Rouge: the Intrinsic Phenomenon in 316L Stainless Steel – a Key Material for Biopharmaceutical Facilities

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Introduction

Because the biopharmaceutical industry has been a major driver of technological change in health care, producing unprecedented benefits by improving and saving human and animal lives around the world, materials and methods utilized in the construction of their manufacturing facilities play a major role in the production and delivery of safe and effective medicines and medical devices.

Traditionally, the preferred material for the manufacturing of tubing/piping, fittings, valves, vessels, and other components utilized in drug/product processing facilities throughout the world has been the austenitic, Type 316L (low carbon) stainless steel (UNS S31603); characteristically non-magnetic, not hardenable by heat treatment, and the most corrosion resistant among the martensitic, ferritic, and austenitic groups.

Two critical facts to keep in mind when discussing this particular alloy and the issue of rouge are:

1. Its predominant composition element is iron.
2. In nature, iron and rust (rouge) are “intrinsically” tied to each other. (See Rouge Composition and Classification).

Rouge – What Is It?

“Rouge” in high purity biopharmaceutical processing systems is a general term used to describe a variety of discolorations on the metal product contact surfaces.

While having always prompted a great deal of concern, much discussion, and proprietary analysis, the issue of rouge has yet to fully reveal itself to the life sciences industry. Its chemistry is understood, its formation is the subject of theories as diverse as there are colors to identify it; it is generally agreed under what conditions it is more likely to appear and progress, but what is not well known is, where specifically originates in diverse systems, what are the specific causes for its appearance, and to what extent may be deleterious to product contact surface finishes or their cleanability. More importantly, there is the need to clearly understand if the presence of rouge in any product contact surface may contaminate the flowing product in such a way to prove dangerous or even fatal to humans and/or animals, and whether there are specific governmental rules/mandates addressing this phenomenon and all its real or perceived associated repercussions. (See Rouge and Regulatory Stances).

Rouge in a process system operating under a single set of fluid service conditions is an anomaly, the cause of which can be attributed to multiple factors rather than resulting from one single originating source.

The propagation of rouge is generally believed to be dependent upon the following four major factors:

1. Material of Construction – variability of factors in the manufacturing of stainless steel components within a process system may be the source in some instances (e.g., sulfur content, alloy composition, traces of non-signature elements from scrap material, microstructure quality, type of thermomechanical processes, mill surface conditioning, etc.); however, it may not necessarily be the entire cause.
2. System Dynamics – how the system was constructed (e.g., welding and welding condi-
Rouge is not corrosion; it is the observed evidence of it. “Corrosion” is the chemical or electrochemical interaction between a metal and its environment, which results in undesirable changes in the properties of the metal.

As mentioned in the Introduction to this article, it is very important to remember that corrosion resistance is one of the main reasons why austenitic stainless steels are used in the life sciences systems. If corrosion may be a threat at all to any system, it is a matter of technical responsibility to choose the appropriate material at the design stages of that system.

Classification of corrosion is based on the appearance of the corroded metal and the specific cause for its presence, which can be either a chemical dissolution of the metal or an electrically (galvanic) driven process. Additionally, whether the corrosion is derived from an active oxide layer metal, such as iron, zinc, aluminum, and copper (anodic or least noble end in the galvanic series of metals and alloys), or a passive oxide layer metal, such as stainless steel, titanium, gold, and silver (cathodic or noble end in the galvanic series) should be considered.

Following are the most commonly recognized corrosion types:

- **General or Uniform Corrosion** – the relatively uniform reduction of thickness across the entire surface of a corroding material. It is expressed as “rate” measured in mm/year or mils/year. Uniform corrosion can occur from an overall breakdown of the passive layer (see passive layer and passivation); the “rate” of corrosion is influenced by material composition, fluid concentration, temperature, velocity, and stresses in the metal surfaces subjected to attack.

