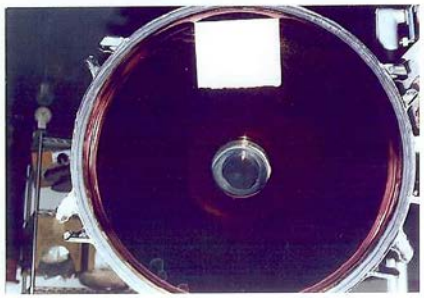
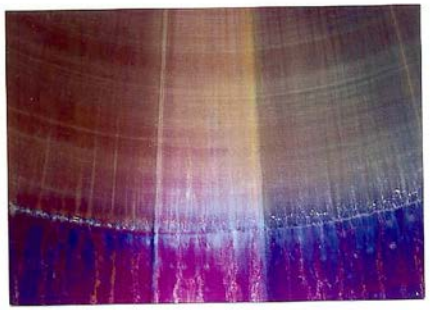
<u>Water storage tanks</u>

- 15 – 20% CIP200 acidic based detergent at 70°C for 3 – 4 hours.
- Now performed annually
- 5 – 10% CIP200 acidic based detergent at 70°C for 1 hour.

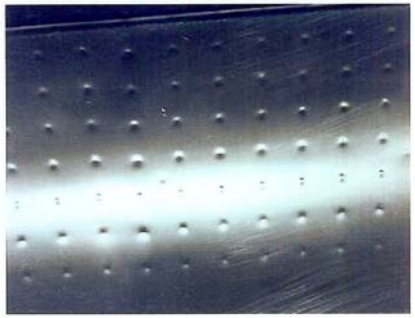


Lid Before

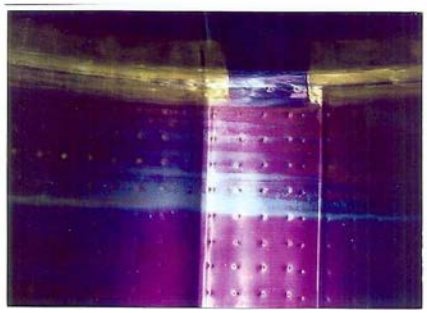
Lid After CIP-200 Treatment

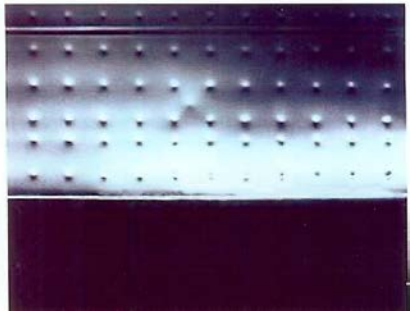


Vessel Before



Vessel After CIP-200 Treatment





Case Study # 4

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Background:

Biopharmaceutical company – vaccine manufacturer
Rouge removal recommendation from DI Water System

PROCEDURE

1. The pipe elbow sample was cut into pieces.
2. A piece of the pipe was cleaned by agitated immersion with 4% v/v formulated alkaline detergent at 80°C for 1 hour and rinsed with water.
3. The piece was then cleaned by agitated immersion with 20% v/v formulated phosphoric/citric acid based detergent at 80°C.
4. The piece was then removed from the solution and visually observed for cleanliness.
5. The piece was rinsed with tap water for 10 seconds at a flow rate of 0.5 gal/min
6. Then rinsed with de-ionized water.

