TESTS ON ROUGING AND EXPERIENCES DEALING WITH ROUGING IN PHARMACEUTICAL PRODUCTION

Thomas Blitz, Ernst Felber, Robert Haas, Birgit Lorsbach, Andreas Marjoram, Roland Merkofer, Tobias Mueller, Nathalie Schuleit, Marc Vernier and Thomas Wellauer

The present technical article (in 3 parts) discusses the current body of knowledge on the subject of rouging. It is based on insights from tests and operating experiences of companies that manufacture pharmaceutical medicinal products.

By means of a generic risk-based approach and a test setup derived from this, it is shown that the danger resulting from rouging for products and patients may be regarded as slight. As regards products, however, a conclusive appraisal may be obtained only by means of specific risk analyses. The risks resulting from derouging actions must also be considered in the overall assessment.

Part 1 of this article described the background on rouging, rouging formation, derouging and a risk overview. Part 2 of this article described tests and practical experiences in rouging formation and the influence of rouge coatings on cleaning efficiency.

Part 3 of this article describes test and practical experiences using different cleaning methods, discusses the influence of different derouging chemicals on stainless steel surfaces and gives a summary of the results and assessment (Part 1 to 3).

Tests and Practical Experiences

Cleaning Methods

To permit appraisal of the possible effects of an acid-based derouging solution on the surface of process equipment, a test tank (material 1.4435, mechanically polished; R_a ≤ 0.8 µm), which has been exposed to rouge-forming conditions (see part 2 section 2.3), was cleaned by means of acid derouging (mixture of sulfuric, phosphoric and citric acids; see section 2.2, solution C). The following results were found:

▶ The rouge coatings present were completely removed from the tank surface (see Figure 1c).

▶ After derouging, the tank surface had a matt appearance (see Figure 1c).

▶ The measurement of the arithmetic average height Ra by means of profilometry did not reveal any increase in roughness compared with the initial condition.

▶ Compared with the initial condition, faster redevelopment of rouging was observed (see Figure 1d).

After the acid derouging, the tank was exposed once again to rouging-promoting conditions as part of the test procedure, then at the end of the test was subjected to pH-neutral derouging (mixture of sodium dithionite, phosphonic acid and potassium hydroxide; see section 2.2, solution D). The following results were found in this case:

▶ The rouge coatings present were completely removed from the tank surface (see Figure 1f).

▶ The time needed for pH-neutral derouging was very much shorter than the time required for acid derouging.

▶ The tank surface did not exhibit any visible differences compared with the surface condition after acid derouging (see Figure 1f).

▶ The dark discolorations that the hot sodium hydroxide solution caused on the tank surface in the zone of the liquid level were clearly visible after derouging (see Figure 1f).

The comparison of the two derouging methods can be summarized as follows:

▶ Significantly shorter time consumption for the pH-neutral derouging variant

▶ No change of the tank surface by the pH-neutral derouging solution

▶ High selectivity of the pH-neutral derouging solution toward rouge coatings (see also section on determination of specific surface loads due to rouging)

The surface conditions of the test tank before and after the respective derouging method used are illustrated in Figure 1.

The derouging solutions used in derouging were quantitatively analyzed as regards their metal concentration in order to determine specific surface loads due to rouging, i.e. the amount of corrosion products (rouge) formed per unit time and surface area under the CIP and SIP conditions employed here.

The specific surface loads due to rouging permit an estimate of which amounts of rouge will be formed under the given conditions within a specified time on a defined surface.

The rouge formed on the tank surface (material 1.4435) was completely removed and transferred into solution by both derouging methods. It was possible to determine specific surface loads due to rouging on the basis of the metal concentrations of the derouging solutions used as well as the known tank surface area and the times of exposure to cleaning and sanitizing operations.

Figure 1
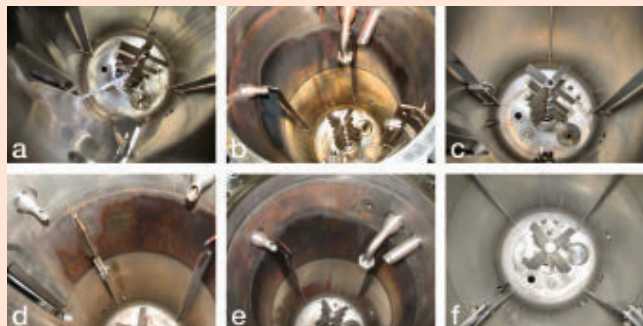
(a) Test tank in the initial condition, (b) test tank before the acid derouging after 545 combined cleaning/sanitizing cycles, (c) test tank after the acid derouging; the slightly orange color can be attributed to the illumination of the tank, (d) derouged test tank after 48 combined cleaning/sanitizing cycles, (e) test tank before the pH-neutral derouging after 545 combined cleaning/sanitizing cycles and (f) test tank after the pH-neutral derouging

The calculated specific surface loads were $5.01*10^{-3}$ kg/(a*m²) (kilograms per year * square meter) for the acid derouging and $3.56*10^{-4}$ kg/(a*m²) for the pH-neutral derouging. The specific surface load determined for acid derouging therefore represents a worst-case value for any calculations of rouge ingress that may be carried out.

The value for the pH-neutral derouging is lower approximately by a factor of ten, thus confirming the higher selectivity (iron selectivity) of this derouging method. Because of the etching effect of acid derouging solutions, material is removed not only from the rouge layer but also from the base metal itself. The metal concentrations listed in Table A illustrate this circumstance.