- **Galvanic Corrosion** – sometimes called dissimilar metal corrosion, galvanic corrosion is an electrically driven process by which the materials in contact with each oxidize or corrode. There are three conditions that must exist for galvanic corrosion to occur:
  - The presence of two electromechanically dissimilar metals
  - An electrically conductive path between the two metals
  - A conductive path for the metal ions to move from the more anodic metal to the more cathodic metal.

If any of these three conditions does not exist, galvanic corrosion will not occur.

- **Crevice Corrosion** – considered a form of galvanic corrosion, crevice corrosion is a localized corrosion of a metal surface at or immediately adjacent to an area that is shielded from full exposure to the environment because of close proximity between the metal and the surface of another material. To function as a corrosion site, a crevice has to be of sufficient width to permit entry of the corrodent, but sufficiently narrow to ensure the corrodent remains stagnant.

- **Pitting Corrosion** – is another form of galvanic corrosion and is an extremely localized type leading to the creation of small pits or holes at the surface of the metal. Pitting corrosion is the most common failure mode for austenitic stainless steels. For specific acceptance criteria of pits in the surface of stainless steel components utilized in the life sciences industry, refer to the ASME Bioprocessing Equipment (BPE) International Standard.

- **Stress-Corrosion Cracking** – a type of corrosion that occurs because of sudden failure of normally ductile metals subjected to a constant tensile stress in a corrosive environment, particularly at elevated temperatures. Particular austenitic stainless steels alloys crack in the presence of chlorides, which limit their usefulness for being in contact with solutions (including water) with greater than a few ppm content of chlorides at temperatures above 50°C (122°F).

- **Intergranular Corrosion** – a form of relatively rapid and localized corrosion associated with a defective microstructure known as carbide precipitation. When austenitic stainless steels have been exposed to high temperatures and allowed to cool at a relatively slow rate, such as occurs after welding, the chromium and carbon in the steel combine to form chromium carbide particles along the grain boundaries; the formation of these carbide particles depletes the surrounding metal of chromium and reduces its corrosion resistance, allowing preferential corrosion along the grain boundaries. Steel in this condition is referred to as “sensitized.”

The solution to corrosion problems can often be obtained through careful observation of corroded test specimens or failed equipment. For more information, refer to the ASME BPE International Standard, Nonmandatory Appendix F, “Corrosion Testing.”
**Rouge Composition and Classification**

The following discussion will look at the raw materials of rouge, which are iron and oxygen. Iron is the major element (approximately 60% to 63%) found in the composition of 316L stainless steel throughout the various applicable standards or specifications (tubing has been chosen as the example for this article), while oxygen is present in all aerated fluids, water, and steam. Not all rouge being equal in composition, a general identification/classification has been adopted as follows:

- Iron oxide or ferrous oxide (FeO) has been identified as being the most prevalent among other oxides and hydroxides found in the migratory rouge (Class I rouge).
- Iron oxide or ferric oxide (hematite) (Fe₂O₃) has been identified as the most prevalent agent in in-situ oxidation of non-passive surfaces (Class II rouge).
- Iron sesquioxide (Fe₃O₄), an extremely stable form of magnetite that initiates as a stable surface oxidation film and that is rarely particulate in nature, has been identified as black oxide produced by hot-oxidation (Class III rouge).

It must be understood that the existing rouge classification (Class I, Class II, and Class III) is not an industry regulatory standard, but rather a valuable practice adopted by the industry at large, and based on analytical observations and technical processes originally presented in October, 1999 at the Validation Council, a Division of the Institute for International Research, New York, NY.¹

**Rouge and the Key Role of Chromium**

To fully understand the interaction between 316L stainless steel and biopharmaceutical processes, it also is necessary to learn about the other two major elements in 316L stainless steel. They are:

- Chromium (approximately 16% to 20% depending on technical organization standard/specification) which gives the stainless steel its corrosion resistance and participates in the formation of a complex chromium oxide layer known as the “passive layer” – not “passive film” – on the surface of the alloy.
- Nickel (approximately 10% to 15% depending on technical organization standard/specification) stabilizes the austenitic structure so the alloy is non-magnetic and ductile over a wide range of temperatures.

