

ISPE Newsletter – Operation & Maintenance

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Pharmaceutical Water and Steam Workshop on

*Topic
Operation and
Maintenance of Pure
Steam & Pure Water
Systems*

ISPE rCoP D/A/CH

Contact:
Rolf Sopp
ISPE Affiliate Manager
(D/A/CH)
Germany / Austria /
Switzerland
Rolf.Sopp@ispe-dach.com

The fourth workshop of the Pharmaceutical Water and Steam rCoP took place from November 26th – 27th, 2008.

After introductory presentations, a number of workshops were held on the following subjects:

- Plant Design and Service
- Calibration and Maintenance - Intervals
- Organizational measures (Standardisation)
- Elastomer & Diaphragm Valves
- Energy requirement & Possible savings – Pure Steam & WFI
- Efficiency of energy

About 50 professionals from fields such as OEM, planning, regulatory agencies, instrument manufacturing, service industry, consulting, QC and pharmaceutical manufacturing took part. All participants actively contributed to the workshops.

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

Chapter 1

Plant Design and Service

Introduction and General Requirements

The design of a system can have a significant impact on maintenance (spare parts and labor). Meant by design is the technical and functional implementation including all hydraulic calculations as well as the consideration of regulatory requirements (safety- and GMP-related). The definition of the usage of the water/steam based on the respective pharmacopoeia(s) and purpose should be clear at the beginning of a project.

Cost savings in maintenance start with proper planning.

A first step could be getting additional support by selecting an appropriate Consultant for planning and execution of the project, in case the required competency is not available in-house and utilize specific experience and expertise related to water/steam systems. In addition, proven existing standards in system design should be preferred. For complex as well as large systems, a customized system design may be required.

Incomplete planning in the beginning can lead to higher cost in the routine operation, which includes maintenance.

Critical aspects for Design:

▪ **Location**

Consider the location of the manufacturing facility as well as the water/steam system itself. This leads to requirements in the surrounding environment of the system:

○ **Feed Water Quality**

Water quality usually is impacted by numerous factors relative to its source, which can be different geographically. While in Europe potable water quality is available for the most part, other regions/countries may have only minor raw water qualities. An analysis of the raw water and a respective well-designed pre-treatment can help to protect the purification system components relative to major cleaning and maintenance activities that otherwise might be required in rather short intervals.

Since the temperature of raw water (or feed water) impacts the recovery and thus quality of the purification process, the question also might be, whether to install a heater/cooler?

○ **Environmental conditions at point of installation**

It is recommended to consider aspects like temperature, humidity and possible amount of airborne dust when selecting the point of installation of a water/steam system. As an example, the environmental temperature impacts the temperature of the water in the storage tank and thus the design or size of a cooler. Another example is airborne dust, which may shorten the lifetime of vent filters significantly.

- **Availability of Spare Parts**

Local site standards for eg. components or process connections (specific brands, dimensions of gaskets, ASME requirements DIN-ISO, etc.) should be taken into consideration when planning a system, since these may have an impact on availability and cost of spare parts and consumables.

- **Qualification of Staff**

Depending on complexity of a system and availability of qualified staff, the partial or total outsourcing of maintenance activities should be considered. As one option, a service provider with proven expertise or the system manufacturer company itself could be of support in this matter.

- **Culture / HR-Philosophy**

The willingness of an increased number of resources for maintenance activities can be discussed during the design phase of water and steam systems. The end-user might be open for designs that would offer a lower capital expenditure on the one hand and a higher maintenance effort or operational expenditure on the other hand, if the local cost of labor would justify this decision. This would also require the local maintenance staff being well-trained in the system technology (good system knowledge = improved system availability).

Capital Expenditure vs. Maintenance Cost

Experience, focus on the necessary, user requirements

For diligent planning in the early project stages, the acquisition of existing experiences (internal/external) is recommended. A central role has the balance between investment and maintenance cost. Therefore, considerations about what is crucial for the operation and validation of a system versus what might have an added value, but is not essential for the process itself should be part of the user requirement specification. This differentiation may be useful to limit the investment as well as the maintenance expenditures for the system.

Challenge the required water quality

In addition to the check for consumption at the individual points of use at different times, the required water quality should be challenged. During their life cycle, water systems tend to be extended and points of use are added, which could possibly be supplied with a different quality than pharmaceutical grade water (eg. without microbial limitations).

Points of use that could be supplied with treated water other than pharmaceutical water, open up the opportunity of a separate and maybe smaller water system with a much lower requirement for maintenance.

In a new project, the same thought process should be applied, since it could lead to lowering the maintenance cost.

On the other hand, the opposite thought process can apply as well. Assuming the case of replacement of two old water systems, where historically a small softening system supplied water to points of use with a smaller consumption level (and no USP requirements), while at the same time all taps with USP requirements were supplied by a separate large Purified Water (PW) system. In such a case it might make economically more sense to build just one new PW-system that would supply the water to the non-USP grade points of use with smaller consumption as well. Two old systems would now be replaced by one new system, because the need for water with a lower quality requirement is rather small. By doing so, the maintenance requirements now would only apply to one instead of two water systems.

System Capacity

As a rule of thumb, consider „no Over-Engineering“! Safety margins in the capacity of a system can include visible (i.e. investment cost) as well as hidden cost, especially when considering the need for required maintenance activities and replacement and spare parts cost.

It is not unusual that additionally calculated back-up capacities in the purification system, the storage and distribution are not actually required. The consideration of a modular system expansion to address possible higher future demands during the planning phase might be an option.

Level of Automation

In state-of-the-art water purification systems, the instrumentation and automation system should be included in maintenance programs. Is a high level of automation included in the water/steam system, it usually relies on respective instrumentation (online/at-line) installed as an integral part of the system and requires a certain amount of maintenance and calibration. The measurement components in the system are assembled with detachable connections, which require regular replacement of gaskets and sealings in set intervals.

In case of an automated use-point management, additional components like diaphragm valves are needed and should be included in the maintenance program.

Adjustment to local conditions

Utilities:

In general, when planning systems for clean media, the existing utilities that are required for the operation (in quantity and quality) at place of installation should be reviewed and checked. In case, pure steam is considered to be the sanitizing agent for the system, but there does not such a pure steam generating system exist, the additional equipment and investments can easily lead subsequently

to higher maintenance cost. Here, the sanitization with ozone or hot water (heated electrically) could be an alternative to pursue.

Accessibility:

During installation of water/steam systems the required space for maintaining a proper operation should be considered. Sufficient space and easy access for sampling points as well as for calibration activities of critical instruments can help to significantly reduce the shutdown or maintenance time.

The need for pedestals or other supporting structures to be able to service certain system components or take samples should be minimized during the planning phase. Although these accessories facilitate the accessibility, they also do increase the investment for the entire system.

Utilizing preconditions of existing systems

Technology, Process, Spare Parts:

When existing systems on site or in the same region already successfully meet the requirements of the Pharmacopoeia, the product itself and the operator or user, then adapting a new system to the same or similar purification processes can make a lot of sense. Therefore, an evaluation of what is already in place and what kind of performance does this system supply can save cost for the operation of a new system later on. To be considered here is the familiarity of the maintenance staff with the process, the actual availability of staff for maintenance (internally/externally), the scope of spare parts and their availability as well as local standards for spare part sourcing, which all can lead to an optimization in maintenance cost.