To check the resistance of materials 1.4404, 1.4435 and 1.4539 to an acid derouging solution, test plates of these materials were mounted in the test tank while it was undergoing acid derouging and were then investigated as regards their weight change.

The resistance of the test plates to an acid derouging solution based on a mixture of sulfuric, phosphoric and citric acids (see solution C) is illustrated in Figure 2 on the basis of the measured weight losses. The material surface of material 1.4404 underwent the greatest change toward a matt surface and also exhibited the most pronounced weight loss due to the derouging solution. Material 1.4435 also exhibited clearly discernible surface changes, right up to a likewise matt appearance, and also suffered a significant weight, albeit to a smaller extent than material 1.4404. In contrast, material 1.4539 did not exhibit any significant weight loss or visually perceptible changes of the material surface (surface condition illustrated in Figure 7 in part 2).

The surface changes as well as the weight losses of material samples 1.4404 and 1.4435 can be attributed with high certainty to etching attack caused by the acid derouging chemicals.

Above and beyond the derouging of the test tank with acid and pH-neutral derouging solutions, a test was carried out to improve the understanding of the chemical and physical mechanisms during cleaning with phosphoric acid or a combination of phosphoric acid and sodium hydroxide solution. A particular goal was to investigate acid CIP in order to appraise its suitability for removing rouge coatings. Furthermore, it was planned to investigate the extent to which phosphates are formed on the rouged material surface due to such a treatment.

Two rouged test places of material 1.4435 from test 2.3 in part 2, "Rouge Formation due to Alternating stress of materials by cleaning and sanitizing Processes", were used as starting material in this test. In this test, one test plate was subjected to combined cleaning by means of phosphoric acid and sodium hydroxide solution and a further test plate was used as the rouged reference sample. Furthermore, an intact (non-rouged) test plate was used as an additional reference. This permitted a direct comparison between a rouged non-cleaned, a rouged cleaned and an intact non-cleaned material surface.

The cleaning with phosphoric acid comprises the following treatment steps:

Table A	Metal concentrations of spent and fresh acid and pH-neutral derouging solutions			
Element	Metal Concentrations (mg/L)			
	Acid-based, spent	Acid-based, reference sample	pH-neutral, spent	pH-neutral, reference sample
Chromium	364.06	0.54	1.28	0.06
Iron	1535.90	2.68	12.90	0.60
Molybdenum	46.65	1.08	0.09	0.07
Nickel	250.29	0.21	2.50	0.09
Manganese	27.30	0.07	0.13	0.06
Total	2224.20	4.58	16.90	0.88

Figure 2 | Weight variation of the test plates exposed to CIP/SIP and additionally subjected to acid derouging after 325 CIP/SIP cycles
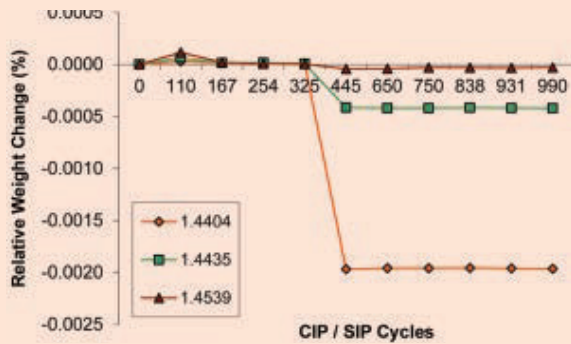
Figure 3
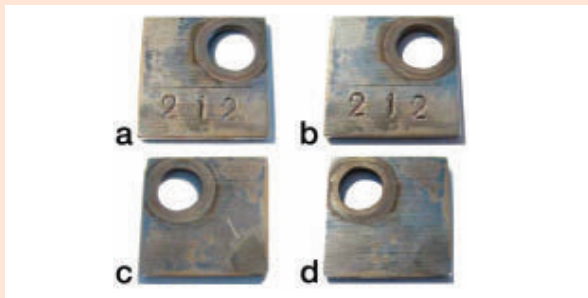
(a) Front side of the material sample (1.4435) before cleaning, (b) front side of the material sample (1.4435) after cleaning, (c) back side of the material sample (1.4435) before cleaning and (d) back side of the material sample (1.4435) after cleaning

1. Rinsing for 4 hours with 10% phosphoric acid at 60 ± 1°C

2. Intermediate rinsing with PW at room temperature

3. Rinsing for 15 minutes with 1% sodium hydroxide solution at 80 ± 1°C

4. Final rinsing with PW at room temperature

After the cleaning with phosphoric acid, only small, visually perceptible surface changes could be observed on the rouged test plates in comparison with the non-cleaned test plates (see Table B and Figure 3).

From the comparison of the two ESCA profiles of the cleaned and non-cleaned test plates (see Figures 4a and 4b), it was particularly obvious that the iron oxide content in the cleaned test plate is much smaller than that of the non-cleaned test plate in the near-surface layers (down to approximately 20 nm). A significant difference in the content of metallic iron can also be observed

down to a depth of 90 nm.

The chromium oxide peak of the cleaned test plate is much broader than that of the non-cleaned test plate. In both test plates, the oxygen content is bound mainly in the form of chromium oxides (main content at 0 to 40 nm). From a depth of approximately 90 nm on, the elements of both samples again approach a distribution corresponding to the alloy composition.

