ISPE Newsletter - Rouging

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Workshop Pharmaceutical Water and Steam

Topic Rouging

ISPE CoP
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Contact:
Rolf Sopp
ISPE Affiliate Manager (D/A/CH)
Deutschland/Österreich/Schweiz
Rolf.Sopp@sanofi-aventis.com

The first workshop regarding **"Pharmaceutical Water and Steam"** took place on September 1, 2005. During this meeting, the core team of the German/Austrian/Swiss Community of Practice COP for Pharmaceutical Water and Steam was chosen, consisting of 10 members with the goal of steering further activities of the CoP. The team evaluated the results of the first workshop and came to the conclusion that Rouging is the topic with the highest interest among participants.

The second Pharmaceutical Water and Steam COP Workshop was held on 20th-21st of September 2006.

Several presentations were held to introduce the subject matter followed by workshops covering the following main aspects:

- Choice of materials, Quality control
- Engineering, System design
- Service and Maintenance

Fifty experts from fields such as OEM, engineering, material production, instrument manufacturing, consulting, QC and pharmaceutical manufacturing attended. All participants actively contributed to one of the three aspects.

This newsletter presents the discussion points and results from the workshops. These can be used as suggestions and/or guidelines. The statements below are based on observations, experience and considerations regarding possible causes or solutions. Scientific studies have been initiated but are currently not complete.

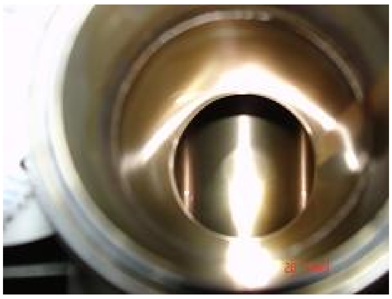
Engineering, System design

Influencing factors (explanation)

How can rouging be avoided through engineering and system design of the water treatment plant?
Various aspects under consideration of possible influencing factors such as the design itself and monitoring should be considered.

The following **factors**, which all could possibly effect the development of rouging, were considered in the workshop:

1. CO_2
2. Temperature
3. Nitrogen
4. Oxygen
5. Particle carryover
6. Ozone
7. Feedwater
8. Choice of materials
9. Sanitization process



1. CO_2

Elevated CO_2 concentrations cause a decrease in pH. This can lead to destabilization of the passive layer, particularly in hot systems (80°C).

2. Temperature

Since rouging is a form of corrosion, it is expected there is a system specific temperature above which the rouging will increase with further temperature increase.

3. Nitrogen

Nitrogen blanketing of storage tanks removes the presence of oxygen in the tank atmosphere. This leads to a drop in the oxygen concentration of the water, reducing the redox potential, which results in a change in the passive layer.

4. Oxygen

Oxygen facilitates the natural continuous re-passivation of the steel surface.

5. Particle carryover

Possible particle carryover from the water purification equipment or WFI still into the distribution system can be avoided or minimized through proper design.

- For example: by avoiding the use of non-alloyed steels for construction or piping material as well as through appropriate operating conditions.
- Further measures can only be defined once the possible formation mechanisms for ferrous compounds have been fully identified.

It's assumed as being common practice that Semi- Intermediate- and Final Products (bulk) will pass particle filtration steps during the production process.

6. Ozone

Ozone, frequently used in cold storage and distribution systems, is thought to favorably effect the formation of the passive layer on the steel surface. However, ozone concentrations over about 1 ppm can lead to corrosion when chlorides are present and standard alloys such as AISI 304 and 316 are used.

7. Feed water

A detailed examination of the feed water quality is necessary during the equipment engineering phase to identify possible corrosion sources.

The goal is to eliminate iron, manganese, silica, CO_2 and chlorides.

8. Choice of materials

The choice of materials is handled in detail under "Choice of materials, QC".