Existing SOP's:

When replacing existing systems during modernization and upgrading activities with new ones of a similar process design, the maintenance SOP's used for the old systems can be used as templates for the new equipment. Adjustments should be made to address the requirements of the new components, but general activities might be the same or at least similar compared to the old system.

Another important aspect is the training demand for staff working on one or more systems. Especially, when multiple systems are operated with different designs or functions (eg. water system vs. steam system or PW system vs. WFI system), training of the operating staff on how to operate and maintain the desired functionality is essential.

When working with external service providers for system maintenance, a uniform system/maintenance concept can also support a reduction in cost for maintenance.

Design

Accessibility within the system

In case no detail plan should be available for a new water/steam system (dimensional drawing(s) and/or layout of a package unit), it is recommended to request an appropriate document like a piping diagram or manufacturing schematic of the entire system. The accessibility within the system for maintenance, calibration and sampling can only be reviewed with accurate schematics or drawings prior to the manufacturing process.

Sizing of new systems

- The capacity of the tank(s) should support a continuous operation.
- Consider the replacement of the entire tank capacity during times of consumption and non-consumption.
- The number of tank capacity replacements should be planned.
- Use the lowest number of systems with a maximum of utilization.
- Also, consider required redundancy for securing the production. For example, two smaller sized purification modules instead of one large system, which operate at a higher capacity rate.
- A modular concept and system design is recommended to ensure the possibility of a future expansion by using the same technologies and processes. This facilitates the maintenance approach.

Design for efficient Maintenance and Calibration

Care should be taken that all components of a system that require maintenance and/calibration fulfill a respective installation concept. This includes, but is not limited to detachable process connections and adapters, cable length of instruments for calibration, accessibility without major need for disassemblies, simple replacements of parts or components by avoiding system drainage. Devices that require a lot of maintenance ideally are easy attachable and detachable.

Site standards to support easy maintenance (examples):

Connections that do not require gaskets

Pure Steam Ball Valves

Valves without diaphragms

Pumps for easy maintenance

Minimize detachable connections

Detachable connections can facilitate the access to certain system components or instruments. However, each detachable connection also bears the risk for leakages, since they usually require gaskets

or sealings. Therefore, it is recommended to completely avoid detachable connections in parts of the system that are difficult to get access to, in so-called “blind spots”.

Purification systems that are planned using modular assembly systems and components are usually assembled with detachable connections or joints. Instead, the use of weldable steel or PVDF mouldings and parts that meet the specifications relative to material, stability and surface quality are widely available in the market is recommended.

Optimization of Sampling and Points-of-Use

Already in early planning stages of a project, the scope and location of analytical sampling should be discussed and decided upon in collaboration with Quality Assurance (QA) Department. The piping and instrumentation diagram of the entire system is a useful base for this discussion. To be mutually defined besides the location of a sampling point should also be the brand and type of the desired sampling valve or the sampling equipment.

During the PQ-Stages 1 and 2 the installation of sampling ports with a lower standard can be accepted for the sampling between the individual purification and treatment steps, while a higher standard is required after the final treatment as well as in the loop and distribution system. Whereas in some cases, the ports for draining the respective part of the piping or component in the pre-treatment section of the system can also be utilized for sampling, while the sampling ports for the routine monitoring should be of a consistent standard.

Sampling at manually operated points of use is usually done by using the installed valves.

Additional sampling ports as often used in ring mains or loops of pharmaceutical water systems should be completely avoided.

These sampling ports are used for testing the water that is circulating in the system, but not at the point of use. Instead, testing the water at the loop return supplies adequate evidence.

As a result, the planning engineer, the operator and QA should mutually discuss the sampling plan (PQ plan) in the early stages of the design phase prior to the execution of a pure media system. Unnecessary changes can be avoided during the project which support the optimization of the scope of sampling as well as limits the maintenance requirements later on.

Sampling cooler for Pure Steam Generators

In case a sampling cooler is required in the system; it is recommended that it is easily accessible and equipped with a cooling and waste water connection. The respective cooling water supply and waste water pipe should be installed as well.

Pressurized hot water vs. Steam vs. Ozone

Another important aspect that should be clarified at the beginning of a project is the method of sanitization of the system(s). Existing experience with certain methods, recommendation in guidelines and the required regulatory requirements (from local/international

Pharmacopias) should be used for consideration. Besides the differences in cost for energy for a sanitization with ozone, hot water or steam; a hot sanitized system is thermally more impacted by the effect of heat. This could lead to a higher wear on impacted components and subsequently to a shorter replacement frequency. In addition to this, additional cost for support structures and designs that are needed to compensate the thermal expansion of piping, etc. should not be disregarded.

Challenge the current status and local “standard”

It is recommended to investigate for maintenance efforts and scope in existing systems. In a design review, the aforementioned aspects could be used as benchmarks. Such design reviews should include the sampling concept (or plan) and organizational means besides the technical and functional aspects. Hence the review team should consist of representatives of Engineering/Maintenance, Operations and Quality Assurance.

Scope of Instrumentation and Calibration

During the definition of the User Requirement Specification the critical measurement parameters and instrumentation that are relevant for the monitoring of the water/steam quality should be specified. Even if the final system concept and piping and instrumentation diagram (P&ID) should not be clear at this point, the minimum requirements of respective Pharmacopias (local and/or international) and known guidelines in relation to quality monitoring and process operation should be considered. This relates to the so-called GMP- or quality-relevant measurements. The owner of the system (Production, Operations, Utilities/Facilities, or other respective department) should qualify the need for instrumentation by balancing the cost of investment and maintenance versus the quality of supplied data to support informed decisions and assist in root-cause analysis for deviations during operation. The sufficient minimum of instrumentation should be determined in the team.

This can be achieved by classification into:

- GMP-/quality-relevant: Registration, documentation, alarm function
- Safety-relevant: Protection for system and staff, locking of taps/use points, alarm function
- Functionally relevant: technical function, supervision, control functions and system

Impact on maintenance by system design (rinsing/cleaning, sanitizing, sterilizing post maintenance activities)

Procedures for starting the system following a maintenance activity, repair, deviation or change should be discussed early during the planning phase as well in correlation with the discussion about release criteria (together with QA) and sampling.

In general, the concept applies that a validated process for the restart of the system and its release for production must be in place for all maintenance actions that require:

- The system being partially or completely shut down,
- The system being set from “normal operation” into a “maintenance

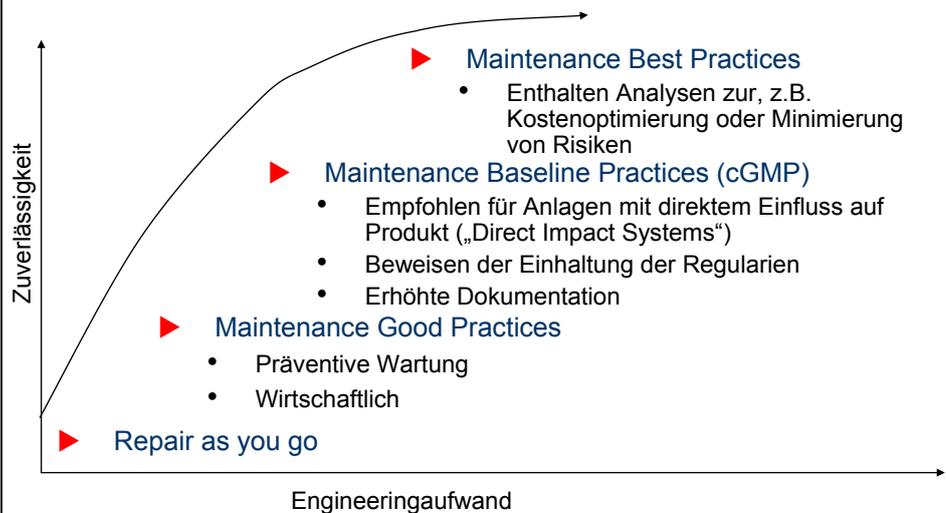
mode”,

- The system needs being partially opened.