Phosphating of the cleaned test plate was discernible only on the basis of the general ESCA spectrum. Thus as much as 1% phosphate (P2p) is bound at the surface of the cleaned test plate, but even at small sputter depth it was no longer detectable (Figure 4d).

Furthermore, the comparison of the ESCA profile of the sample after cleaning with phosphoric acid with that of the intact, non-rouged reference sample (see Figure 4c) made it obvious that the initial condition could not be restored by cleaning with phosphoric acid.

Judging by experience, acid CIP with phosphoric acid may have a positive effect on the visual appearance of stainless-steel surfaces with light rouge coatings. On the other hand, this method is hardly suitable for removal of heavier rouge layers. Nevertheless, neither can any detrimental effect be observed by such a treatment. In particular, it is noteworthy here that only slight traces of phosphorus bound to the material surface are present (see Figure 4d).

Influence of Different Derouging Chemicals on Stainless Steel Surfaces

In the following studies, the influences of different derouging solutions on the surface of steel alloy 1.4435 are investigated. It is often asserted that derouging of pharmaceutical systems does not cause any change of the electropolished surface condition.

Two independent approaches were followed to check this thesis. The first approach relates to investigation of the influence of different derouging solutions on non-rouged surfaces, while the second approach considers the influence of different derouging solutions on already rouged surfaces.

Part 1: Non-rouged Test Plates
The test plates are made from stainless steel 1.4435, ground and electropolished. No rouge is present on the test pates.

Positions to be used for repeated investigation by means of the scanning electron microscope and the optical profilometer (FRT Microprof) were defined for all test plates. The investigations were carried out respectively at the beginning of the test and after completion of 15 derouging cycles with the different derouging solutions. No repassivation is carried out between two cycles.

Table C lists the derouging solutions used. These correspond to the various state-of-the-art derouging solutions currently used in the pharmaceutical industry. One derouging cycle includes the steps listed below:

Table B	Change of weight of material sample 212 treated with phosphoric acid and sodium hydroxide solution
Weight before cleaning (mg)	5349.15
Weight after cleaning (mg)	5348.87
Weight decrease (mg)	0.28
Relative weight decrease (%)	0.000052

Table D	Composition and concentration of the investigated solutions
Solution ingredients	
20% Nitric acid (HNO_3) + 5% hydrofluoric acid (HF)	
3% Citric acid	
5% Phosphoric acid (H_3PO_4)	
5% Nitric acid (HNO_3)	

1. Cleaning (degreasing) with isopropyl alcohol/water (70/30)
2. Complete immersion in the derouging solution at the temperature indicated in Table C for six hours
3. Rinsing with demineralized water
4. Drying in air

The corrosion rate was calculated after 15 cycles (Figure 5). For all derouging solutions it is smaller than 0.004 mm/a, except for solution E, which has a corrosion rate of 0.3 mm/a. Neutral solution D exhibits the smallest corrosion rate, of slightly over 0.001 mm/a.

The small corrosion rate of neutral solution D compared with the acid derouging solutions is therefore consistent with the results of the derouging tests on a test tank (see part 2, section on "Influence of Rouge Coatings on Cleaning Efficiency"). This means that the neutral solution has higher selectivity and derouging efficiency while at the same time causing less material removal.

The metal surfaces before and after the 15 derouging cycles are illustrated in Figure 6 to Figure 10. For the most part, the electropolished surface was changed only slightly by the treatment: defects and grain boundaries are still clearly discernible. In the case of solution B, which is based on citric acid, oxalic acid and sulfuric acid, the grain boundaries are attacked but no further attack of the grains themselves is observed in the investigated zone.

In the case of solution E, which is based on hydrofluoric acid, the grains are attacked so intensively that it was no longer possible to relocate the same site after the 15 derouging cycles. Locally

grains are completely removed (Figure 10b). The surface exhibits matting.

After the treatment with solutions B and D, isolated stains are present on the metal surfaces.

A significant change of surface roughness as represented by the Ra value could not be observed after the treatment, even in the case of the sample most severely attacked by solution E (Figure 11).

With the exception of solution E, the electropolished surface was not significantly influenced by the other investigated derouging solutions.

Part 2: Rouged Steel Samples
The cleaning ability, the influence on surface roughness and the corrosion rate or rate of material removal at various temperatures is investigated by means of various acid solutions. Pipe samples of stainless steel 1.4404 are used as the material. The pipe samples are taken from a sterilization process using pure steam. Because of the regular contact with this medium, they exhibit light rouging. The acids or acid mixtures that were used are shown in Table D.

The pipeline to be investigated was cut apart longitudinally and samples of approximately 2.5 × 5.5 cm were prepared from the half shells. The exposure time, the temperature and the calculated corrosion rate are listed in Table E. The derouging efficiency (cleaning ability) was estimated from an optical comparison with the untreated sample.

An attempt was made to determine the cleaning ability by means of Raman spectroscopy. Because of the inhomogeneous signals and the rouging distribution on the surfaces, it was not possible to evaluate the obtained spectra quantitatively. The cleaning ability was therefore estimated only visually.

At room temperature, the rouge coating could be completely removed only by 30 minutes of "etching" (20% HNO_3 + 5% HF). The corrosion rate under these conditions was 13.4 mm/a.