9. Sanitization process

Since high temperatures support corrosion, the temperature in a given system should be kept as low as possible without compromising safe operation. Frequent steam or hot water sanitizations could support rouge formation, with the temperature and time being the deciding factors. Reasonable sanitization intervals should be set based on monitoring results (qualification phase PQ, routine).

Design

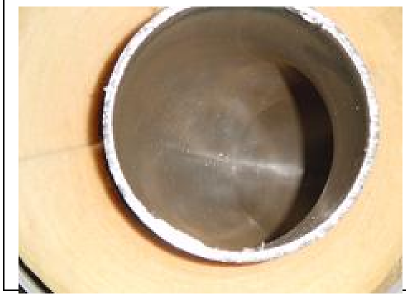
The following design criteria should be critically analyzed as part of a risk analysis. The focus should be on the effects on the equipment itself, on the operation of the equipment as well as on the product.

- Sanitization and Cleanability
  - Drainability
  - Rinsable pure steam piping, for example design the condensate piping system in a way in which it can be used to provide circulation during future chemical treatments (passivation, de-rouging).
  - Optimization of the cleaning procedure to simplify as well as reduce the amount of cleaning agent needed.

- Allow for removable inspection spool pieces in the piping
  - Installation of easy to access spool pieces such as elbows or bends at reference points in the piping system where rouging is expected.
  - These pieces should be easily replaceable to allow detailed analysis with destructive testing in the lab when necessary.
- Demisters in the form of wire mesh should be avoided when possible due to their large surface areas. Cyclone separators are acceptable.
- Welds are seen as a risk factor.

  Correctly welded seams using WIG-process and with sufficient weld seam protection (inert gas shielded) do not add to the corrosion risk.

  - Cold bending offers a possibility to reduce the number of welds in a system, particularly for smaller pipe diameters (i.e., up to DN25).
  - The material is more susceptible to local corrosion depending on the degree of cold forming; however, this isn't relevant for high purity water systems.
  - Bending pipework is often preferred due to economic reasons.



- CO_2 Elimination
  - Protecting WFI stills and pure steam generators by installing selective degassing steps upstream.
  - CO_2 traps can be installed on the product water storage tanks to prevent CO_2 from entering the distribution system. The

	CO_2 trap shouldn't be allowed to collect moisture as this can cause blockage.
Monitoring	• Visual inspection using sight glasses, inspection pieces or opening the pump housing • Inline measurement – Direct quantitative measurement of rouge is not commercially available. Such monitoring technologies are currently in development. • Other parameters and measurements – Measuring methods for parameters such as pH, particle quantification and size and CO_2 concentration are available. Their influence of rouging has not been conclusively studied or proven.
"Choice of materials, QC-Service" **Steps to take System startup**	The desired condition for new systems (zero or initial-state) should be well defined. • Sufficiently detailed specifications should be available for all components (material, surface roughness, and tolerances) and these should be tested during the qualification phase. The thermal and chemical resistance should also be checked. Furthermore, special care should be taken regarding the cleanliness of all components from the time of delivery onwards. • NB: if possible (cost feasibility) the materials for pipes, fittings and valves should be the same to avoid different behavior (welding).
	**Definition of "Treatment"** At the end of the installation phase, the entire assembly must be dry. The following methods are considered treatments: • Removal of any installation debris, i.e. using compressed air, degreasing, etc. • Pickling, passivation, rinsing Each method should be executed, tested and documented in accordance with an SOP (Standard Operating Procedure). The SOP can be created with the support of the expert / qualified company. The responsibility for the execution should be defined in the SOP.

Methods:

Compressed air

- Removal of large debris
- Check for blockage

Rinsing

- Rinsing is used to remove:
  - Loose debris or water soluble substances
  - Detergents, etc.
- Rinse after each treatment step.
- The water quality for each rinse step should be defined individually. Purified Water (PW) is usually sufficient.
- The PW should have a pH of 5 to 7 at the end of the rinsing cycle.