Depending on the sanitization concept, the time, effort and expenditures for a disruption in water/steam supply for rinsing/cleaning procedures (CIP), subsequent hot water sanitization, ozonization, steam-in-place (SIP) including tank filling and draining can be very different and thus deviate significantly from each other.

Chapter 2 Calibration and Maintenance Interval

Service & Maintenance Plan



Reliability Cost of Engineering

- Maintenance Best Practices
 - Include analysis for eg. Optimization of cost or minimizing risks
- Maintenance Baseline Practices (cGMP)
 - Recommended for systems with direct impact on product(s) (Direct Impact Systems)
 - Confirm compliance with regulatory requirements
 - Increased level of documentation
- Maintenance Good Practices
 - Preventive maintenance
 - Economic
- Repair-as-you-go

Service Plan (Outsourcing)

A service plan can be created together with a supplier of that service (service provider).

- Utilize experience and expertise of service provider
- New system setup after Maintenance execution – system know-how
- Specific tools

Preparation of Maintenance Plan of (In-house)

- Instruction of service provider
- System and maintenance know-how
- Experience
- Responsibility In-house

Default settings for systems

- OA-Settings (Qualification during operation) => Criteria for hand-over / operation data. Settings, which were applied during

commissioning and which were used for system qualification should be documented as “default” settings.

Periodic review of Maintenance Plan

Experiences made with following topics should be taken into consideration during review of maintenance plan:

- Monitoring - Results
- Change in materials (material compatibility)
- Experience in efficiency and performance
- Change in usage of water and steam
- Change in technology (Stop/Start > continuous, hot > cold)

Risk analysis (as first step)

Question: Does the respective component have a DIRECT/INDIRECT impact on the product → the final product of the site (intermediate product, drug)?

A partial result of the risk analysis could look like this:

<i>Part of system</i>	<i>DIRECT</i>	<i>INDIRECT</i>
Pressurized air		X
N ₂ Nitrogen (tank blanketing)	X	
Media for cooling/heating		X
Brine solution		X
Feed water		X
Chemical media (CIP)	X	

The requirement for maintenance of a water/steam system can be risk based segmented into critical and non-critical parts or components. Check of system parts and components if CRITICAL/NON-CRITICAL:

Critical from where (define starting point in system)?

- From last measurement point on
- Last purification / treatment stage → active impact in process

Critical in the water system?

- From sampling point after last purification / treatment stage
- Conductivity measurement
- Temperature Measurement
- TOC Online (if installed) and official quality relevant measurement
- Pressure Measurement
- Material of sealing/gaskets
- Vent filter (storage tank)
- O₃-Messung / UV Licht

Critical in Pure Steam system?

- From sampling point at effluent of pure steam generator
- Conductivity Measurement
- Pressure Measurement
- Temperature Measurement
- Material of seals / gaskets
- Filter (if installed)

Intervals of Maintenance

- Control operation modes
 - Frequency of cleaning
 - Scheme in defining intervals
- 1. Step – Starting points
- Recommendation of supplier
 - Self-made experiences
 - Requirement
 - Safety of operation

Recommendation of Supplier

Why Maintenance?

- Purified Water/WFI and Pure Steam Systems are „Critical Utilities“
- Avoid interruption in operation through early determination of necessary repairs
- Shutdown in pure water supply results in shutdown in production
- Financial risk is higher than investment in maintenance

Maintenance supports maintaining the value of a system:

- A flawless function and performance of a system can be achieved by define intervals for preventive maintenance
- A pharmaceutical company proves through intelligent maintenance plans that it implements a maximum of care to maintain a high level of quality in production

The following table ist a general example on how der replacement of wear and tear materials can be executed. Intervals are to be defined system specific.

Wear parts	1. Year	2. Year	3. Year	4. Year	5. Year	On-site storage
Gaskets for sampling valves	1x	1x	1x	1x	1x	
Conductivity sensor			1x			recommended
Diaphragm for diaphragm valves		1x		1x		
Pre-Filtration cartridges	4x	4x	4x	4x	4x	recommended
Pressurized air filter	1x	1x	1x	1x	1x	

Sterile air filter	2x	2x	2x	2x	2x	
UV-lamps	1x	1x	1x	1x	1x	recommended
UV-quartz glass		1x		1x		recommended
Resin for softener					1x	
RO membranes			1x			
EDI-Module			1x			
Geasket kit for pumps			1x			
Soda Lime pellets	1x	1x	1x	1x	1x	
Gaskets for Clamp		1x		1x		

- 2. Step → Increase intervals
 - Mode of operation (Monitoring)
 - Possible shutdown periods
 - Occupancy rate
 - Redundancy (spare parts)

➤ Examples for adjusted intervals:

System Component	Start Interval	Recommended Interval
Valve diaphragms & gaskets in WFI system (hot – 85°C)	6 Months	1 Year ⁽¹⁾
Valve diaphragms & gaskets in cold storage system (20°C)	1 Year	According to supplier recommendations
Pump sealings	If redundant pump system is installed, replace when failing, otherwise keep a spare pump or define a replacement interval	
Vent filter	3 Months	1 Year
UV Lamps	According to supplier recommendations	
⁽¹⁾ usage in system can be extended when conditions have been regularly checked		

Spare Parts Storage

- Reasonable lifetime in use and on stock → In accordance with supplier's recommendations
- Check of respective components prior to installation and during maintenance activities.
- Where to store the spare parts – in accordance with manufacturer's

/ supplier's recommendations

Common Recommendations of Manufacturer/Supplier

Membrane service life

- RO-Membranes
 - 3-5 years are common
 - Ageing of membrane polymers; they change over time which has a negative impact on the recovery rate
 - Fouling or Scaling can be irreversible

- EDI Modules
 - Raw water quality is very important for service life
 - If organic substances, chlorine or hardness are present, the service life of the module is substantially shorter
 - -> Design and Operation of upstream purification processes in the system have a significant impact on the service life.

Storage and Distribution – The sanitization concept does influence the required maintenance expenditure.

- Ozone
 - Ozone-Generator
 - Ozone-Measurement
 - Ozone-Destruction unit (UV)
 - Exhaust catalyst
- Hot water (also UV)
 - Control valves
 - (UV Lamps & quartz glass pipes)
- Steam
 - Control valves
- Chiller + UV
 - Control valves
 - UV Lamps & quartz glass pipes

Calibration

- Decision to be made
 - Which kind of calibration is depending on parameter
 - Organization of device to be tested
 - In-house or Outsourcing to a third party

- Calibration plan
 - Utilize Manual of Manufacturer/Supplier
 - Analysis of possible errors
 - All instruments to be checked 1x per year (according to GMP), plan organizes service and maintenance ideally in Calibration Management System

- Periodic revision of calibration plan
 - Implement necessary changes in plan
 - Option: In case, test results remain stable and within

- specification over a period of time (eg. 2 years), then calibration interval can be extended (document your decision)
- Recommendation: If one test result is outside of specification, then reduce the calibration interval (eg. from 12 months to 4 months)

Calibration classification

The selection is based on the following criteria:

- Impact on product quality
- Impact on process functionality
- Frequency of usage
- Desired availability of instrument

One example for a classification can be:

Classification	
A	Direct impact on quality of final product. An official calibration is required. The calibration protocol/certificate to be signed by QA.
B	Impact on function of process/plant, which could impact the quality of final product. The required calibration report to be signed by process/plant supervisor.
C	A measurement verification is sufficient. Documentation of event not required.