Table C	Ingredients, pH values and temperatures of the investigated derouging solutions		
	Solution Ingredients	**pH Values**	**Temperature**
A	Phosphoric acid; citric acid	pH < 1	approx. 70°C
B	Citric acid; oxalic acid, sulfuric acid	pH < 1	approx. 70°C
C	Sulfuric acid; phosphoric acid; citric acid	pH < 1	approx. 70°C
D	Sodium dithionite, phosphoric acid and potassium hydroxide	pH = 7	approx. 70°C
E	Sulfuric acid, hydrofluoric acid, hydrochloric acid	pH < 1	approx. 30°C

Passivation at a temperature of 60°C with 5% nitric acid for an exposure time of 24 hours also led to almost complete removal of the rouge coating. In this case also, even shorter exposure times would be sufficient. The corrosion rate was lower than 0.1 mm/a.

Even three hours of treatment with 5% phosphoric acid at a temperature of 80°C was able to remove the rouge coating almost completely, although the corrosion rate in this case was approximately 0.1 mm/a. At room temperature, on the other hand, 5% phosphoric acid was not sufficient for removal of the rouge coating.

A treatment with 3% citric acid during an exposure time of 3 hours at 80°C led to only a slight reduction of the rouge coating. In contrast, the treatment with an exposure time of 6 hours at room temperature had no effect as regards removal of rouge coatings.

A significant change of surface roughness could not be observed after the various acid treatments. For all samples the Ra values ranged from 0.2 to 0.6 µm (untreated sample 0.2 to 0.5 µm).

The conducted investigations show that only hydrofluoric acid should not be used as a derouging solution, because of the severe material removal that it causes. All other chemicals exhibited slight material removal during the derouging process.

Because the changes of surface roughness due to the different treatments were only small, the Ra measurement has very limited or no suitability for a meaningful assessment of the possible surface changes due to derouging solutions.

Test to Determine the Degree of Rouging by Color Measurement

At present, rouging is usually noted and appraised by visual inspections. Because of the individual color perception of the appraising person, this method proves to be highly subjective. An objective measuring technique would have the advantage of being able to express the subjective color perception by defined parameters, on the basis of which an assessment scale for rouged surfaces could be defined. The assessment scale is intended to permit an objective estimate of the degree of rouging and therefore of the success of derouging actions. In two production tanks, zones exhibiting rouging of different intensity were scanned using the CM-700D mobile spectrophotometer of Konica Minolta.

The color measurement was carried out in the Lab color model. This model covers all visually perceptible colors. This Lab model assigns each color a color location with coordinates L (luminance or brightness axis), a (red-green axis) and b (blue-yellow axis), thus spanning a Cartesian coordinate system in

three-dimensional space. From these three color coordinates it is possible to calculate the color distance ΔE, which is used to describe the differences between two color values.

A triplicate measurement was made for each measuring point. Starting from the metallically bright surface, the color proceeded with increasing rouging through dark-gray and yellow to an intensive red hue.

Even though the L-value, which shows a decreasing trend with increasing degree of rouging, correlates with the visual color impression, the following reasons show that this instrumental technique is not suitable for a completely objective appraisal of the degree of rouging:

On the one hand, the problem exists that different combinations
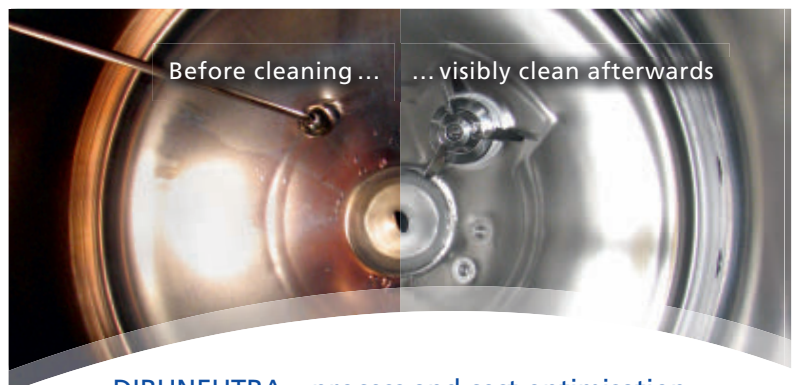
Figure 4
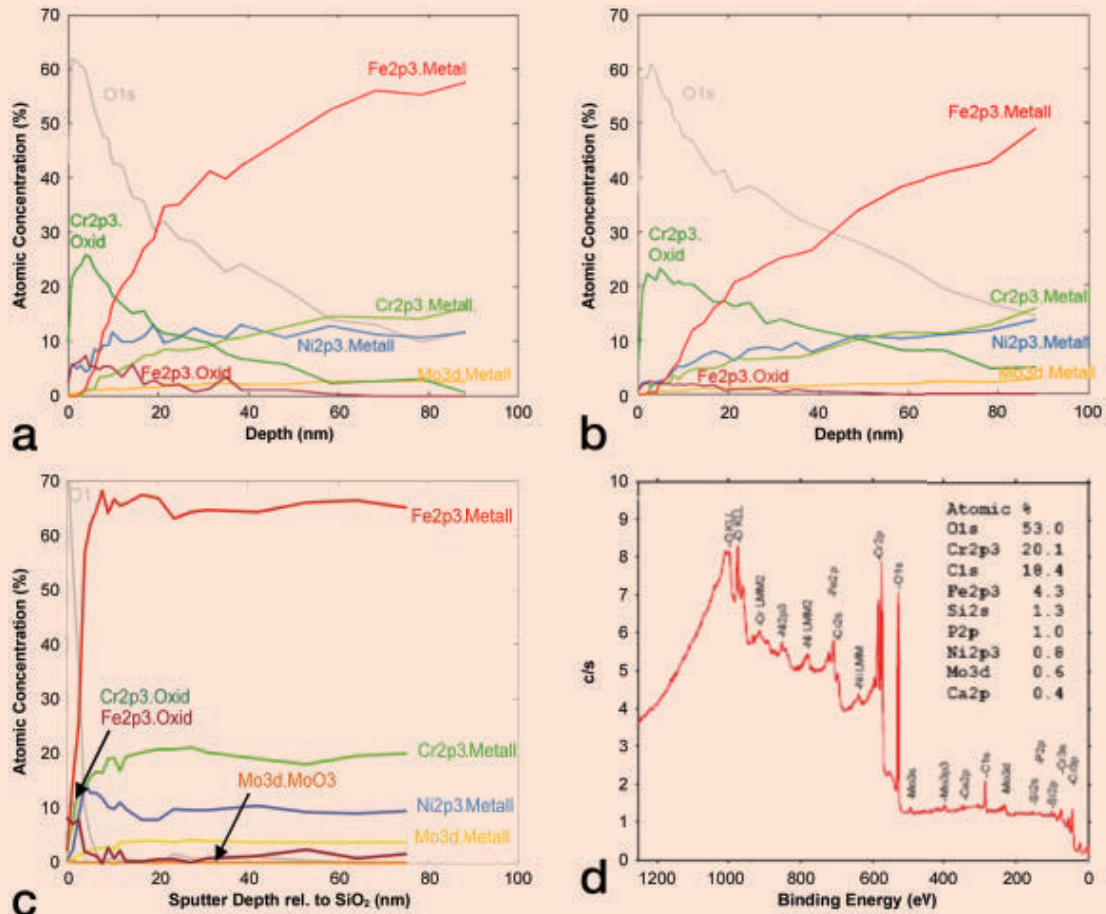
(a) Rouged reference sample of material 1.4435; ESCA depth profile, (b) rouged and cleaned sample of material 1.4435; ESCA depth profile, (c) intact reference sample of material 1.4435; ESCA depth profile and (d) rouged and cleaned sample of material 1.4435; general ESCA spectrum
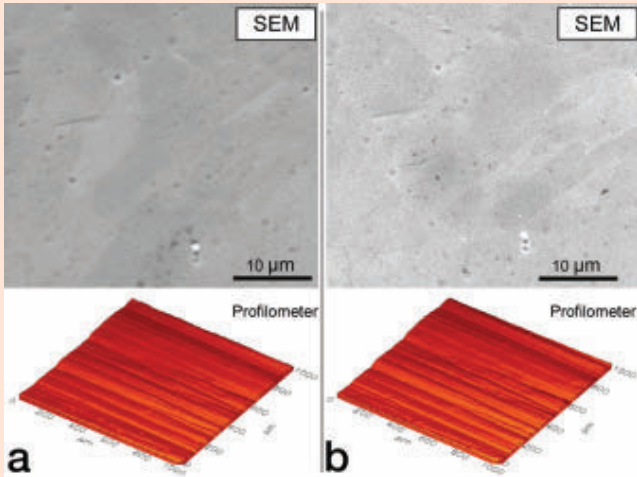

Figure 5 | Corrosion rate determined after 15 derouging cycles for the solutions used
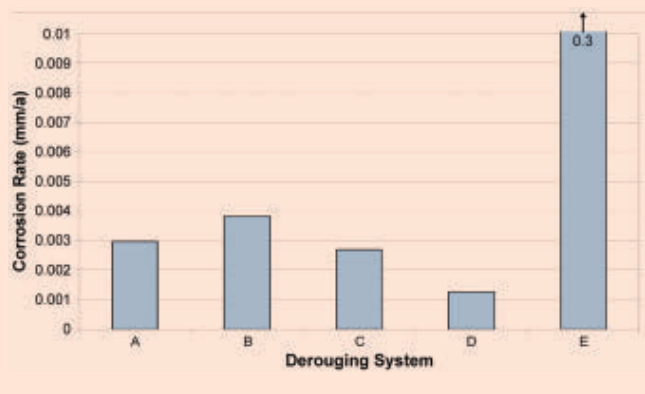
of luminance L as well as of the color values a and b can lead to identical ΔE values. Thus the color distance ΔE can have identical values for surfaces in the initial condition and for surfaces with different rouging intensity, even when the color perceptions are different.
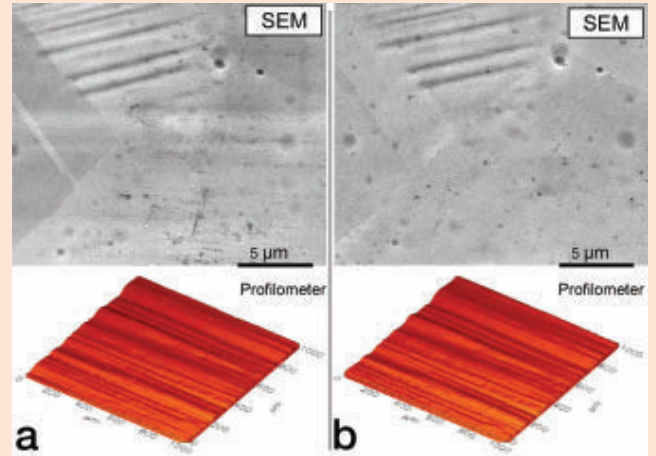
Furthermore, if the discolorations developed in the production equipment are not uniform, the problem arises of deciding which of the discolorations should be measured.
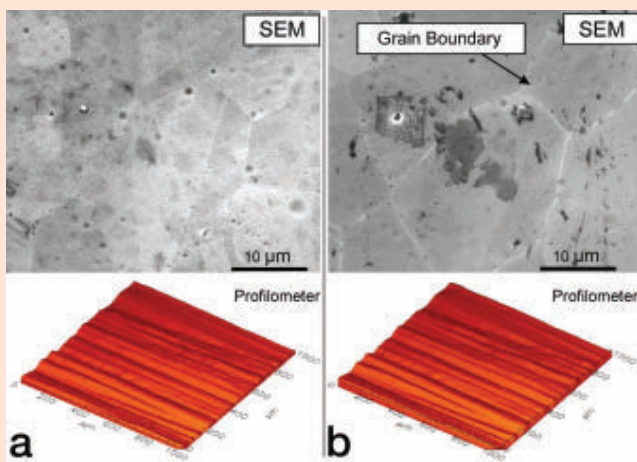
Figure 6	Derouging solution A