Degreasing with alkaline detergents

- Removal of debris
- Wash out fatty or oily substances

Chemical Cleaning/ Pickling

- The makeup of the chemical solution should be suitable for the surface roughness of the system (qualified SOP).
- Removal of contaminants (nonalloyed ferrous components, shavings (alloy and nonalloy), construction dust, discoloration, etc.)
- In special cases, such as surface damage, with removal by chemical reaction (erosive)
- Electro polished systems, if pickled, are pickled without material removal (see following comments).

Comments regarding “Pickling”:

Pickling (cleaning) with weak acids (citric acid, phosphoric acid) dissolve just surface contamination without damaging the material. The passive layer remains intact. Erosive pickling only takes place using reducing acids or acid mixtures, such as nitric acid or nitric and hydrofluoric acid mixtures and results in the chemical removal of the passive layer. This is usually not necessary for the pharmaceutical industry.

In general, the comments regarding erosive and non-erosive pickling are necessary because pickling always removes something. A film or discoloring could be seen but are removed during pickling, revealing the layer below.

Passivation

- The passive layer is always present in a neutral, water based system at ambient temperatures, even at atmospheric exposure with air (oxygen environments, chemical equilibrium)
- The stability and homogeneity of the passive layer is dependent on

the redox potential

  – An oxygen supply is necessary for an optimal redox potential
  – A low pH is unfavorable. Since CO_2 reduces the pH value, its concentration should be minimized.

Developing the passive layer

- The presence of O_2 or other oxidizing agents such as ozone supports the development of the passive layer.
- The passive layer can be artificially developed with chemical treatment. The results of such a treatment are only temporary and not permanent. In time, the system will return to the equilibrium state dictated by the redox system.

Testing the passive layer (*Thickness*)

- The passive layer doesn't normally need to be tested since it's naturally present.
- There is no regulatory requirement to test the passive layer.
- The thickness of the passive layer is dependant on the surrounding conditions and therefore varies according to the conditions in the pipe (for example, if the pipe is filled with liquid or air). Due to this variability, testing the thickness of the passive layer only gives information on the state of the layer at the time of the testing.
- Possible measuring methods can be conducted by qualified experts. Laboratory tests (destructive testing), such as X-ray photoelectron spectroscopy are time consuming and expensive.
- Non-destructive online measurements which characterize the condition of the material have been proven in the chemical industry. These are indirect measurements using sensors made of the same material, which are evaluated using complex algorithms.

Final rinse

- With *Water for Injection*, *Highly Purified Water* or *Purified Water*
- The minimum required water quality should be defined (potential cost savings). This quality should be at least equal to the operating medium. For instance, if WFI is required for the production, then the final rinse should be conducted using WFI.

Handover criteria

- The success of the rinse should be proven using suitable acceptance criteria, for instance, conductivity and TOC are frequently used. The tolerance range should correspond to the same predefined range as the rinsing water.
- Visual control at accessible points or with video endoscope can be used to ensure that no installation debris (non-suspended particles) has been left behind.

Measures for existing installations

The system components for existing installations should have documented specifications. If this isn't the case, then the current state of the system components should be documented through an detailed system analysis. At least the following aspects should be considered as adapted treatment methods or processes may be required:

- Material qualities
  - Corrosion resistance is dependant on these characteristics. Therefore, if rouging is corrosion, it follows that the material quality influences the rouging tendency.
- Surface condition (surface roughness, visual evaluation of the surface condition, type and extent of the rouging, such as if it can be wiped off,…)
- Safety aspects such as solid connections rather than flexible tubing
- Disposal of treatment and rinsing solutions

System analysis and evaluation should regularly take place using existing monitoring results.

Definition of treatment

If the system analysis shows a need to take action, suitable treatment methods from the list above should be used.

Measures for de-rouging

De-Rouging of existing installations

The derouging method should be conducted, tested and documented in accordance with an SOP (Standard Operating Procedure). If necessary, existing warranty conditions should be taken into consideration.