The balance of elements that are part of the 316L stainless steel base material include molybdenum, manganese, silicon, phosphorus, carbon, sulfur, and in some related alloys, nitrogen and copper as seen in Table A.

**Passive Layer and Passivation**

The forming of the passive layer is a naturally occurring phenomenon when the surface of stainless steel is exposed to air, aerated water, or any oxidizing atmosphere. The mentioned natural process is known as “oxidation,” which is a common form of electrochemical reaction where one element yields an electron, while at the same time, another substance absorbs an electron; the complete process constitutes a “redox” reaction, which in this case, is the combining of oxygen with various elements and compounds in metals or alloys in interaction with their environment, such as exposure or use.

Once the layer has formed, the metal surface becomes “passivated” and the oxidation process will slow down to inconsequential limits. This layer consists primarily of chromium oxide, a mixture of iron oxides and iron hydroxides, and small quantities of nickel hydroxides; its precise thickness and constitution cannot, generally, be predicted or calculated. However, this chromium rich layer being the key defense or barrier against corrosion for the base metal, and considering its extreme thinness (normally measured in Angstroms) and relative fragility, is not impregnable; airborne impurities, high temperatures, lack of oxygen, surface conditions, and other direct contact materials can compromise its integrity causing the material to lose its ability to ward off corrosive processes.

<table>
<thead>
<tr>
<th>Element</th>
<th>ASTM A 270</th>
<th>DIN 17457</th>
<th>BS316S12</th>
<th>EN DIN 1.4404</th>
<th>EN DIN 1.4435</th>
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<td>0.03 max.</td>
<td>0.03 max.</td>
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<tr>
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<td>16.5 – 18.0</td>
<td>16.5 – 18.5</td>
<td>16.5 – 18.5</td>
<td>17.0 – 18.0</td>
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<tr>
<td>Mn</td>
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<td>2.0 max</td>
<td>0.50 – 2.0 max.</td>
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<td>2.0 max</td>
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<tr>
<td>Mo</td>
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<td>2.5 – 3.0</td>
<td>2.25 – 3.00</td>
<td>2.0 – 2.5</td>
<td>2.5 – 3.0</td>
</tr>
<tr>
<td>Ni</td>
<td>10.0 – 14.0</td>
<td>12.5 – 15.0</td>
<td>11.0 – 14.0</td>
<td>10.0 – 13.0</td>
<td>12.5 – 15.0</td>
</tr>
<tr>
<td>P</td>
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<td>0.04 max.</td>
<td>0.045 max.</td>
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</tr>
<tr>
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<td>0.75 max.</td>
<td>0.20 – 1.0 max.</td>
<td>1.0 max.</td>
<td>1.0 max.</td>
</tr>
<tr>
<td>S</td>
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<td>0.03 max.</td>
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<td>0.015 max.</td>
<td>0.015 max.</td>
</tr>
<tr>
<td>N</td>
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<td>0.11 max.</td>
<td>0.11 max.</td>
<td>0.11 max.</td>
<td>0.11 max.</td>
</tr>
<tr>
<td>Fe</td>
<td>Balance</td>
<td>Balance</td>
<td>Balance</td>
<td>Balance</td>
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</tr>
</tbody>
</table>

Table A. 316L Stainless Steel tubing chemical composition – comparison.
Rouge in Stainless Steel

In a process system, the passive layer is the product of the interaction between the stainless steel basic material and the corresponding flowing solutions. A well passivated system will show rouge after a time, as the passive layer characteristics will change to the appropriate level resulting from the equilibrium between the flowing product and the corresponding product contact surfaces.