(a) surface before derouging and (b) surface after 15 derouging cycles

Figure 7	Derouging solution B

(a) surface before derouging and (b) surface after 15 derouging cycles; stains and slight grain boundary attack

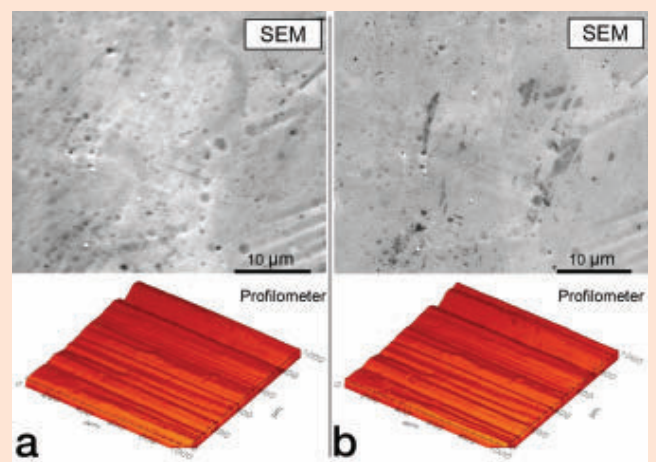| Figure 8	Derouging solution C

(a) surface before derouging and (b) surface after 15 derouging cycles.

Figure 9	Derouging solution D

(a) surface before derouging and (b) surface after 15 derouging cycles; stains

Summary of the Results and Assessment

The results from the "Tests and Practical Experiences" section of Part 2 and the "Tests and Practical Experiences" section in this part are summarized and assessed below on the basis of the risks listed in Table 7 from Part 1.

Conclusion

The tests conducted on the risks considered in part 1, table G show that rouging does not cause any risk to product safety.

No evidence was found that the water quality in a WFI system is negatively influenced by rouging. This is also the finding after many years of study. The requirements of the pharmacopeias were always safely complied with.

On the basis of this knowledge, the following recommendations can be made for dealing with rouging in pharmaceutical production:

▶ Rouging within pharmaceutical production should be monitored. In particular, it must be ensured that the discolorations are due to rouging and not to other kinds of surface changes.
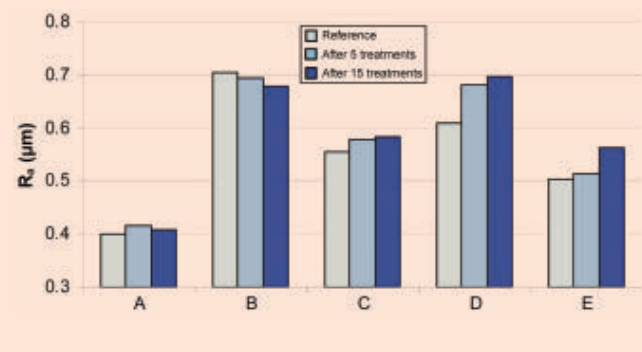
Figure 10	Derouging solution E
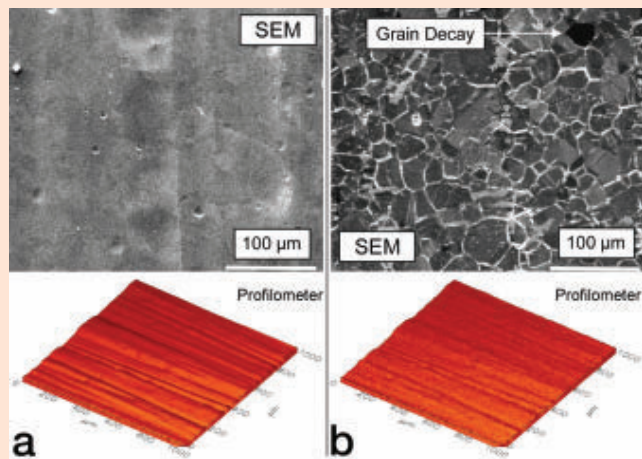
(a) surface before derouging and (b) surface after 15 derouging cycles; severe grain boundary attack and grain decay

Figure 11	Surface roughness Ra determined by means of profilometer after 5 and 15 derouging cycles for the solutions used

▸ In the case of rouging in systems having direct contact with product, the following rule applies: Derouging must be considered if any signs appear of a reduction of cleaning efficiency or if impurities due to rouging can no longer be detected with certainty.

