Fritz Röder

GMP Series

Qualification of Pharma Water Supply Systems

Meeting the GMP Requirements for every Qualification Phase

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Excerpt from the GMP Compliance Adviser

Contents

Qualification of water supply systems

Here you will find answers to the following questions:
- Overview: How is the qualification of a water supply system organised?
- What requirements must the qualification of a water supply system meet?
- When can the water be used for the manufacture of medicinal products?
- What does a typical risk analysis involve?
- What do the qualification documents contain?
- How are warning and action limits determined?
- How is sampling organised and carried out during the qualification?

1 Introduction

Pharmaceutical water systems are used for a number of different applications by pharmaceutical manufacturers. These include, for example, the cleaning of various pieces of equipment, the generation of pure steam and the use of water as an ingredient for solid, semi-solid and liquid medicinal products. As a result, an pharmaceutical water system has a significant direct and indirect impact on the quality of the medicinal product which means that qualification is absolutely essential. For technical and inherent reasons, the qualification of a water supply system can be a lot more complex than for other system types. As a result, water treatment systems are also high-maintenance. In addition, the likely seasonal fluctuation in the quality of drinking water forces the operator to engage in extensive qualification activities.

The qualification is carried out formally in accordance with the model that is used for all other systems:
- design qualification (DQ)
- installation qualification (IQ)
- operational qualification (OQ)
- performance qualification (PQ)

Each phase of the qualification follows an approved plan in which the test points are specified. A report is created based on the plan, and the results of the tests carried out are entered in this report. The approved report completes the qualification phase.

For further information on qualification in general, please refer to Chapter 6 of the GMP Compliance Adviser. This chapter endeavours to address the specific aspects that need to be considered during the qualification of an pharmaceutical water system.

Qualification and commissioning

Only the GMP-related aspects of the water supply system require qualification. There are many other aspects of a water supply system that are not GMP-related, but must be tested nevertheless, e.g. compliance with the requirements of the machinery directive. This is done during commissioning. As can be seen in figure 1, qualification and commissioning are normally carried out simultaneously.