The passive layer may be artificially enriched by a treatment known as "passivation" that removes exogenous iron or iron compounds from the surface of stainless steel by means of a chemical dissolution, most typically, an acid solution that will remove the surface contamination and potentially augment the passive layer, but will not affect the base metal itself. Since the top layer of iron is removed, passivation diminishes surface discoloration as shown in Figure 1. The passivation treatments are generally applied after completion of construction/fabrication of new systems or the installation/replacement of new components (tubing/piping, fittings, valves, vessels, etc.) within an existing system; these procedures ensure that all product contact surfaces that may have been disturbed during the course of construction/change functions, are appropriately protected. Some of the most commonly utilized passivation treatments, applied for limited time periods, include the use of specific percentages of nitric acid; phosphoric acid; phosphoric acid blends; citric acid; and chelant systems. Electropolishing processes also provide passivating results. For more information, refer to the ASME BPE International Standard, Nonmandatory Appendix E, “Passivation Procedure Qualification.”

The passive layer is mainly characterized by the chromium/iron ratio in the passive layer, which is often given as a measure of corrosion resistance; in the biopharmaceutical industry, the Cr/Fe acceptance criteria regardless of test method should be 1.0 or greater.

Rouge – Is It Acceptable, Unacceptable?

Rouge is the “intrinsic” phenomenon in 316L stainless steel. When visually detected, rouge may be considered unsightly, and because the alloy's qualification of being “stainless,” there is the logical expectation for it not to be there at all. Consequently, it is somewhat understandable the frequent reactive, rather than proactive approach of addressing the issue of its presence in any part of a processing system, by the application of treatments that are supposed to eliminate it; unfortunately, the results are always only temporary in nature. The inescapable reality is, that considering the stainless steel composition, which includes mostly iron, the presence of rouge cannot be completely avoided in this extremely popular material; rouge will always be apparent on any product contact surface under processing conditions, and more so when operating at high temperatures.

If the presence of rouge is completely unacceptable in any process product contact surface, the alloy should be replaced by one that contains no iron or very low amounts of it.

Rouge and the Industry Opinion – A Survey

In May 2009, the ISPE Critical Utilities (CU) Community of Practice (COP) conducted a 20 question survey that revealed that although the biopharmaceutical industry has well established practices and procedures to address facilities engineering design, construction, operation, and maintenance, there is still a lot of applied scientific knowledge and disciplines interaction left to be dealt with to fully understand the behavior and utilization of materials that are a key to the functional success of these facilities. Some of the most interesting responses/opinions provided by the participating 200 biopharmaceutical professionals (engineering, Q&A, maintenance, operations) included:

- **Which rouge classification requires priority attention?** The response was somewhat equally divided into, “all rouge is unacceptable regardless of Class” (39.4%), and “rouge regardless of its classification does not require priority attention” (37.1%).
- **For the most part, rouge has not caused product failure, agency citations, or equipment failures;** the response was that rouge had not caused either a product failure, an agency citation, or equipment failures (74.6%).
- **Can rouge management be improved?** The responses were quite revealing and included, “rouge management can be improved by a better understanding of the phenomenon” (59.6%), and “by standardized industry practices” (41.4%); some additional overlapping opinions included, “with online detection instrumentation” (7.6%), or “all of the above” (30.3%).
- **Rouge management…is a growing concern and strategies are being generated” (31.2%), “we are aware of issues, but with no plans to change practices” (30.2%), “we are waiting for guidance to be published” (25.7%), “we are aggressively and actively managing it” (24.8%), and “rouge management is not a concern” (6.9%).

Based on these survey results, some clear messages emerge: most facility engineering personnel, including those that find the presence of rouge unacceptable in their operating systems, have not had product or equipment failures, or more critically, any regulatory agency citation; in contrast, there is the expressed opinion that better understanding of system management is strongly needed, together with industry stan-
dardization of methods and means, including detection and analytical problem solving rather than random approaches for elimination of a phenomenon that cannot be separated from the nature of the material widely utilized in the construction of drug products/devices manufacturing systems.