▸ Derouging always necessitates a risk analysis, which should be undertaken in cooperation with specialized firms. In particular, risks to occupational safety as well as product and GMP risks must be assessed here. It must be ensured that the surface quality is not negatively impaired by derouging.

▸ The derouging procedure should be set forth in local instructions.

▸ In order to keep the influence on the material surfaces as small as possible, pH-neutral derouging methods are preferred over acid-based solutions.

▸ The success of derouging should be demonstrated on the basis of methods agreed beforehand, such as wipe samples and/or visual investigations. ◂

Glossary

API	Active Pharmaceutical Ingredient (pharmaceutical, active substance)
CIP	Cleaning in Place (usually with hot NaOH solution)
Carry Over	Entrainment of impurities into the next batch or into a subsequently manufactured product
EDX	Energy dispersive X-ray spectroscopy
el.pol.	Electrolytically polished, electropolished
EMEA	European Medicines Agency
ESCA	Electron Spectroscopy for Chemical Analysis (also known as XPS, or x-ray photoelectron spectroscopy)
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
mm/a	Millimeters per year
PW	Purified Water (as defined in the European Pharmacopoeia)
RD	German abbreviation for Clean Steam (Reinstdampf)
REM	German abbreviation for Scanning Electron Microscope (Raster Elektronenmikroskop)
Rouging	Denotes both the surface color change due to oxidative corrosion products of corrosion-resistant steel alloys as well as the process by which these corrosion products are formed
RT	Room Temperature

Table E	Results for the cleaning ability of the investigated solutions			
Medium	Exposure Time (h)	Temperature (°C)	Corrosion Rate (mm/a)	Cleaning Ability (derouging) (%)
20% HNO_3 + 5%HF	0.5	24.0	13.4	95
3% Citric acid	6.0 3.0	24.0 80.0	0.02 0.06	0 40
5% H_3PO_4	6.0 3.0	24.0 80.0	0.02 0.09	30 95
5% HNO_3	24	60.0	0.02	95

Figure 12 | Results of the action of various chemicals on the pipe samples

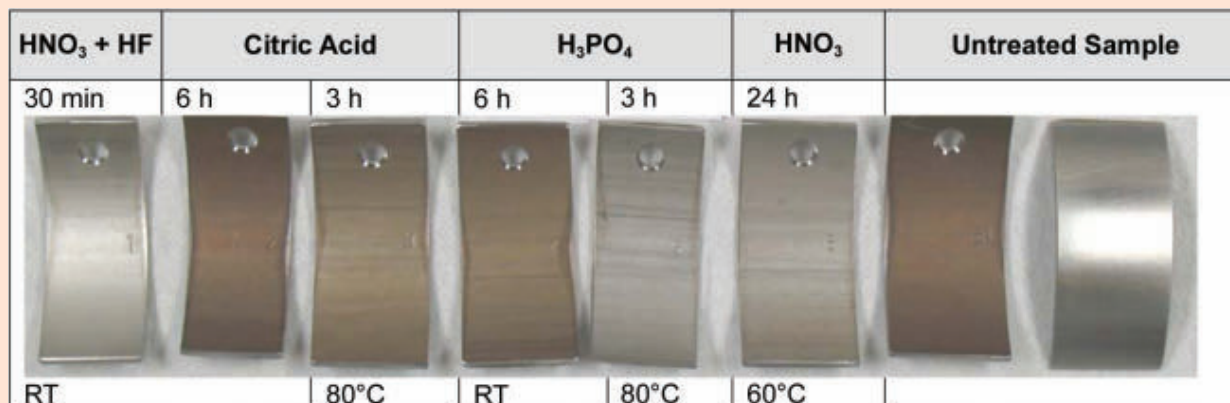| Table F	Summary of the results
Risk	**Summary of the Results**
Rouge ingress into the final product	▶ By virtue of the very small weight changes of the test plates, the tests for gravimetric determination of a material-specific corrosion rate (see part 2) yielded the knowledge that the rouging-related corrosion rate for systems having contact with clean steam and alkaline solution and subject to alternating stresses (CIP / SIP) is very much lower than the corrosion rate of $3.4*10^{-3}$ mm/a cited in the literature[9] and is also lower than the values of $4*10^{-4}$ mm/a (1.4435) to $1.8*10^{-3}$ mm/a (1.4301) determined in part 2 section on "Investigations by Surface Analysis".
	▶ Analyses performed on WFI samples from rouging-stressed distribution systems in part 2, section on "Heavy Metal Concentrations" revealed an increased content of nickel only after prolonged circulation times without media replacement. Under normal operating conditions, no elevated concentrations of heavy metals were detectable, and the water quality therefore conformed with the legislative requirements.
	▶ During the heavy-metal investigations of various APIs (see part 2, section on "Heavy Metal Concentrations"), an increased heavy-metal content was not detected in any of the investigated active substances.In this connection, no relationship between system age or potentially existing rouging and the heavy-metal content is perceptible.
	▶ The investigated color-measurement method is not suitable for determining the degree of rouging of a surface (see part 3, section on "Rouge Formation").
Influence of rouge coatings on efficiency of cleaning of the process equipment	▶ Despite the adjusted worst-case conditions, the test of the influence of rouge coatings on the efficiency of cleaning (see part 2, section "Influence on Rouge Coatings") did not reveal any violation of the specified protein limit values for the test duration of 545 combined CIP/SIP cycles.
Derouging	▶ Acid CIP with phosphoric acid (see part 3, section on "Cleaning Methods") may have a positive effect on the visual appearance of stainless-steel surfaces with light rouge coatings. On the other hand, this method is less suitable for removal of heavier rouge layers.
	The tests on derouging of the test tank and determination of the specific surface load of rouge from derouging solutions (see part 3, section "Cleaning Methods") showed that the pH-neutral derouging method used selectively removes iron oxides (rouge), whereas acid derouging may also remove base metal in addition to the rouge coatings (etching attack), thus causing micro-roughening of the treated surfaces.
	Furthermore, the experience with acid-based derouging solutions in the first derouging action on the test stand showed that rouging proceeds much more rapidly after acid-based derouging than was the case in the initial condition of the test tank.
	▶ In accordance with the investigations in part 3, sections on "Cleaning Methods" and "Influence of Different Derouging Chemicals" measurements of the surface roughness before and after a derouging operation are not suitable for appraising the surface condition.