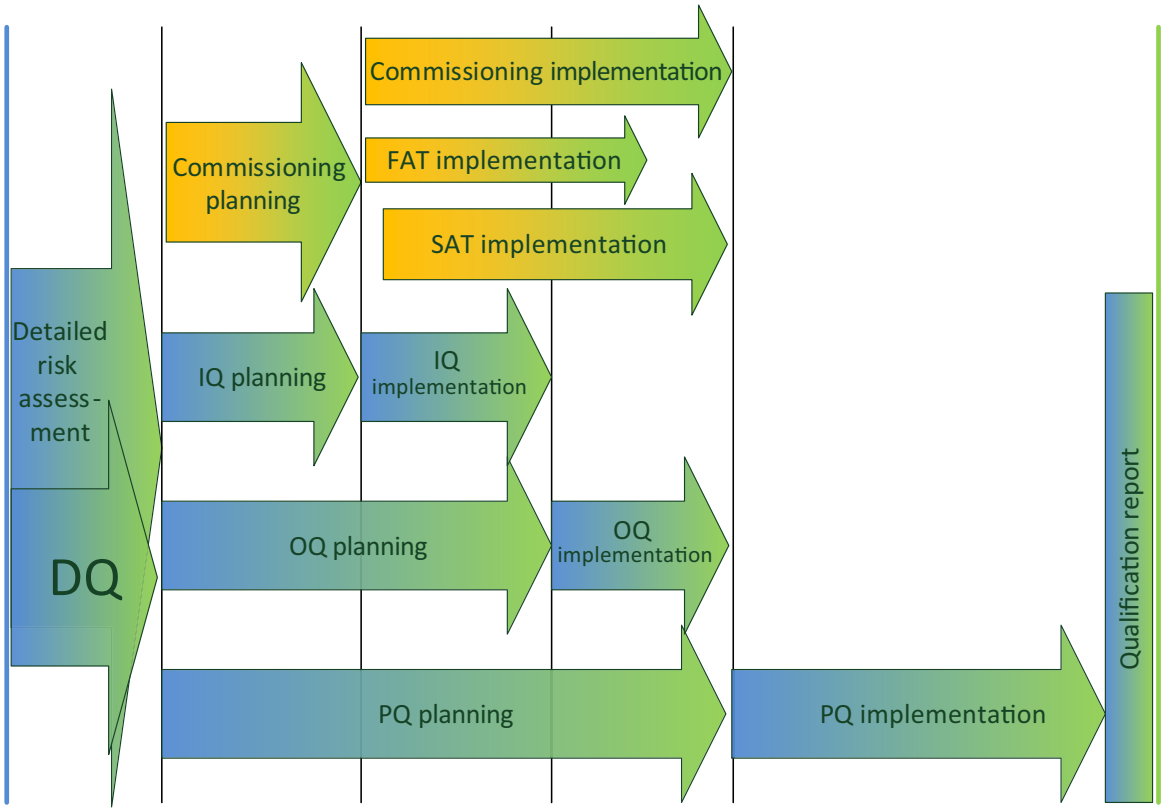

Figure 1 Overlapping of qualification/commissioning

In the schedule for the qualification of water supply systems, the planning and implementation of the different phases always overlap with commissioning activities that are not GMP-related.

Needless to say, commissioning and qualification activities are also carried out together, e.g. during the factory acceptance test (FAT). However, a clear correlation between the FAT and IQ and the SAT and OQ is not possible, as shown in figure 1.

Schedule and time required

A buffer should always be factored into the qualification schedule. Problems occur during every qualification that need resolving. This takes time. Even if the design of water treatment systems is now generally standardised and reproducible, special cases do occur in practice. At the end of the different phases of the *performance qualification/PQ* (see chapter 6 *Performance qualification (PQ)*), the results with regard to the quality of the water must always be acceptable. The microbiological aspects should be looked at most critically. The incubation period of the samples must be observed until a representative result is obtained. There can be no approved qualification report without acceptable microbiological results! The *performance qualification* is divided into three phases. When the first two phases have been successfully completed, the water can be used for pharmaceutical production.

Figure 2 contains an example for a project schedule.