- The SOP can be developed with qualified experts.
- The responsibility for the execution should be decided in advance.

The recipe should be based on the following:

- Current state (see above)
- Suitability tests (effectiveness) should influence the choice of the process.

The frequency of derouging should be based on the following criteria:

- In accordance with monitoring results (months, years)
- In accordance with experience and knowledge of the installation
- Dependent on the state

Testing and documentation can be assigned to the contracting company.

- Visual inspection in accordance with agreed acceptance criteria (colors, film, etc)
- Wipe test
- Photos, etc.

"Choice of Materials and Processing / Machining"

The choice of materials influences the formation of rouging.

Plastics

Pros: - No rouging because it's a nonmetallic material

Cons: - Thermal deformation from variance in temperature (hot operation or sanitization)

- New design of piping supports (high expansion value)
- Aging stability (hot sanitizations)
- Not always feasible for hot systems. Pressure and vacuum tolerances must be observed, also regarding the piping connections.
- Mix of materials – for instance, a stainless steel tank, piping in PVDF. A rouging layer can be transported onto the plastic surfaces.
- The chemical tolerance of PVDF is limited to a maximum of pH 12 (relevant for treatment chemicals).

Metal alloys

The austenitic stainless steels used most frequently in the pharmaceutical industry are 1.4404/1.4435 (316L), 1.4571 (316Ti).

Pros: - They can be used for cold and hot media. Almost all components are available in these materials.

Cons: - Stainless steel is susceptible to rouging

Specific characteristics of individual alloys:

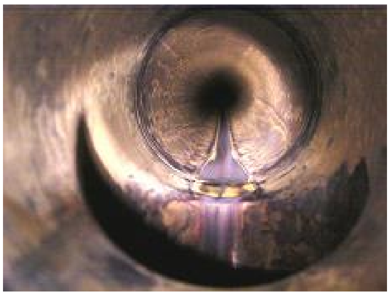
- 1.4404 – somewhat less Mo (0.5%), slightly reduced corrosion resistance in hot systems. Good availability (tubing, fittings, instruments, valves, etc)
- 1.4435 – limited availability of fittings and instruments. Expensive material. Also susceptible to rouging.

Other alloys are also possible; however, they may be more difficult to procure and are significantly more expensive.

1.4539, 1.4462 (Ferritic-Austenitic Duplexsteel), Ni-Basic-Alloy, Alloy 33 (high content of chromium), Titanium.

Pros: - These special materials could be more resistance to rouging; however, this has not been proven yet.

- 1.4462 is resistant to rouging for a wide redox range in pure water systems, but doesn't solve all problems.
- Optimizing the passive layer through higher chromium content. The Alloy 33 with 33% Cr shows a chromium content in the passive layer of 83% after exposure to 95°C pure water.
- No experience with Nickel based alloys. Rouging has been observed with Hastelloy C-276, which is not surprising considering the lower Cr content.

 	- Titanium stabilized materials: valves and regulating valves in WFI systems are often made of 316Ti. Cons: - Due to cost and availability, 1.4539 und 1.4462 are only used in special cases!!

Delta Ferrite-Content

- The delta ferrite criteria can be traced back to the BN 2 (Basler Norm, a guideline of the Swiss chemical and pharmaceutical industries), where a very low delta ferrite content of 0.5% is defined. The original intention of BN2 was to just take the delta ferrite content into account. The delta ferrite limit was specified as a preventive measure and is not based on scientific proof. The limit is too strict and is not practical. It dictates the use of steel which is considerably more expensive and compliant welds are considerably more difficult to achieve.
- Many of the participants have found that 3% is a more feasible limit. Since several participants have also had positive experience with considerably higher delta ferrite levels (no unusual rouging observed), 5% was suggested as the maximum for a preventive measure. It should be noted that calling 5% a preventive measure against rouging is not quite correct as lower delta ferrite levels won't have a negative effect on rouging, but could drive up the material costs.
- The goal (specification) should be 3%. Specifying < 3% is not recommended based on the experience of the group. An absolute maximum value of 5% should not be exceeded.
- A complete lack of iron can result in a significantly higher susceptibility to heat cracks and therefore require the use of special weld filler metal.
- This aspect is overvalued regarding its potential negative influence on rouging. The delta ferrite has a more elevated Cr content and is therefore fundamentally more resistance to rouging than austenitic (bulk) structure.
- This does not protect against rouging!
- The limit for delta ferrite was created as a measure of corrosion resistance and it can be used as proof of weld quality. The delta ferrite measurement is therefore an economical and useful method to test weld quality and if the weld filler material is fully alloyed.
- The delta ferrite content does not have an effect on the prevention of rouging.

