Agenda

- 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

• 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

• 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

<table>
<thead>
<tr>
<th>ASI Type</th>
<th>Chromium</th>
<th>Nickel</th>
<th>Carbon (max)</th>
<th>Iron</th>
<th>Silicon</th>
<th>Molybdenum</th>
</tr>
</thead>
<tbody>
<tr>
<td>304</td>
<td>18-20</td>
<td>8-10.5</td>
<td>0.08</td>
<td>65-71</td>
<td>1.0</td>
<td>--</td>
</tr>
<tr>
<td>304L</td>
<td>18-20</td>
<td>8-12</td>
<td>0.03</td>
<td>65-71</td>
<td>1.0</td>
<td>--</td>
</tr>
<tr>
<td>316</td>
<td>16-18</td>
<td>10-14</td>
<td>0.08</td>
<td>62-69</td>
<td>1.0</td>
<td>2-3</td>
</tr>
<tr>
<td>316L</td>
<td>16-18</td>
<td>10-14</td>
<td>0.03</td>
<td>62-69</td>
<td>1.0</td>
<td>2-3</td>
</tr>
</tbody>
</table>

S = 0.03, Si = 1.0 and Mn = 2.0

Passive layer: \( 3 \text{ Cr} + 3 \text{ O}_2 \rightarrow 2 \text{ Cr}_2\text{O}_3 \) (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

• 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

• 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

- Reduces cleanability and sanitization
- Increases microbial excursions
- Increases surface roughness
- Reduces equipment life
- Product contamination
Types of Rouge

• 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

• 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$_2$O$_3$ layer
      – Cr$_2$O$_3$ + 6Cl$^-$ + 6H$_2$O $\rightarrow$ 2CrCl$_3$(aq) + 6OH$^-$
    • Oxidation of iron in the substrate
      – 2Fe + 4H$_2$O $\rightarrow$ 2FeO(OH) + 3H$_2$
Types of Rouge

• 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

- 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

• 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 environment
  ➢ Chromium carbide deposits along grain boundary
Types of Corrosion

• Uniform corrosion:
  ➢ Uniformly distributed over entire surface

• Galvanic corrosion:
  ➢ Electrically driven process

• Crevice corrosion:
  ➢ Shielded from full environment exposure
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 ....

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

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?

- 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 efficiently residues
  - Optimal frequency of sanitization

- Periodic Maintenance
Derouging and Passivation Considerations

- 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

• 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

• 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

• 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

<table>
<thead>
<tr>
<th>Detergent Type</th>
<th>Solubility [Fe], gm / 100 gallons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline Detergent</td>
<td>None</td>
</tr>
<tr>
<td>Phosphoric/Citric Detergent</td>
<td>257</td>
</tr>
<tr>
<td>Glycolic Detergent</td>
<td>9.59</td>
</tr>
<tr>
<td>Neutral Detergent</td>
<td>0.387</td>
</tr>
</tbody>
</table>
Solubility of Fe(III) Oxide in the Phosphoric/Citric Acid Detergent

Grams of Fe(III) Oxide per 100 Gallons vs. % 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

- [Fe], ppm
- Time, minutes

Lines represent different concentrations:
- 1%
- 5%
- 10%
- 15%
Suggested Approach

Iron Concentration

Time

Initial iron increase

Plateau

Secondary increase

Add acid detergent

No increase

Add acid detergent

No increase
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

- 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

• 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$_2$O$_3$ 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

<table>
<thead>
<tr>
<th>Process</th>
<th>Reference</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitric acid</td>
<td>ASTM A380/A967</td>
<td>10-40%, 30-90 min</td>
</tr>
<tr>
<td>Phosphoric acid</td>
<td>ASME BPE 2009</td>
<td>5-25%, 1-4 hrs</td>
</tr>
<tr>
<td>Phosphoric acid blends</td>
<td>ASME BPE 2009</td>
<td>5-25%, 1-4 hrs</td>
</tr>
<tr>
<td>Citric acid</td>
<td>ASTM A967</td>
<td>10%, 1-4 hrs</td>
</tr>
<tr>
<td>Chelant systems</td>
<td>ASTM A967</td>
<td>3-10%, 1-4 hrs</td>
</tr>
</tbody>
</table>
## Test matrix for evaluation