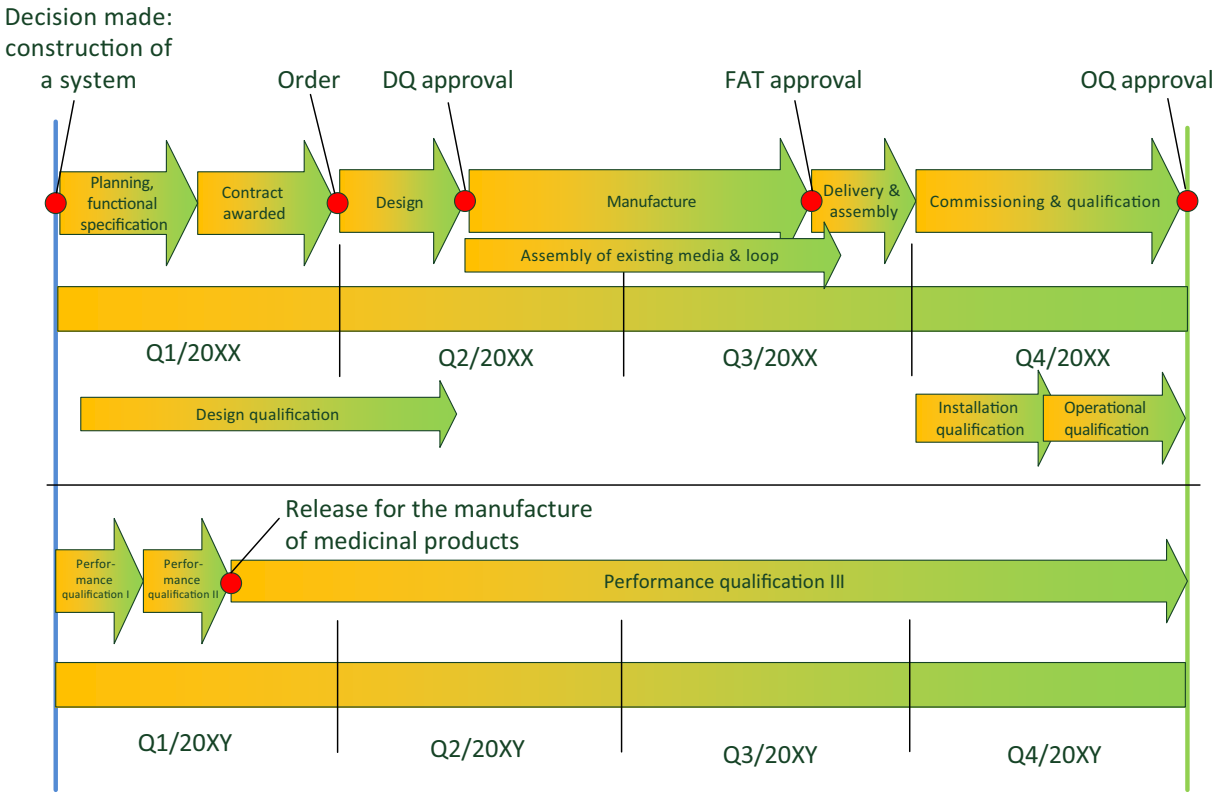

Figure 2 Sample schedule: construction and qualification of an pharmaceutical water system

Water qualities and their uses

A differentiation in water quality is generally made between "Purified Water" (PW), "Highly Purified Water" (HPW) and "Water for Injection" (WFI). The USP uses a number of further differentiations with regard to the quality of water, however, they are not discussed in this chapter.

The water quality required depends on the dosage form being manufactured and can be taken from the EMEA "Note for guidance on quality of water for pharmaceutical use". Purified Water is generally used for solid dosage forms (e.g. tablets, capsules) and semi-solid medicinal products (ointments). When manufacturing parenterals, the use of WFI is mandatory because the medicinal product is distributed in the bloodstream immediately after injection. The risk to the patient is therefore higher. HPW was introduced by the EU as an intermediate form and is subject to the same specifications with regard to constituents; however, the process to be used is not specified. The planned change to the EU monograph (0169) will mean that in future, WFI can also be produced using methods other than distillation, which would make the term HPW redundant.

Manufacture

The process of a PW system can be organised in the following way:

- Pre-filtration
- Softening
- Reverse osmosis
- Membrane degassing
- Electro-deionisation (EDI)
- Storage tank and distribution system

The technical documentation includes the elements listed in figure 5. The documentation is created and/or provided by the system manufacturer.

Technical documentation
Documents that should be included with the functional specification/available for the DQ • Lists of alarms, messages and automatic locks when the system fails • Functional flowchart and software documentation (source code) • Installation plan • Electrical plan • I&C list • Functional specification • Flow charts and process charts • Layouts and diagrams • List of instruments • Lists of parts and replacement parts • Functional descriptions • Operating instructions • Valve position matrix • Pipe network calculations/pipe network design plan • Channel layout plans

Documents that eventually become an integral part of the technical documentation
• Data sheets for individual components
• Material certificates
• Material specifications, treatment of pipe materials
• Calibration lists and calibration certificates, if applicable
• SOPs (standard operating procedures)
• System labels (e.g. CE marking, pressure tank documents)
• Welding seam documentation:
  • photos
  • endoscopy
  • isometry
  • welding equipment parameters
  • welding samples, if applicable
• Maintenance instructions
• List of all filters used with the respective proof of integrity
• List of sampling points including the installation location
• Maintenance documentation, maintenance procedures
• Training certificates
• Lists of interfaces

Figure 5 Elements of technical documentation

7 Sample documents

7.1 User requirements specification

SAMPLE PHARMA CO.	Functional specification Pharmaceutical water system	Page 1 of 2 Functional specification Pharmaceutical water system Date

Project description

A new state-of-the-art pharmaceutical water system is to be created. The system will have to meet the requirements of the current GMP guidelines. Because the medicinal products manufactured in the factory will be sold in the EU and in the USA, the EU GMP Guidelines and US cGMP regulations will apply.

The new system will be installed parallel to the existing system and must be qualified before being connected to the loop that already exists.

All work must be agreed with the contract giver because arrangements must be made in relation to construction and organisation with a view to keeping any negative impact on the manufacturing site to a minimum.

Installation location of the system
4th floor, room 4711.
The room is air conditioned all year round.
Target values in the room: temperature 18 to 22°C, humidity 30 to 60%.

Delivery
A crane will be used during delivery. This will be provided by the customer. Relevant information about the weight and centre of gravity should be provided by the contract acceptor in advance. System packaging, if there is any, must be removed before transporting the system by crane.
The smallest delivery dimension is W x H = 3000 x 3000 mm.