Surface quality

Stainless steel is always produced with a specific surface quality. The many variations which are common for piping are well defined in industry standards. There are also standards which described terms and conditions for delivery.

Common design:

- Seamless tubing or longitudinal welds
- Mechanically polished or honed (bright finish, bright rolled and cold drawn)
- Not pickled, just rinsed with water

Pros: - More economical that electro polished tube

Cons: - These surface qualities are often treated in situ.

With the exception Ti or Nb stabilized steel, all steel is available with electro polished surfaces which can lead to further improvement

- A roughness of Ra < 0.8 µm should be specified.

Pros: - Due to the reduced surface area and the more compact, clean (free from defects) passive layer in comparison to non electropolished surfaces, electro polished surfaces generally show less tendency to rouging.

- Better cleanibility with higher surface quality.

Cons: - Treatment with strong acids roughens the surface.

- Special care must be taken if any secondary welding is required.

- The welds in the pipe system can influence the surface quality.

Welding Procedures

The Processing of the materials should be clearly defined while taking into account the following criteria:

- Goods-in quality control (QM, QS, Documentation)
- Storage conditions and environment (low dust) should be specified

A) Weld preparation

Attention: - Cutting of non alloyed ferritic materials ➔ these develop very aggressive particles!

- Cutting of alloyed materials leads to conversion to martensite (magnetic, less corrosion resistant)

- Do not use a cutting disc, grinder.

B) Welding procedure

- Define welding procedure in advance (orbital or manual)
- Develop and qualify site specific welding procedures
- Welder’s qualifications should correlate to the qualified welding procedures (see above)
- Automatic welding procedures (MIG, WIG)

	• Laser, Plasma welding procedures (tanks, etc.) • Manual welds allowed as exceptions ***C) Weld filler metal*** The corrosion resistance is improved when higher alloyed filler metal in comparison to the welded material is used. This also helps maintain a low Delta ferrite content (Experience: of the same kind as basic material). ***D) Weld testing and documentation*** • All welds should be visually examined (naked eye, endoscope). A predetermined percentage of the welds should be documented with photos, DVD or video. • Examination of the weld formation and any discoloration should be included. • An alternate testing method should be set for welds which can not be visually examined (X-ray, sample weld before and after the true welding, etc) Further Documentation: • Risk analysis, sample welds • Weld plan, weld supervision, work instructions, welding procedure qualification • Welder qualification • See also: (only in German) “Technische Regel TR 153 "Gütesicherung von Schweißnähten an Apparaten und Rohrleitungen" issued by BCI (Basel Chemical Industry).