Chapter 3
Org. Measures
(Standardization)

Service and Maintenance require organizational pre-conditions and measures, since they contribute to keep the process in a validate state. In accordance with current GMP requirements, a pharmaceutical manufacturer shall have a program in place that supports preventive maintenance. Plants for production of clean media should be part of that program. The following organizational aspects should be considered.

Service / Maintenance contract

It has been proven and is recommended to sign a service/maintenance contract with the manufacturer of the treatment system. The manufacturer does have the know-how and expertise for the system, especially for package units. A service/maintenance shall comply with GMP guidelines.

To consider:

- Analysis of usage
- Availability and lead times of spare parts
- Proposals of supplier/manufacturer
- Quality of PW, WFI, Pure Steam
- Critical / non-critical
- Scope of service/maintenance
- Required reaction time of service team
- Plant availability
- Experiences made during operation should be considered

- Scope of maintenance protocol
- Manufacturer supplies material and spares and executes the service
- Maintenance cycles to be defined by Operator/End-user
- Scope of Maintenance for water/steam production unit and/or entire water/steam system
- Quality Management System, objective of Operator/End-user

Package Units can be handled using a service contract (standard contract of supplier) to be able to evaluate the Opex (operational expenditures) of the first years of operation before the investment has been made.

Quality Assurance

- Supplier audit of service contractor
- Execute Maintenance in accordance with current GMP requirements
- Check of successful service/maintenance activity (eg. Monitor conductivity after service/maintenance)
- Only rely on Trained and qualified staff
- Consider Quality Management System of Operator/End-user

Dokumentation of Service/Maintenance

Dokumentation of service/maintenance activities should be in accordance with Good Documentation Practice.

- Maintenance Plan (to be created and acknowledged prior to execution of activity (-ies)), can be part of service contract
- Maintenance protocol = Report of service provider
- Maintenance protocol review, sign off if documented activities and document it self are OK

Organisation of Service/Maintenance

This is usually part of a concept for preventive maintenance. Consider the following items:

- Timely planning of activity (-ies)
 - Coordination with impacted departments or staff
 - Planning of required resources (availability, Laboratory resources)
- Maintenance tool, (eg. CMMS) validated software
- Maintenance staff (internal, external)
 - External companies (general service provider or Manufacturer or Supplier of system)
 - Internal staff (maybe consisting of resources of different departments)
 - Periodic training of end-user and maintenance staff of a clean media system should be described in a training schedule/plan to avoid errors during operation and maintenance in advance (preventive measure).
- Consider possible audits/inspections on short notice when organizing service/maintenance on the system

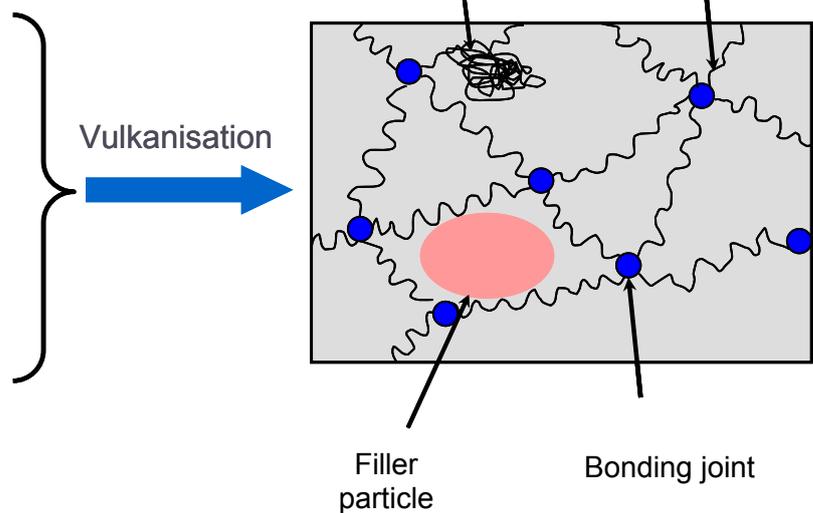
- Planning of resources for analytical measurements
- Responsibility remains with the end-user, he can delegate certain activities

Chapter 4
Elastomers & Diaphragm valves

Basics of elastomers and their composition

Elastomers can be part of many components of a water purification system. Such as diaphragm valves or sealings. This chapter provides insight into the chemical and physical structure of elastomers as well as the changes in their characteristics when exposed to certain stress factors. This is essential for the understanding of the service life of components in combination with the required maintenance efforts. Elastomers are coarse-meshed polymers with a variety of fillers and additives, which impact the characteristics of the material (see picture 1).

- Rubber (raw material)
- Fillers
- Plasticizer
- Vulcanisation activators
- Bonding chemicals
- Aging protection



Picture 1: Components of an elastomer

The basic characteristics of the material are primarily defined by the non-bonded raw polymer.

- Basic types according to ASTM D 1418 with abbreviation
 - Ethylene-Propylene-Diene-Monomer (EPDM)
 - Nitrile Rubber (HNBR)
 - Fluoroelastomer (FKM)
 - Perfluoroelastomer (FFKM).

Given these basic types there is a great variety of different raw polymer suppliers and therefore variety in chain length and characteristics. Besides rubber as basic material, fillers have the largest proportion in

	<p>relation tot he mass off he material.</p> <p>Fillers:</p> <ul style="list-style-type: none"> ▪ Soot (Carbon) ▪ Silicic acid ▪ Minerals
	<p>Special additives can provide desired characteristics relative to an optimization of ageing or shapeing of the final product. Compared to steel, rubber materials are individual compositions of manufacturers rather than standardized materials. They can consist of around 20 different compounds. Since already the basic rubber types can be very different, it needs to be considered that “EPDM is nit exactly like EPDM”. Manufacturers of components usually can be of support in selecting the appropriate material for the application.</p> <p><i>Regulatory requirements for elastomers in food and pharmaceutical applications</i></p> <p>Elastomers in contact with food are regulated in the U.S. by the FDA - 21 CFR 177.2600 <i>Rubber articles intended for repeated use</i>. These regulations include a so called <i>white list</i> with tolerated substances and limitation of certain proportions.</p> <p>A similar requirement is installed within the EU directive 1935/2004 for manufacturers in Europe. There is no such list of tolerated substances on EU level, which allows for national regulations – as an example, in Germany the book of “Lebensmittel-, Bedarfsgegenstände- und Futtermittelgesetzbuch (LFGB) §§ 30 und 31” as well as the XV. und XXI. Recommendation of the “Bundesinstitut für Risikobewertung“ (national authority for risk assessment).</p> <p>For applications and use in pharmaceutical manufacturing it is not always sufficient to comply with FDA conforming qualities. In some cases additional test for USP Class VI conformity are required. Here, the extracts of rubber materials are tested against their toxicity when being injected or implanted in a body (animal tests, subcutane implantation and/or injection).</p> <p>In addition, the EU directive EMEA/410/01 provides information about „free of animal derived ingredients“ – „ADI-free“).</p> <p><i>Sealings</i></p> <p>Sealings have to withstand a variety of mechanical, thermal and chemical influence factors. Besides abrasion (mechanical wear) it is heat, which leads to ageing of elastomers in industrial applications. It is important to know, that usually the specified operational temperatures for elastomers in data sheets are based on the use in air. Depending on medium and material there can be significant differences to specified data.</p>