Available media connections
- Drinking water in accordance with the Drinking Water Regulations, flow pressure of 6 bar
- Black steam 8 bar OP, without additives
- Cooling water feed/return 6/12°C
- Compressed air 6 bar OP, quality in accordance with ISO 8573-1:
- Class 1 (oil and particle content)
- Class 3 (water content)
- Power/emergency power/UPS
- Network connection: TCP/IP

Requirements

Table 1: Product water specification

Parameter	Unit	Limit value USP	Limit value EP
Conductivity	µs/cm @ 25°C	<1.3	<5.1
Total microbial count	CFU/ml	<100	<100
TOC	ppb	<500	<500
Nitrate	ppm	n/a	<0.2
Heavy metals	ppm	n/a	<0.1

Figure 6 User requirements specification

7.3 Risk analysis (extract)

Failure Mode Effect and Criticality Analysis — Last revised: 22.09.2015

Project	New PW system	**Date**	**22.09.2015**	**System**	Pharmaceutical water system		
Contract giver	Sample Pharma Co.			**Documents**	Design documentation: flow chart, layout plans, electrical & I&C plans, process description; USP: <62>, <643>, <645>, <1231>, PW monograph; EP: 2.2.44 TOC, PW Monograph (0008); ISPE Guide Volume 4+5, GAMP 5, VDI 2083 Part 13; factory-specific instructions xy		
Responsible	**Project Manager**		**F. Röder**	**Participants**	J. Smith, P. Silie, P. Ingelig, L. Müller		
Project No.	xy						
	12345678						

S = severity; O = occurrence; D = detection; RPN = S x O x D; from an RPN ≥30 measures are necessary; rating scale 1–10

No.	Function	Fault	Cause	Effect on process or project	S1	O1	D1	RPN1	Action	Tracking	S2	O2	D2	RPN2
X01	Supply media	Feed water failure	Operator error, leakage, layout error, component failure	System stops, switches to standby; in the case of longer downtimes; risk of contamination; no production of pharmaceutical water	7	2	3	**42**	Monitoring of feed water flow rate; send a malfunction report; alarm and emergency concept	OQ	7	2	1	**14**
X02	Drinking water	Backflow of treated water or waste water into drinking water network	System separation is not sufficient; incorrect component fitted; insufficient distance between water supply line and waste water line	Microbial contamination of drinking water; feed water was in the medium-term not suitable for treatment	7	2	6	**84**	Fit a system separation in accordance with EN1717/EN806; check during qualification; monitoring of drinking water	IQ; PQ	7	1	4	**28**
X03	Treatment	Microbial contamination in softening system	Unfavourable flow conditions; feed water microbiologically contaminated (see R02)	Product water microbiologically contaminated; filters and membranes microbiologically contaminated; formation of biofilm in the system	10	5	6	**300**	Routine monitoring of treatment and feed water; periodic sanitisation	OQ; PQ	10	1	3	**30**
X04	Treatment	Conductivity after EDI increased	Fault in EDI system (e.g. resins, power supply, back pressure at the EDI cell)	Water cannot be used for manufacture and cleaning	8	3	6	**144**	Fit a conductivity measuring device; monitor power/voltage/pressure at EDI cell; define limits values with alarm messages; create an operation SOP; power/voltage maintenance standard; set as critical process parameter (CPP)	IQ; OQ; M/S	8	1	1	**8**
X05	Storage/distribution	Increased TOC in product water	Organic substances in water	Water cannot be used for manufacture and cleaning	8	4	8	**256**	Measurement of TOC level in return line of distribution system; online monitoring system in accordance with USP <643> and calibration + SST; regular sanitisation of the loop; defined as critical process parameter	IQ;OQ; M/S	8	1	3	**24**
X06	Operation	Formation of biofilm	Water is stored and distributed in an unfavourable temperature range; no regular sanitisation; microbial contamination at sampling location	Continuous microbial contamination of the water; cannot be used for manufacturing medicinal products; system in worst case totally out of order	8	5	8	**320**	Create a turbulent flow in the distribution system (check during OQ); monitor the temperature in the loop, determine warning and alarm limits; continuous cooling to below 20°C; creation of a sanitisation and monitoring plan; set as a CPP	IQ; OQ; PQ	8	1	3	**24**

Figure 8 Risk analysis (extract)

SAMPLE PHARMA CO.	Installation qualification Pharmaceutical water system Plan	Page 2 of 4 Installation qualification Pharmaceutical water system Date