SE	Secondary Electrons
SEM	Scanning Electron Microscope
SIP	Sanitization/Sterilization in Place
Specific surface load	Defined as the amount of rouge formed in a certain time unit per unit surface area The specific surface load is expressed in units of kg/(a*m²) (kilograms per year * square meter)
Swab	Polyester fabric cloth
TOC	Total Organic Carbon
VE-Wasser	German abbreviation for Demineralized water (Vollentsalztes Wasser)
WFI	Water For Injection

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About the Authors

Thomas Blitz studied chemical engineering at the University of Darmstadt and holds a Dipl. Ing. He was the head of the materials engineering laboratory for Merck KGaA, Darmstadt, Germany, for over 10 years. His main responsibilities include the implementation of materials engineering studies (corrosion tests) and the processing of damages. He is a member of the Society for Corrosion Protection (GfKORR).

Ernst Felber was educated as a technical glass blower, p rocess engineer (AVOR), and draughtsman; he received further education in material engineering. He has many years of practical experience in engineering and organization of manufacturing plants and production facilities (material management). He is a field expert for the State Secretariat for Economic Affairs (SECO), Accreditation Service for pressure equipment. He is currently head of Technical Standards department at F. Hoffmann-La Roche AG in Basel, Switzerland.

Robert Haas (Dipl. Ing. (FH)) graduated with a degree in bioengineering at the University of Applied Sciences in Munich. In his diploma thesis, he investigated the impact of rouging on biopharmaceutical production. He has worked for Roche Diagnostics GmbH in Penzberg since 2010. His area of expertise includes material and corrosion related issues in biopharmaceutical production.

Birgit Lorsbach studied materials engineering at the University of Applied Science in Aalen and graduated as an engineer (FH). She has worked for over 23 years in the materials technology department at Bayer AG. One of her main tasks is assisting the healthcare department in areas related to the corrosion resistance of materials, surface technology and discoloration, and failure analysis. She is a member of the Society for Corrosion Protection (GfKORR).

Andreas Marjoram studied chemical engineering at the University of Applied Science in Berlin completing studies in chemical engineer (biological process) and industrial engineering (same university, 2006-2010) where he completed a MSc in industrial engineering. He works as technical plant manager for Bayer AG in Wuppertal for a biopharmaceutical facility and contributed to the ISPE Baseline® Guide Vol. 4 – Water and Steam Systems new chapter on rouge. He has longtime experience with pharmaceutical water systems from the operational perspective.

Roland Merkofer studied mechanical engineering FH and business administration FH. He has worked for many years in the plastics and food industry. For the past six years he has been responsible for the clean utility systems at the Novartis Pharma Stein AG site in Stein, Switzerland.

Tobias Müller is with Roche Diagnostics GmbH, Penzberg, Germany. He graduated as a master craftsman in chemistry in 1998 and has worked for over 20 years in the chemical and biotechnology industries. As a general assistant in the fermentation department and as a quality assurance specialist within production support, he has been working on the issue of rouging for more than six years with regards to production and quality assurance.

Dr. Nathalie Schuleit graduated in material science at engineering school from the University of Paris and received her PhD from the Ecole nationale supérieure des mines de Saint-Étienne, France in the area of hard thin coatings for forming tools. Since 2008, Dr. Nathalie Schuleit has worked at Intertek (Schweiz) AG in Basel, Switzerland as expert in material science. Her work is wide-reaching, from plant inspection and material consulting to failure analysis, mainly for the chemical and pharmaceutical industries.

Marc Vernier studied chemical engineering at the University of Applied Science Northwestern Switzerland, with additional education in business administration. In 2004 he became a founding member of Ateco Services AG (today Ateco Tobler AG) and has been the managing director of the company since then. Vernier has many years of practical experience in the topic of rouging and rouging removal and is the inventor of the pH neutral derouging procedure and holder of EU and US patent. He is a member of the Society for Corrosion Protection (GfKORR). In 2007 he was a founding member of the Rouging Workgroup with members from the pharmaceutical industry (Bayer, Roche, Merck, Novartis and DSM).

Dr. Thomas Wellauer, PhD, received his PhD in Chemistry from the University of Basel. Previously he was a research and development chemist at F. Hoffmann-La Roche and a plant manager in chemical and pharmaceutical production. Since 2010 he is a senior scientist and head of the Materials and Corrosion Group at DSM Nutritional Products in Sisseln, Switzerland.