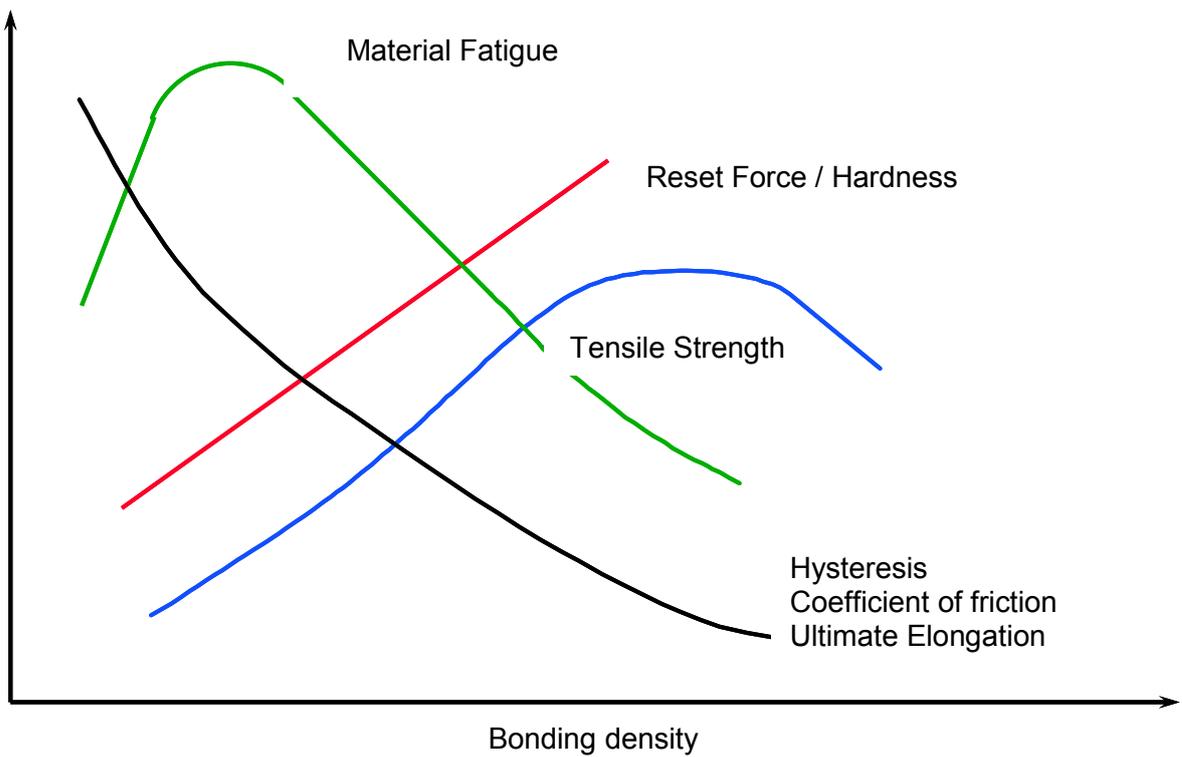
Besides mechanical and thermal influences it is also important to consider the chemical environmental conditions for the service life of a sealing. Lab tests only provide information on pre-defined and usually very stable conditions and are to be taken „with a grain of salt“.

Due to differences in temperature profiles, frequency of operation and concentration of chemicals in different water systems, there can still be variability in the service life of a sealing. It is therefore difficult to exactly predict the service life of a sealing, if not supported with data of a similar plant or system. An additional safety margin is recommended to rather replace a sealing too early than too late. The supplier of the sealing or component that carries the seal usually can be of assistance and support in solving this challenge.

EPDM in de-ionized water (ultrapure water)

As already discussed, elastomers consist of numerous different substances and compounds. Especially low molecular organic compounds (plasticizer, monomers, derivate of chemicals used for vulcanization, etc.) and mineral fillers can be extracted from the matrix by respective solvents. Even water can extract compounds of elastomers and enhanced is this effect with ultrapure water. The effect is a measurable shrinking in volume. Depending on polarity, solvents can also diffuse into the matrix and expand its volume. In occurrence of both effects at the same time, the result is a considerable change in composition and hence properties of the material. Chemical processes are possible besides physical processes: post-bonding, breaks of joints or decomposition of chains.

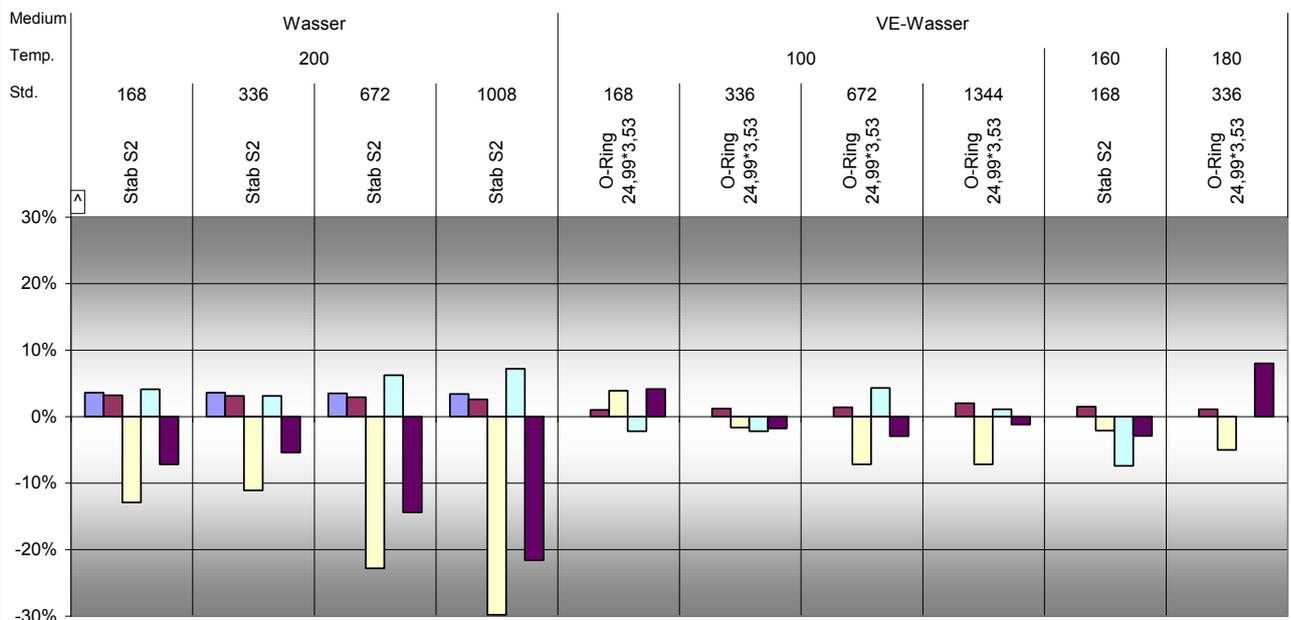
Picture 2 presents an overview of areas of properties and their changes.