Test No.	Risk No. from RA	Test description	Acceptance criterion
Installation check			
IQ06	X02	System separation	A system separator in accordance with EN1717 (e.g. a CA or BA model) is installed.
IQ07	X24	I/O checks – inputs and outputs	The I/O checks of the system's electrical connections correspond to the electronic documentation.
IQ08	X21 X51	Check for residual emptying	1. The pipelines were laid with a minimum gradient of 1%. 2. All of the installed components can be emptied completely.
IQ09	X37	Initial cleaning	1. The system was flushed after assembly and before commissioning. 2. A cleaning and flushing protocol is in place.
IQ10	X23	Check of the installation direction and location	1. This is correct for all components with a specified installation direction or location. • Check valves • Measurement of flow devices, water meters • Condensate separators • Conductivity measurement • Filtering unit • System separator • Pumps
IQ11	X41	Valve design	All of the valves are fitted in such a way that a non-critical state is achieved during a power failure.
IQ12	X50	Check 3d/6d rule	All stub lines comply with the 3d/6d rule.
IQ13	X64	Design of the sampling points	1. The sampling points are easy to reach. 2. The sampling points are +++flame-resistant, or at least easy to disinfect. 3. The sampling points all have a properly dimensioned output.
IQ14	X43	Vapour pressure	A vapour pressure measuring device is installed in the system's vapour feed.
IQ15	X28	Check of the pipe diameters	The pipe diameters were calculated and the pipelines installed according to the calculated values.
IQ16	X09	5µm filter	A 5µm filter was installed after the softener. The data sheet is available
IQ17	X10	Compressed air line fitted for membrane degassing	A particle and carbon filter as well as a flow monitor are fitted to the compressed air line for membrane degassing.

Figure 12 Installation qualification: Plan (cont.)

SAMPLE PHARMA CO.	Performance qualification (PQ) Pharmaceutical water system Plan	Page 4 of 6 Performance qualification Pharmaceutical water system Date

Table 1: Phase I and II sampling plan

Sampling valve	Location	Reference risk analysis	Sampling frequency	Mon.	Tues.	Wed.	Thur.	Fr.	Sat.	Sun.
V01	Feed water	X03 X04 X39	5 times per week	X	X	X	X	X		
V02	After softening	X05 X49	5 times per week	X	X	X	X	X		
V03	After RO	X48	5 times per week	X	X	X	X	X		
V04	After degassing	X48	5 times per week	X	X	X	X	X		
V05	Downstream of EDI	X48 X49	5 times per week	X	X	X	X	X		
V06	Feed line distribution	X16 X48 X49 X50	5 times per week	X	X	X	X	X		
V07	Return line distribution	X16 X48 X49 X50	5 times per week	X	X	X	X	X		
V08	Compound	X48 X50	5 times per week	X	X	X	X	X		
V09	Filling	X48 X50	5 times per week	X	X	X	X	X		
V10	Packaging	X48 X50	5 times per week	X	X	X	X	X		
V11	Wash room	X48 X50	5 times per week	X	X	X	X	X		
V12	Pure steam generator	X48 X50	5 times per week	X	X	X	X	X		

Figure 18 Performance qualification: Plan (cont.)

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Fritz Röder is a recognised expert in the area of water and ultrapure media technology. He also has extensive experience in GMP environments. He has worked in a number of different positions which has allowed him develop a deep understanding of the different perspectives in a company.

Mr Röder has worked in facility construction in procurement and as an operator, and knows the difficulties that can arise during the procurement of facilities. He is also an expert in the area of solid, semi-solid and liquid (sterile) dosage forms. Over recent years, he has been involved in several audits and inspections.

After completing his studies, Fritz Röder started working for a facility engineering company where he acquired the necessary technical knowledge and experience. Afterwards, he worked as a responsible operator and also in the procurement of all water systems for a medicinal product manufacturer for solid dosage forms.

He then took on a position at Bayer AG Grenzach where he managed various larger projects involving semi-solid and liquid sterile dosage forms and took part in an important FDA inspection.

From 2015 to 2017 he was engaged as a project leader at Allergan plc. Since June 2017 he is working as Senior Manager Validation, Qualification & Engineering at Merck KGaA, Darmstadt (Germany). Fritz Röder is a member of the ISPE D-A-CH[1] Expert Group "Water and Steam" and of the PDA (Parenteral Drug Association).

1. *Germany-Austria-Switzerland*

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