**Rouge and Regulatory Stances**

Although the presence of rouge on any biopharmaceutical manufacturing system and its possible impact on surface finishes/cleanability in high purity water, pure/clean steam and other process systems fabricated with 316L stainless steel, has been known to be questioned by regulators during numerous facility inspections, there are no existing governmental guidelines or regulations dealing with its existence or the need or frequency to eliminate it when detected. At the writing of this article, the known stances of existing regulatory agencies are:

- The US Food and Drug Administration (FDA) has no written position specifically addressing rouge, its existence, prevention, or remediation methods. Their criterion is to meet established standards of quality for those systems, 21CFR, Chapter I, Part 211, Subpart D, Sections 211.65(a) equipment construction, and 211.67(a) equipment cleaning and maintenance.
- The United States Pharmacopeia (USP) covers the quality of pharmaceutical waters that are used, not the systems that deliver them; rouge is a matter that relates to material selection for those systems.
- Owner/user should decide if the water quality obtained from a system that shows rouge is still compliant with the USP as well as with internal requirements for the process.
- The European Pharmacopoeia (EP) monographs do not address rouge or give any guidance in the matter; however, the European Medicines Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP), offers a document that can be applied as a guide for risk assessment on heavy metals in product streams, the “Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents” – February 2008.

**Systems Inspections and Repercussions**

Routine internal system inspections performed by owner/user or other related personnel trained in the assessment of rouge, frequently may classify its presence, albeit only in those locations where visual inspection is possible, by color and adherence to the surface, by physical traits such as pitting, or by analytical laboratory testing.

Regulatory facility inspections rely in part on owner/user generated documentation that may, in some instances, address rouge identification, quantity, and remediation/removal – a.k.a. “derouging” – treatments applied to whole systems or specific system components such as vessels, etc. Regulatory bodies, as previously stated do not have specific stances regarding rouge, but their representatives may question the need, purpose, or practicality of any procedure that owner/user may have instituted and formalized in those inspection documents. As a result of the previous statements, a rather significant question arises. Is it possible during a regulatory facility inspection to satisfactorily explain to officials why an issue where they do not offer any related specific set of rules or mandates, is being addressed with complex, non standardized, risky remediation treatments, particularly when there may not be any known negative effects to the quality, identity, safety, or purity of the flowing process product?

Remediation/removal treatments do not provide a permanent solution to the presence of rouge, and they may be potentially detrimental to exposed base metal surfaces when applied with the most aggressive chemicals and the presence of variations in rouge deposits, thus increasing the chances of surface etching and/or erosion. Chemical removal of rouge requires for a system to have the passive layer restored or enhanced with an additional corresponding passivation treatment, commonly referred to as “re-passivation” that may involve increased systems downtime and mounting economic concerns. Some critical points to remember: identification, prevention, and remediation treatments of rouge are subjective and not standardized at all.

**Rouge Detection and Monitoring**

There are various means to detect the existence and/or presence of rouge in a process system; they include highly limited visual examination of product contact surfaces, instrumentation measuring devices for various physical conditions, and analytical methods of process fluid and product contact surfaces. The presence of rouge in a process system cannot be detected using methods involving temperature, flow, pressure, conductivity, or Total Organic Carbon (TOC) measurements.

Let us now look at each one of those detection means:

- **Visual.** It is well known that there are no systems or techniques that would allow complete visual examination of all product contact surfaces in any process system. Since rouge is not corrosion, but the observed evidence of it, we are left facing an almost impossible technical conundrum, not being able to offer proof positive of any active corrosion site that may be the originator of the detected rouge, except where visual inspection may be possible (e.g., interior of vessels, pump impellers, diaphragm valves, etc.) - Figures 2 and 3. The fact of not being able to positively identify active corrosion sites becomes the common denominator for all existing detection methods.
- **Instrumentation.** There are various commercially available instruments that monitor rouge presence and rates. They use diverse equipment to either, visually measure the reflection rate of the stainless steel surface and provide alarms when the reflection changes; measure in real time the rouge rate and accumulation (metal loss) over time or by measuring very low corrosion rates in the high resistivity of ultrapure water.
- **Analytical.** The focus on detection and monitoring, however, must be directed to analytical methods which provide specific information that will help support the effort to estimate risk of negative events or potential failures for
a particular process/product; the analysis and estimation of results requires knowledge and experience in the field of material science and should be performed only by a trained expert. Analytical detection techniques establish the barrier properties of the passive layer and identify the presence of rouging through:

- **Process fluid analysis (non-invasive techniques)** which provides identification of mobile constituents [normally, concentration of heavy metals (Fe, Cr, Ni, Mo, etc.) and other possible inorganic particulates] within a subject system and represents the current quality status of the media, and the result of rouging. Fluid analyses require the periodic collection of representative samples from various major locations throughout a given system.

- **Solid product contact surface analysis (invasive techniques)** which provides information on the nature, microstructure, and composition of surface layers and may represent the future status of the media, and the possible threat of rouging to the media quality. Surface analyses require the periodic removal of a representative fixed surface medium (such as a sacrificial spool or test coupon) for visual and destructive analysis of the surface.

The methods described above may help detect and analyze rouge; however, they only provide information about the rouge itself, and cannot help to make the decision of whether any remediation treatment may be required. For example, an electron microscope picture of rouge may show a very detailed surface with rouge on it, but does not answer questions about product quality or whether rouge could be deleterious to the flowing product and by association, if it may be a threat to human or animal life. Surface analysis may provide a better understanding of what is happening, but the liquid analysis provides more valuable information about product quality.

Owner/user should establish a unique baseline level of acceptance for particulates and metal oxides, based on a risk assessment analyses that should include:

- Potential damage to the individual process/product
- Consideration of remediation procedures based on an observed and quantified escalating level of particulates and surface accumulation of those oxides
- The event (e.g., particles of rouge may end up in the final product)
- The effect of failure (e.g., negative effects of rouge particles on patients are to be expected).

Risk Control should describe actions to be taken and/or risk reduction strategies (e.g., calculate the amount of rouge from process media that can contaminate the final product and compare with limits set for heavy metals such as Fe, Cr, Ni, Mo, etc.).

**Rouge – Is Removal a Solution?**

Rouge presence may be slight and uniformly distributed or more concentrated or localized; in both cases its appearance is normally judged to be not esthetically pleasing on any product contact surface that it is supposed to be stain free (clean/shiny) as the name of this family of alloys indicate. As stated previously in this article, there is a common, visually influenced, reactive approach that ends-up utilizing treatments that are supposed to eliminate rouge although only temporarily.

A few questions are commonly asked when referring to the previous situation. The most notable, is it necessary to eliminate rouge every time it shows up in a process system? The answer is a clear and concise “no.” The common belief is that rouge may create long term damage to the stainless steel that could result in catastrophic system failures if not remediated; the author of this article does not have supporting or contradicting evidence regarding this belief, but after spending more than 30 years of her professional life dealing with technical issues regarding biopharmaceutical facilities, she has never heard about or witnessed any such drastic failure.

With one major question answered, more questions of no lesser importance require appropriate thought and practical responses; some of these questions and answers may have already been discussed throughout this article, and they may include:
• What if it has been established that the presence of rouge is absolutely unacceptable on any stainless steel product contact surface? In this case, and without hesitation, the alloy should be replaced by one that contains no iron or very, very low amounts of it.

• Is rouge actual corrosion? No, rouge is not corrosion, but rather an observed evidence of its existence.

• Can rouge be removed from product contact surfaces? Yes. Although remediation methods do not provide a permanent solution to the presence of rouge, there are multiple available methods to remove specific rouge (Classes I, II, and III) from the process contact surface of the various biopharmaceutical process systems; they are designed to accomplish their mission by removing iron oxide and other surface constituents of rouge.

• Does rouge remediation treat the cause or source of rouge? No, rouge remediation treatments normally deal with the symptoms and not the cause or source, and should only be considered as part of a well designed monitoring system that should include individual process fluid and product contact surface analysis.