Picture 2: Dependence of different material properties relative to the bonding density

An objective visual capture of these processes is impossible; in addition to the changes in mass and volume it is also important to detect deviations in mechanical properties. Besides the less meaningful hardness (according IRHD or Shore A) it is the elongation at break, the Modulus 100% and the tensile strength. Only when all these properties are known, realistic statements on the stability of elastomers in specific media are possible. The following limits are approved in relation to changes in mass and volume; +/- 5% or +/- 10% respectively and for changes in mechanical properties +/- 15% or +/- 30% respectively, depending on a dynamic or static use of the gasket.

media group|(Alle)|material group|(Alle)|producer|(Alle)|conc. |(Alle)|material|70 EPDM 291



Aspects of elastomers in a real application

(Membrane diaphragms in a clean media system in relation to maintenance and service)

An individual system concept can always be considered based on the aforementioned statements. A focus should be on the thermal/mechanical strain on the gasket in relation to the construction of the component in which it is used. Especially the chemical and thermal sanitization concept of a system can determine the impact on rubber gaskets and sealings. The following factors require consideration of an overview of the system as a whole, since they significantly can influence the service life of sealings:

- Ozone concentration
- Dossage periods of ozone
- Radiation
- Period and intensity of UV radiation
- Chemical cleanings
- Applied chemicals (concentration, exposure time, temperature, rinse time of applied chemicals)
- Hot water sanitization of use of Pure Steam
- Temperature of sanitization
- Pressure
- Heating up to the sanitizing temperature and cooling down back to operating temperature
- Stop-and-go or continuous operation of purification system
- Operation of purification system or the storage and distribution systems
- Static or dynamic use of gaskets
- Number of switches of operation
- Temperature and exposure time on sealings

Service

Ideally, the check of components in a clean media system is executed in cooperation between operator, skid manufacturer and manufacturer of the gaskets or sealings. For determination of the appropriate service cycles the service team and the operator should collaborate. The visual inspection of rubber gaskets, seals or diaphragms should be included in the maintenance protocol. Reproducibility and clear identification is important. This can be facilitated by appropriate marking, documenting, packaging and storage of gaskets, sealings and diaphragms. Together with the skid manufacturer and component supplier(s), the operator can define respective maintenance procedures in advance. As an example, the allocation of the gaskets or diaphragms in the system to the respective component in the bill of

materials or itemized component list facilitates the search for the correct gasket and material, when needed. It is not uncommon, that the skid manufacturer or system supplier can be of assistance in creating a spare parts database.

The technical application, design and construction of a system determine indirectly the selection of acceptable rubber materials.

Guidelines, specific operations and recommendations for maintenance of valve diaphragms can usually be sourced from valve manufacturers.

Chapter 5
Energy demand & cost savings potential of WFI and Pure Steam Systems

Cost savings potential

- Each set into operation mode → additional energy demand
- Pure Steam generator → Stop-and-go operation?
- Multieffect distillation → savings of cooling water
- Multieffect or Thermocompression distillation unit?
- Improvements in insulation for new systems / repairs during maintenance activities

Energy demand for production of Pure Steam

Assuming a 95% recovery and without consideration of heat losses:

$$\dot{Q} = 1,05 \cdot \dot{m} \cdot c_p \cdot \Delta T + \dot{m} \cdot h$$

- \dot{Q} - Energy demand
- \dot{m} - Pure Steam Mass
- c_p - Specific heat capacity of water
- ΔT - Temperature difference ($T_{\text{evaporation}} - T_{\text{feed water}}$)
- h - Evaporation enthalpy of water

- Energy demand is depending on energy source

When utilizing the steam condensate to preheat the feed water, savings on energy depending on the feed water temperature are possible.

$$\dot{Q} = \dot{m} \cdot c_p \cdot \Delta T$$

- \dot{Q} - Energy demand
- \dot{m} - Pure Steam Mass +5%
- c_p - Specific heat capacity of water
- ΔT - Temperature difference ($T_{\text{preheated water}} - T_{\text{feed water}}$)

Maximum theoretically possible energy savings by preheating of feed water up to boiling temperature at 3 bar pure steam pressure.

$$\dot{Q} = 105 \frac{\text{kg}}{\text{h}} \cdot 4,2 \frac{\text{kJ}}{\text{kg} \cdot \text{K}} \cdot (143,6 - 20) \text{K} + 100 \frac{\text{kg}}{\text{h}} \cdot 2133 \frac{\text{kJ}}{\text{kg}}$$

$$\dot{Q} = 74,4 \text{ kW}$$

$$\dot{Q} = 105 \frac{\text{kg}}{\text{h}} \cdot 4,2 \frac{\text{kJ}}{\text{kg} \cdot \text{K}} \cdot (143,6 - 20) \text{K}$$

$$\dot{Q} = 15,1 \text{ kW}$$

- This equals to energy savings of approx. 20%
- Depending on design of preheater
- Typical values range between 7-12%

Maximum theoretically possible energy savings by cooling waste water while preheating the feed water

Equals to energy savings of <1%

Savings potential in Pure Steam production

- Preheating of feed water with steam condensate; savings 7-12% of steam mass
- Preheating of feed water with waste water; savings <1% of heat energy

Energy demand for WFI production:

Multiple-effect Distillation Systems

Steam demand decreases with an increasing number of columns in the system in comparison to a single-effect system as shown below:

$$\dot{Q}_{HD} = \frac{I}{n}$$

$$\dot{Q}_{KW} = \dot{Q}_{HD} - \dot{Q}_{SW}$$

$\frac{\dot{Q}_{HD}}{n}$ - Heat Energy Demand
 n - Number of Effects

\dot{Q}_{KW} - Cooling Energy Demand
 \dot{Q}_{SW} - Energy absorption Feed Water

- The consumption of cooling water is reduced by increasing the number of columns in the system and the use of preheaters in between the individual steam stages or effects.
- The energy demand is independent of the type of evaporator

	<ul style="list-style-type: none"> ▪ The energy consumption is depending of the constructive realization of heat utilization (preheater) as well as the operation ▪ Optimization to a minimum steam or cooling water consumption respectively is possible ▪ Energy savings through performance control and subsequently less shutdown periods and water discharge <p>Savings potential in WFI production</p> <ul style="list-style-type: none"> ▪ Installation of preheaters in between the columns can lead to heating energy savings of up to 10% and a reduction in cooling water consumption of up to 50% ▪ Use of WFI distillation units with high recovery, reduction of cost for feed water treatment and waste discharge ▪ Use of an appropriate cooling medium, chilled water is not always necessary ▪ Use of Variable Frequency Drives (VFD) for feed water pumps and compressors ▪ Ideal system design to allow for shortest possible shutdown periods. Each procedure of setting the system in operation and shutting it down requires additional energy and time. <p>Operational cost or expenditure (OpEx)</p> <ul style="list-style-type: none"> ▪ Feed water treatment ▪ Energy for heating <ul style="list-style-type: none"> – Electrical Energy – Steam – Hot water ▪ Energy for cooling <ul style="list-style-type: none"> – River water – Chiller – Cooling tower – Closed cooling loop with air cooler (heat exchanger) ▪ Wastewater <p>With an increase in production rate and time, the savings in OpEx pay off and compensate for a higher investment (CapEx).</p>
<p>Chapter 6</p> <p>Energy Efficiency</p>	<p>Energy Efficiency</p> <p>System Design</p> <p>The energy consumption of a water purification system is already pre-defined in the system planning and design. The design is therefore of the essence for the consideration of the operational cost.</p> <p>To be able to design the system correctly it is important to know the demand of all users including the peak consumption. An over-sized system will always need more energy as normally would be required for the same purpose. The result will impact primarily the cost for stand-by periods.</p>

Consideration of cost for stand-by periods

If a system is designed with a safety margin that is too high, in other words the system capacity is too large, it will remain in stand-by-mode (no water or steam production) most of the time. The energy demand during these stand-by periods is of no value. Hence, a consideration of appropriate safety margins in the design is useful to eliminate unnecessary and inefficient stand-by times.