Case Study # 4

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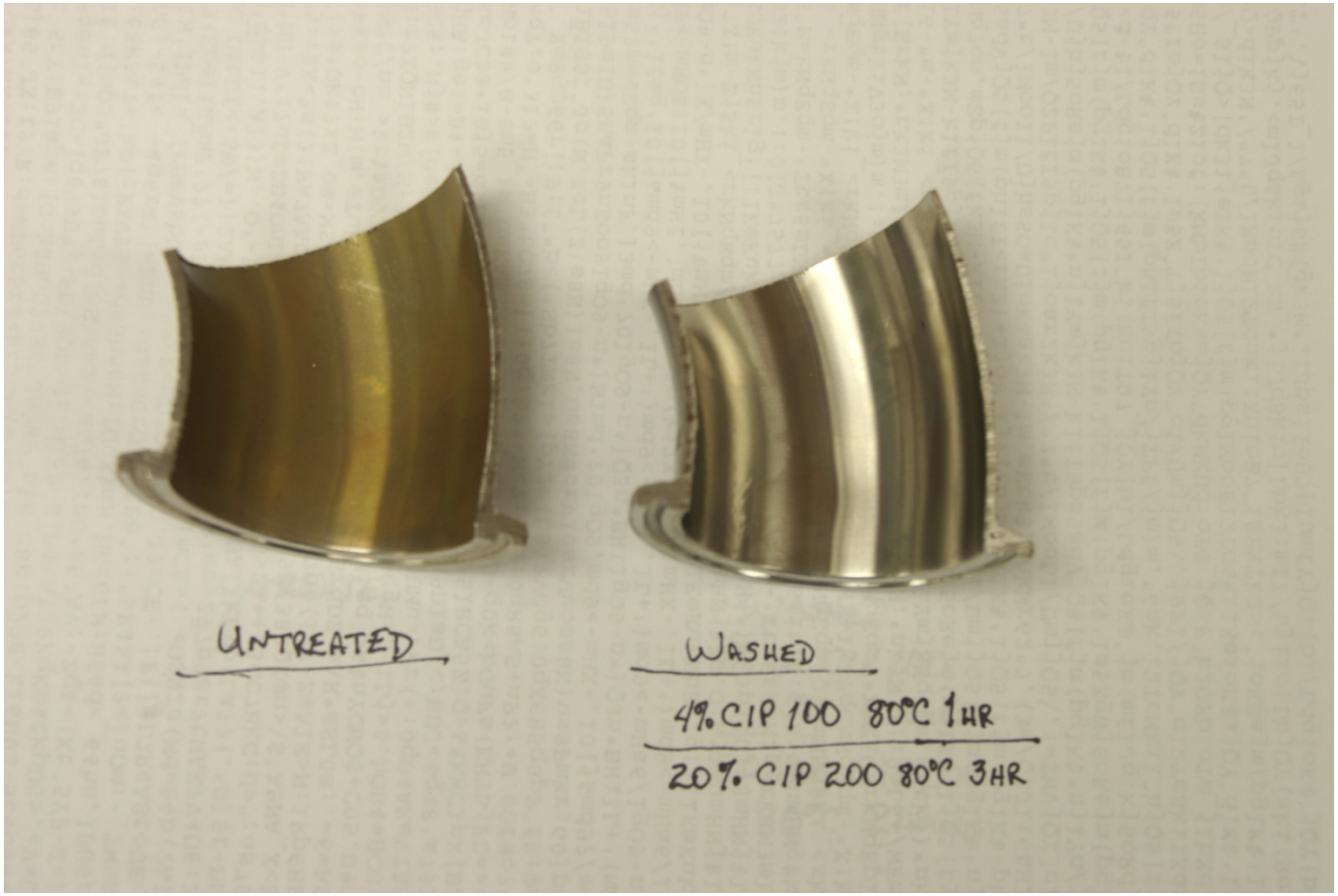
The rouge was effectively removed by agitated immersion using a solution of 20% v/v formulated phosphoric/citric acid based detergent at 80°C for 3 hours.

CLEANER	CONC	TIME / TEMP	VISUAL OBSERVATION
Formulated alkaline detergent	**4% v/v**	**1 hr / 80°C**	**Yellow**
Phosphoric /citric acid based detergent	**20% v/v**	**1 hr / 80°C**	**Reddish Yellow**
		2 hr / 80°C	**Metallic Silver**
		3 hr / 80°C	**Bright Metallic Silver**

Case Study # 4



Case Study #5

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Process tanks

Pre-cleaning

- 10% CIP100 at 80°C for 1 hour

Derouging & Passivation

- 25% CIP200 acidic based detergent at 80°C for 3.5 hours

Case Study # 6

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Case Study #7

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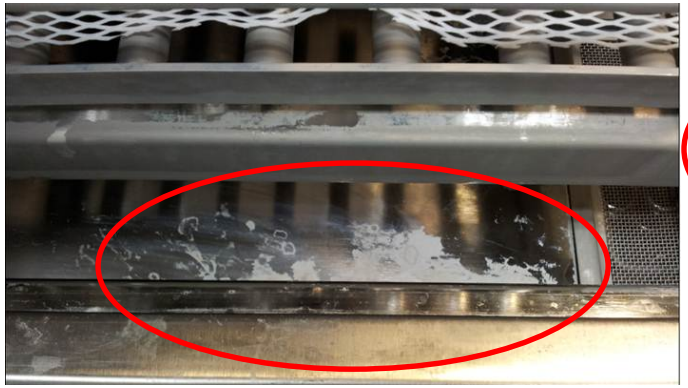
Case Study #8



Case Study #8

Descaling 5% CIP200 @60DegC, 1 hour

Rouge Formation and Remediation

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Questions ?