<table>
<thead>
<tr>
<th>Test Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water-wetting and drying</td>
</tr>
<tr>
<td>High humidity</td>
</tr>
<tr>
<td>Salt spray</td>
</tr>
<tr>
<td>Copper sulfate</td>
</tr>
<tr>
<td>Potassium ferricyanide-nitric acid</td>
</tr>
<tr>
<td>Cyclic polarization</td>
</tr>
<tr>
<td>Koslow test kit</td>
</tr>
<tr>
<td>Electrochemical pen</td>
</tr>
<tr>
<td>Auγar electron spectroscopy (AES)</td>
</tr>
<tr>
<td>Glow-discharge optical emission spectroscopy (GD-OES)</td>
</tr>
<tr>
<td>X-ray photoelectron spectroscopy (XPS) or Electron spectroscopy for chemical analysis (ESCA)</td>
</tr>
</tbody>
</table>

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

• 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

<table>
<thead>
<tr>
<th>Millivolts</th>
<th>Indication (Light Color)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+1000 to -199</td>
<td>High Non-Passive Range (RED)</td>
</tr>
<tr>
<td>-200 to -400</td>
<td>Passive Range (GREEN)</td>
</tr>
<tr>
<td>-401 to -1000</td>
<td>Low Non-Passive Range (RED)</td>
</tr>
</tbody>
</table>
Process Equipment – Suggested Approach

Step 1: Thorough pre-cleaning
- Formulated alkaline detergent at 5% +/- additive
- 60 to 80°C for 1 to 2 hours
- Rinse with water

Step 2: Acid cleaning and passivation
- Formulated phosphoric or citric acid based detergent at 15% concentration
- 80°C 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

- Narrow, Deep
- Elliptical
- Wide, Shallow
- Subsurface
- Undercutting
- Horizontal
- Vertical
Buffer Storage

• 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)

• 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)

- 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)

Soak passivated SS coupon in buffer

Step 1: Remove SS coupon and measure passive layer after 14 days

Step 2: Rinse SS coupon with 0.4% acid detergent at 60C for 10mins

Put SS coupon back into buffer

Repeat step 1 and 2 after every 14 days
Controls

• 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:

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

**Negative control** - Stored in buffer while mixing at ambient temperature. – **FAILED** after 21 days
# Results at 60 °C

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

**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: 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
Results: pH 5 Acetate

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

Expose passive coupon to buffer and periodically test passive condition

<table>
<thead>
<tr>
<th>TIME (Hours)</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>PASS</td>
</tr>
<tr>
<td>48</td>
<td>PASS</td>
</tr>
<tr>
<td>72</td>
<td>PASS</td>
</tr>
<tr>
<td>96</td>
<td>FAIL</td>
</tr>
<tr>
<td>120</td>
<td>FAIL</td>
</tr>
<tr>
<td>192</td>
<td>FAIL</td>
</tr>
</tbody>
</table>
Results: pH 5 Acetate

- 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)

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>PASS</td>
</tr>
<tr>
<td>7</td>
<td>PASS</td>
</tr>
<tr>
<td>10</td>
<td>PASS</td>
</tr>
<tr>
<td>14</td>
<td>PASS</td>
</tr>
<tr>
<td>17</td>
<td>PASS</td>
</tr>
<tr>
<td>21</td>
<td>PASS</td>
</tr>
<tr>
<td>24</td>
<td>PASS</td>
</tr>
<tr>
<td>28</td>
<td>PASS</td>
</tr>
<tr>
<td>31</td>
<td>PASS</td>
</tr>
</tbody>
</table>
Caste study #2 : Initial Observation (1/3)
Caste study #2: PACE Testing (2/3)

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)

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

Water storage tanks

• 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.
Case Study # 4

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

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.

<table>
<thead>
<tr>
<th>CLEANER</th>
<th>CONC</th>
<th>TIME / TEMP</th>
<th>VISUAL OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulated alkaline detergent</td>
<td>4% v/v</td>
<td>1 hr / 80°C</td>
<td>Yellow</td>
</tr>
<tr>
<td>Phosphoric /citric acid based detergent</td>
<td>20% v/v</td>
<td>1 hr / 80°C</td>
<td>Reddish Yellow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 hr / 80°C</td>
<td>Metallic Silver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 hr / 80°C</td>
<td>Bright Metallic Silver</td>
</tr>
</tbody>
</table>
Case Study #5

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
Case Study #8
Case Study #8

Descaling 5% CIP200 @60DegC, 1 hour
Questions?