The cost for the stand-by operation mode of a system should be included in the calculation of the Opex cost (operational expenditure). If future expansion of the production or plant itself have already been considered, a modular design of the water/steam system can be more efficient rather than a system that is oversized to cover future demands from the beginning.

Optimization of stand-by cost in combination with the elimination of unnecessary safety margins in the design support a more efficient operation of a water purification system.

Water Purification – Feed Water / Waste Water

Increase in Reverse Osmosis efficiency

The Reverse Osmosis (RO) process has a central function in the state-of-the-art design of a water purification system for pharmaceutical waters. The RO can produce a high water quality with relatively low energy consumption. In comparison between distillation and RO, the energy demand of a RO-process and thus cost is a lot less than for the distillation system.

A downside of the RO is the continuous production of water that goes to drain. However, this concentrate flow to drain is essential for the process to avoid blockage of the membrane modules and maintain the operation of the RO. Therefore, care should be taken when considering an optimization of the RO by increasing the efficiency or recovery rate. The resulting cost savings can be marginal in comparison to the risk of a failing process. A reasonable approach to enhance the overall efficiency of a RO-system is to minimize the number of stand-by periods.

Proven hydraulic RO designs

Reverse Osmosis	Today	Target
Recovery	75%	90%
Waste water	25%	10%

Recovery is depending on:

- Feed water quality
- Desired Permeate quality
- Feed water temperature
- Investment cost (Capex)
- Stand-by – functionality

Stand-by - Functionality:

- Start / Stop (operation in intervals) to be avoided if possible
- Microbial safety

- Internal recirculation during times of no PW/WFI consumption recommended as an alternative (consider gradual heating of water during recirculation periods; cool down respectively or send water to drain)
- Start / Stop with additional process (CO₂, water to drain)
- Pump control down to 20-30% of full performance capacity
- Disinfect water with UV radiation during recirculation periods

Production unit vs. Storage tank

Tank level: A capacity reduction of the RO from 100% down to 70% can be programmed when tank level is at 50%. Consider though, that a reduction of the RO capacity and with that a reduced cross-flow on the membranes can lead to a higher risk of blockages (see above "Increase in Reverse Osmosis efficiency")

- Smaller RO capacity versus larger tank volume
- Intelligent control → Tank level to „Low“ prior to sterilization of distribution system (less volume to drain)

Distribution system

- Operation overnight → Loop in circulation mode with minimum pressure (Consider spray ball in loop return, if installed)
- Monitoring of turbulent flow can be indicated with the flow measurement
- Flow Measurement / Nominal value
- Reynolds number > 8000 (VDI 2083-13) in loop return
- Flow shall be turbulent at all times
- Storage temperature: hot
- Distillation feed into tank without cooling
- Loop return used to cool down loop supply (in regard to sub-loops of hot water main loops, in case the permanent flow in the sub-loop with cooled water should be necessary. In this case, the sub-loop return could cool down the sub-loop supply, by getting warmed up itself prior to the return into the hot main loop. Since both water qualities on both sides of the heat exchanger would be identical, a double tube sheet heat exchanger design is not critical and a less expensive plate and frame design can be considered alternatively.
- Minimum tank temperature with a nominal value of 75°C +/-5°C

Reduction of feed water flow

When in stand-by mode, the RO system recirculates the water usually and returns at least part of the permeate flow upstream the RO, so that cleaner water runs through the system. The objective of a system optimization can here be to minimize the use of fresh feed water during recirculation periods and rather return a maximum of permeate through the system. The advantage on the one hand is the operation of the RO with very pure

permeate water and much less salt content, while on the other hand the risk of microbial proliferation is increasing.

Utilize heat transfer from all possible sources

Most of the energy that is consumed in a water purification system is used for heating processes. Relative to hot water storage systems the largest energy demand is for heating the water and maintaining it hot. Therefore, the consideration of utilizing heat energy of all available sources offers a significant savings potential. A focus of interest should be laid upon existing heat sources in the system and how to use them most effectively. One example could be the condensate of Pure Steam. The energy of the condensate could be utilized to preheat the produced water prior to the final heating step to storage temperature. This reduces the ΔT and thus the required energy demand to heat the water to the final temperature. As a result, energy could be saved continuously during the process of heating the water up to storage temperature.

A challenge is to identify appropriate energy sources for heating or cooling applications in the system. A consistent realization of the concept leads to a Pinch- Analysis.

Pinch-Analysis

A Pinch Analysis is a method used for a systematic identification of heat sources and heat sinks as well as their integration into each other for as much as possible, with the objective to utilize energy that entered the process for as long as possible and maximize the reduction of external energy sources (and the related cost).

The Pinch Analysis is mostly used today in the manufacturing processes of plastics as well as in refineries. A prerequisite for a Pinch Analysis is a continuous process. Then there is a two-step execution of the analysis; first a schematic of the process shall visualize the heat flow and temperature level. Then, in a second step, the heating and cooling flows are combined in a pattern that allows for an optimal energy transfer of all heating and cooling processes. The result will then be a network of heat exchangers, which allows for the best and most efficient use of the energy within the system by also minimizing the required additional energy supply.

Possible heat sources and heat sinks in a system are:

- Condensate
- Drain of distillation
- Distillation unit itself
- Pure Steam generator
- Cooling system of clean room
- Pipeworks
- Tanks and vessels
- Nitrogen evaporator
- PW/HPW Feed Water
- Drinking water (hot tap)
- Ventilation / Air condition (HVAC) system
- Ventilation heater battery
- Ventilation cooler battery
- Air – exhaust and supply

System modernization

To be able to make a decision for modernization of a system, it is recommended to analyze the actual energy demand. In general, the replacement of individual components (for example: pumps) when necessary (failure of component) by modern ones with lower power/energy consumption is a reasonable approach.

There are no hard and fast rules about a large refurbishment of the system being more economical, since the actual energy demand of the individual systems is very different. This should rather be evaluated on a case-by-case basis. It is more reasonable, to implement the experience of the existing system(s) in new projects and start the planning and design by considering measures for enhanced energy efficiency.

System operation

This chapter is dealing with approaches to reduce energy consumption in existing pharmaceutical water systems.

Energy cost of a hot water system >50% of all utility cost

In pharmaceutical water systems with hot water storage and distribution, the energy consumption can be up to 50% of the overall cost for all utilities. This is by far the largest portion of cost for a single utility. Therefore, the decision which concept to use for the storage and distribution has a significant impact on OpEx.

Reduction

To change existing validated and qualified technical systems is critical. The following chapters discuss savings potentials of individual measures.