• Can rouge indicate the type of corrosion that may have originated it, its amount, or location of origin? No. In most cases, rouge does neither provide a clue to the type of corrosion that may have originated it, nor its amount or point of origin.

• Do removal processes guarantee that rouge will not re-occur? The answer is a resounding no. There is no chemical or mechanical procedure that can guarantee that rouge after its removal from a product contact surface, will not reappear.

• Can the presence of rouge be minimized? Yes, rouge presence can be minimized, but only with one critical caveat, it will sooner or later reappear if exposed to similar pre-existing conditions.

• Are there any specific stainless steel product contact surfaces where rouge may not appear? No, rouge will always appear on any stainless steel product contact surface under processing conditions, particularly, when operating at high temperatures.

• Are there industry or governmental standards/regulations addressing rouge removal? No, rouge remediation/removal treatments are subjective and not regulated or standardized at all.

Application of remediation techniques must be the result of a rigorous Quality Assurance (QA) procedure that will provide indication of significant impact on the quality or safety of the flowing product. Once rouge has been found, it is difficult and expensive to remove it; its progress may be temporarily slowed or perceptively eliminated by the application of “derouging” processes, but because the major element found in 316L stainless steel, iron, it will always reappear.

**Rouge Management, the Rational Solution**

The preeminent concern of the biopharmaceutical industry regarding the rational solution to rouge, should be to adopt sensible management processes of this unavoidable phenomenon, rather than to continue with the indiscriminate application of remediation treatments that may utilize subjective and sometimes confusing procedures with less than uniform and reassuring results. Corrosion (cause) is not a good thing, and as we have already seen, rouge (result) is the observed evidence of it; however, the pinpoint localization of active corrosion sites in any system becomes a rather futile enterprise because of the inherent difficulty of visually examining every single product contact surface in a system. Remediation should not be considered a forbidden treatment, but rather a sensibly applied solution, when and if, localized corrosion sites are positively identified in a process system. Find the cause, and the result would become a lot easier to deal with.

There is an increasing need for the global biopharmaceutical industry to respond with analytical approaches to the challenging subject of rouge management. To help accomplish this end, ISPE has just published a valuable source of positive information and technical suggestions (not regulations, standards, or regulatory guideline documents) contained in Chapter 10 — *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 4 – Water and Steam Systems, Second Edition, December 2011*. Some of the information provided includes:

- Analytical methods for identification of mobile constituents of rouge and surface layers composition, including type of tests, tests descriptions, and pros/cons test criteria.
- An example for a risk-based approach to rouge and its remediation measures.
- Risk analysis of possible events, and effects of failure and risk control actions for risk reduction strategies.
- Rouge remediation methodology including examples of available chemicals to conduct remediation treatment on the different rouge Classes.

Additionally, and thanks to the solid cooperation and coordination of volunteers closely associated with both ISPE and ASME, additional and/or complementary technical information has been provided; this information is contained in the 2009 Revision of the *ASME BPE International Standard, Nonmandatory Appendices D, E, and F*.

**Rouge Remediation – When Needed**

Rouge remediation may in some instances be necessary, but only after careful weighing of acceptable options that may include:

- Upon discovery of rouge on any process system, proper analysis and categorization should take place, and based on evidence of potential active corrosion sites where base metal may have been compromised, then perhaps consider the application of localized remediation/removal treatments, despite knowing that rouge will soon reappear if the product contact surface is exposed to similar pre-existing conditions.

- With the understanding that usually, different chemical solutions as utilized in remediation treatments, may react

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quite differently in contact with potentially diverse factors, such as the various classes of rouge that may be encountered in any given system; the status of product contact surfaces throughout a system; the different composition/quality of materials that may have been used for each component; the length of time those various system components may have been in service, etc., the application of remediation treatments to large or small process systems, should always first consider conducting a thorough risk-based analysis of both, flowing products and corresponding product contact surfaces.