Service and Maintenance

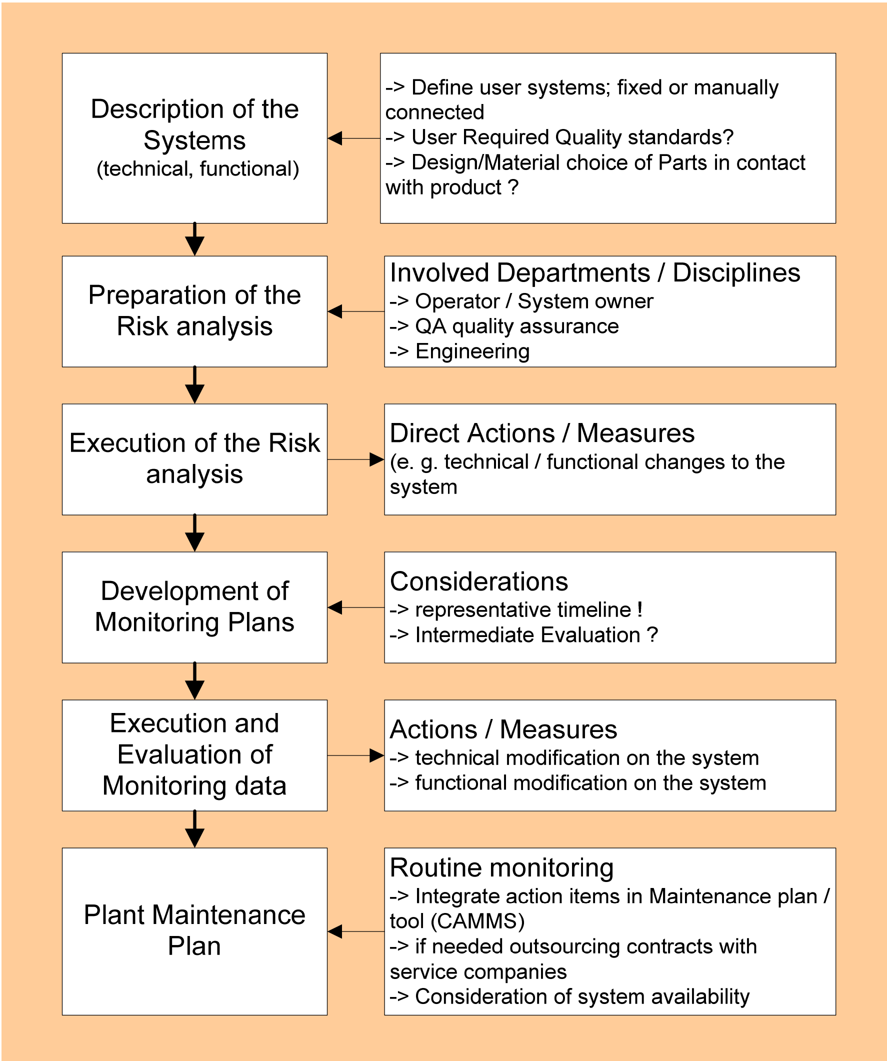
Flow chart Risk analysis

Suggested procedure

A risk analysis is a valuable starting point for the selection or determination of measures which are to be implemented in the service and maintenance plan. The experience of the operator as well as the previous actions of the engineering or maintenance and quality control departments should also be taken into account.

The risk analysis should work out which parts of the system are critical and define the necessary treatment (to what extant, in which intervals, to which time point and with which measures).

The following flowchart shows a possible procedure for the development of a plant specific service and maintenance plan.



It is generally accepted that suspended particles in low concentrations can be present and will be removed at filters.

The usual sample methods based on the Pharmacopeia will usually not discover the presence of particles.

The current findings show no influence of rouging on the mechanical stability of piping and components. It seems prudent to involve all parties, for instance, operator, quality control, engineering and maintenance in the risk analysis process. Some of the issues and problems which they will address are:

- What are the possible effects on the product? Is it an API, end product…? Can dissolved metallic ions occur (such as ferric ions) and what influence would this have on the product? Can adherent metal hydroxides occur (Fe-, Ni-, Cr-) and what influence would this have on the product?
- Are filters in place which would be negatively impacted by particles?
- Can deposits form on measuring probes and sensors?
- If rouging occurs, could it negatively impact downstream plants or equipment?
- Are heat exchangers present and could these be negatively impacted?
- Are components such as injectors present whose function would be negatively impacted by the presence of particles?
- Further critical parts could be: pumps, instrument ports, tanks, valves, spray balls, forged components, vacuum molded components
- Are unplanned events expected whose frequency would influence the availability of a plant, for example when a cause analysis and subsequent service and maintenance measures are necessary after an OOS finding?
- Are measures to restore the defined state necessary after repairs or planned expansions or changes to the system, such as rinsing, passivation, pickling etc after welding work has been done?
- Could the surface finish be changed by deposits? Will this favor biofilm formation?