Flow and Pressure

The energy demand for transporting the water for example from storage in the tank to the use points is determined by flow and pressure. The required output can be calculated by multiplying flow with pressure. By also considering the operation time and the efficiency factor the energy demand can be finally defined.

The flow is partially defined by GMP recommendations. The flow profile shall be turbulent to reduce the risk of a biofilm formation on the pipe walls. The potential to optimize the flow lies in adjusting the right flow rate to support the demand at the use-points. Most common approaches are the velocity (for example: 1 m/s) or the Reynolds number for turbulent flow ($Re > 10000$). The water usage and its flow profile at the use-point is not defined or regulated in common industry guides and standards. However, a good Engineering Practice is to control the flow so that all parts of the ringmain and sub-loops do have flow.

The pressure in the system shall prevent environmental contamination. By applying excess pressure or a positive pressure in the system, the water flow is always directed towards the use-points. Hence, the pressure is an important parameter relative to the water system safety. At the same time, applying pressure continuously is a constant waste of energy, since the applied system pressure is finally completely destroyed when the water returns back into the storage tank. This continuous waste of energy is

calculated in the following example with a flow of 5 m³/h and a pressure of 4 bar (losses of efficiency factor not taken into consideration)

$$P = \dot{V} \cdot \Delta p = 5 \cdot 400000 \frac{\text{m}^3 \cdot \text{N}}{\text{h} \cdot \text{m}^2} \cdot \frac{\text{h}}{3600\text{s}} = 556\text{W}$$

$$E = 556\text{W} \cdot 24 \frac{\text{h}}{\text{d}} \cdot 365 \frac{\text{d}}{\text{a}} = 4866 \frac{\text{kWh}}{\text{a}}$$

Depending on the tariff for electricity, the operational cost would be around 500 EUR per year. This example shall emphasize the importance of an analysis of the planned measures prior to execution. A fundamentally good idea might not be economically the correct one at the same time. The example shown above proves that the change of the flow rate or the system pressure can result in savings of around 500EUR. Usually, savings in this range do not justify a re-qualification of the entire system. As a rule of thumb, the system pressure should not be designed higher than required for the operation.

Storage temperature

The temperature of the storage and distribution system is defined by the requirements at the point(s)-of-use. If the water is used for cleaning or application purposes at an elevated temperature, it is recommended to store and distribute hot water. In addition, this is a good control mechanism for microbial stability.

One often discussed approach is to lower the storage temperature by, for example, 10 °C. This would lead to less energy consumption for heating of the water that feeds the storage tank. Considering an example of 10.000 m³ pharmaceutical water per year and reducing the storage temperature by 10 °C (10 K), the savings potential could be:

$$E = 10000 \frac{\text{m}^3}{\text{a}} \cdot 1000 \frac{\text{kg}}{\text{m}^3} \cdot 4,19 \frac{\text{kJ}}{\text{kg} \cdot \text{K}} \cdot 10\text{K} = 4,18 \cdot 10^8 \frac{\text{kJ}}{\text{a}}$$

$$m_{\text{Dampf}} = \frac{E}{\Delta h_v} = \frac{4,18 \cdot 10^8 \text{kJ} \cdot \text{kg}}{1800 \text{kJ} \cdot \text{a}} = 232777 \frac{\text{kg}}{\text{a}} = 233\text{t}$$

The result would be a saving of 233 t of steam. Now it is depending on the price for steam, if this measure can be economically of interest.

Heat losses

The heat loss increases with the storage temperature, if this is much different from the environmental temperature. In case, the storage temperature is in equilibrium with the temperature of the environment, the system will have no losses. The actual heat losses depend on a variety of factors:

- Quality and thickness of insulation
- Total length of pipework
- Environmental temperature
- Flow velocity

All of the listed factors are very system-specific. Therefore, an example shall visualize potential savings by minimizing heat losses. Assuming a

temperature difference between loop supply and return could be reduced by 1°C, what would be the potential savings with a flow rate of 5 m³/h?

$$E = \frac{5\text{m}^3 \cdot 1000\text{kg} \cdot 4,19\text{kJ} \cdot 1\text{K} \cdot \text{h} \cdot 3600\text{s} \cdot 24\text{h} \cdot 365\text{d}}{\text{h} \cdot \text{m}^3 \cdot \text{kg} \cdot \text{K} \cdot 3600\text{s} \cdot \text{h} \cdot \text{d} \cdot \text{a}} = 1,835 \cdot 10^8 \frac{\text{kJ}}{\text{a}}$$

$$m_{\text{Dampf}} = \frac{1,835 \cdot 10^8 \text{kJ} \cdot \text{kg}}{1800\text{kJ} \cdot \text{a}} = 101957 \frac{\text{kg}}{\text{a}} = 102 \frac{\text{t}}{\text{a}}$$

The reduction of heat losses of 1 K would result in 102 t less steam per year.

A close relationship is also between heat losses and the required cooling of certain rooms. Usually, pharmaceutical water systems are located in selected technical rooms or areas. Depending on other equipment in the same room, it might be required to cool the room to a certain temperature. In this case, the heat loss of the plants is added to the energy demand to cool the room. Both do neither add value to the process nor the company. Therefore, care should be taken when selecting the appropriate location for a water system, since the cost for air conditioning can be significant.

Rooms for pharmaceutical water systems

It is common to install water systems in selected areas. Depending on the requirements, these rooms are classified to certain clean room classes and need to be air-conditioned. An alternative solution can be a technical area for the water system that requires neither clean room classification nor air-conditioning. However, in both situations heat losses are produced by the systems that are installed in these areas or rooms (Pure Steam Generators, Distillation skid, Storage Vessels, Heat Exchangers). These losses are either transported out of the room without being utilized properly or – even worse – are cooled against with a high energy demand and cost.

Instead a technical area is actually ideal for energy integration, since a continuous heat flow is present, unlike other pharmaceutical processes. The only disadvantage of the heat flow is that the temperature level (i.e. room temperature) is in the range of approximately 30-35°C (85-95°F) and thus rather low. A technical use of this heat loss seems impossible. This heat loss though, depending on the system size, can have significant value (>100 kW), so that an integration can be economically reasonable.

One opportunity for integration of this heat flow is the use of a thermal heat pump to increase the temperature level. The obtained heat energy could then be utilized in ventilation systems for example, since the required temperature level for a preheater does not need to be very high.

For the economic analysis it is important to know the heat loss/flow, the cost of operation of a thermal heat pump as well as the possible time of operation (summer / winter).

Insulation

Another option to reduce the heat loss is of course the use of insulation for piping and components of the water system. Many process systems do have weak points in their insulation, usually. For tanks it could be commonly the top of the vessel, on distillation skids it could be rather small gaps in the insulation, on a Pure Steam Generator it could be as well the

top of the Generator that is insufficiently insulated.

Besides this, also filter housings or other components of the system or skid could have a significant amount of gaps in their insulation. Here, solutions for a facilitated assembly and disassembly during maintenance activities should be evaluated.

As a best practice it is recommended to consider the insulation of the system during the planning and design phase. Later, during operation of the system care should be taken that the insulation will be installed correctly, especially after maintenance and service activities, which required its disassembly.

A focus for insulation should be the entire system, the storage vessels, distillation units and Pure Steam Generators.

Maintenance

- Periodic check of condensate traps (for example with ultrasonic waves)