- Rouge should be preferably monitored and then if proven to have a negative influence on the product quality, consider using an alternate metallic or polymeric material.

- As the last and hopefully the most acceptable alternative, consider “learn to live with it safely” by establishing a program of internal monitoring and analysis of individual critical systems, and only when deviating from scientifically and uniquely proprietarily established baselines, both in process fluid analysis of mobile constituents and/or solid surface analysis (see Rouge Detection), consider the application of a pertinent remediation treatment to manage its presence. For more information on methods to remediate the presence of rouge in a system, refer to the ASME BPE International Standard, Nonmandatory Appendix D, “Rouge and Stainless Steel.”

Conclusion

Concern should always be focused on whether the presence of rouge may be detrimental to the pharmaceutical water systems or the drug products to such extent that it may pose dangerous or even fatal results in humans and animals, rather than the repercussions it may present on capital equipment protection. Health and life of patients must be preeminent in all considerations that apply to the fabrication, erection, and maintenance of facilities dedicated to the biopharmaceutical industry. Rouge may not be esthetically pleasing, but it is a reality resulting from the utilization of a material that not only has iron as its main and “intrinsic” element, but that also is never chemically identical in all its forms, and it is exposed to a very complex set of processes and chemical, mechanical, and electromechanical influences.

It is suggested, that in addition to improved facilities planning, engineering design, and utilization of materials, a potential avenue for resolution of concerns presented by rouge in the life sciences industry facilities, should be the close and permanent association of owner/user’s QA personnel in their Research & Development (R&D) divisions, and the QA personnel in their engineering production and facility maintenance groups. The first group would provide the scientific data regarding possible deleterious effects of rouge or any other oxide or metallic trace material (iron, chromium, nickel, molybdenum, etc.) on the safety of the flowing products; the second group should concentrate in the selection of appropriate construction materials and methods to ensure that parameters for the safe production of drug products is maintained at all times.

We must endeavor to improve our understanding of the rouge phenomenon and establish standards and practices that would simplify the various approaches and perceived solutions for addressing the rather controversial presence of rouge in process/utilities systems utilized in the biopharmaceutical industry.

References


About the Author

Michelle M. Gonzalez, P.E. retired in 2007 as an engineering director with Amgen Inc. in Thousand Oaks, California. After an extensive career in industry leadership activities dealing with facilities engineering, process systems design, and management of construction projects with firms such as Shell Oil, Kaiser Engineers, Bechtel Corporation, and Fluor Daniel, she is now involved with her own research projects and biopharmaceutical industry technical consulting. Gonzalez holds an MS in architecture from the Pontificia Universidad Javeriana in Bogotá, Colombia. She is a member of AIChe, and ASME’s Bioprocessing Equipment (BPE) Standard, where she has served as Chair of the Surface Finish Subcommittee, and voting member of the Executive, Main, Dimensions and Tolerances, and Certification Subcommittees. For the past four years, she has been a member of INTERPHEX’s Advisory Board. An active member of ISPE for the last 22 years, she does presently serve as a member of the University Task Team Committee, and the Membership Development Program – Recruitment and Retention Group; Chapter Leader (10 and 15) for the Second Edition of the Water and Steam Baseline® Guide (2011), participating member in the preparation of the ISPE Good Practice Guide for Process Gases (2011), ISPE Good Practice Guide for Commissioning and Qualification of Pharmaceutical Water and Steam Systems (2007), and the Biopharmaceutical Manufacturing Facilities Baseline® Guide (2004). Additionally, she has been a regular technical speaker and contributing writer to Pharmaceutical Engineering and other technical journals, President of the Greater Los Angeles Chapter (2007 to 2008), an active member of the Critical Utilities (CU) Community of Practice (COP) Steering Committee, and the author and editor of ISPE’s Glossary of Applied Terminology for the Pharmaceutical Industry. She may be contacted by email: atmg71@verizon.net.

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