Inspection program

A periodic monitoring program should be established to provide regular controls at the critical points of the system which were defined in the risk analysis, to collect experience and information, for instance through photo documentation. This provides the basis for the service and maintenance plan.

Both on and off-line tests can be used as well as testing the surface of spool pieces removed from the system.

An inspection plan can be created in order to collect enough information and empirical test results to allow optimization.

The following inspection and evaluation methods can be defined and used primarily:

- General visual inspection: i.e. through an inspection glass or with endoscope
    - Possible assessment: color (yellow, orange, red, brown, etc.)

or surface finish (dull, shiny, morbid).

- Swab test (Results: particles are removable, partly removable, not removable)
- Optical inline measurement
- Particle measurement, online / inline
- Filter:
  The water is filtered offline at 0.1 µm and the filter membrane then undergoes laboratory analysis and evaluation, for instance checking if discoloration or particles are present. This type of test should be carried out at predetermined intervals and the test results should influence the testing intervals.
- Inspection spool pieces: the following should be taken into account:
  - The piece should be representative of the system in terms of surface finish, material, etc.
  - Critical points in the system
  - They do not necessarily need to be built into straight piping segments.
  - It is better to use pieces with elbows, valves or instruments. Procedure and use of spool pieces: ➔ The spool piece is removed during maintenance and is used as a reference which is used as a sample for testing different cleaning methods.
- Electro-chemical methods.

Monitoring data can be regularly evaluated on the basis of the monitoring plan. The results are used defining objective acceptance criteria and specifying the required state of the system.

Maintenance plan

One of the most important goals for evaluating the inspection results is their further use towards development of a system specific maintenance plan.

All results from the inspection, particularly from the spool pieces, should be taken into account in the development of the plan and in determining the steps which are to be taken. Depending on the actual situation, the plan can contain the following points and actions to be taken:

- Location of the inspection or actions to be taken
- Responsibility
- Frequency or interval of the inspection or execution of the actions to be taken.
- Experience from previous cleanings, when available
- Execution of a cleaning procedure, when necessary
- For especially critical cases in clean steam systems, a particle filter

can be installed at the point of use. For this application, a filter size of < 0.1 µm is generally acceptable.

- Carbon dioxide absorbers can be used, for instance on water storage tanks.

If the decision has been made that cleaning is necessary, the following issues should be decided, where appropriate:

- Should a general chemical clean take place?
- Choice of the cleaning media (anodic clean, electro polishing)
- Definition of success factors, using monitoring methods such as conductivity, inspection spools etc or use of Passive layer measuring device , Ferroxyl test (ASTM-A380)
- Definition of cycles and time periods, dependent on process
- In the case of older systems: special attention should be placed when defining parameters to take into account design, material and components

The operator must ensure that the following is met:

- Execution description exists and is accepted
- Critical parameters such as the treatment temperature and soak time are defined
- The execution is properly documented
- The scope of documentation is defined
- The execution and scope of evaluating if the treatment was a success is defined
- Procedure or maintenance plan is approved

Regulatory aspects

In order to ensure that the current regulatory requirements are understood, it is advisable to keep up to date on the available Audit information (FDA-Warning Letters) as well as literature and publications.

Should the regulatory agency check how rouging is handled, it should be possible to present and explain how the procedure defining the maintenance and inspection plan was conducted as well as the results.

The operator must ensure that cleaning (derouging), monitoring etc.is documented. In particular, a treatment report should be available which documents the results (also with photos) and in which all relevant points are systematically addressed.