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GOOD PRACTICE GUIDE:

Critical Utilities GMP Compliance

How to Be Compliant and Ready to Prove It



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Preface

Because of their hidden nature, critical utility systems are vulnerable to noncompliance. With their potential to impact product quality or performance in a significant way, critical utilities consistently receive close scrutiny by regulatory inspectors. This ISPE Good Practice Guide: Critical Utilities GMP Compliance – How to Be Compliant and Ready to Prove It aims to assist pharmaceutical organizations achieve and maintain their critical utility systems in a state of control, and then efficiently demonstrate these systems' GMP compliance to regulatory inspectors and auditors.

It is not the goal of this Good Practice Guide to provide tips on how to pass an inspection; rather the intent is to provide guidance on achieving and maintaining compliance, and to be an aid to organizations when preparing the documents, personnel, and site logistics to help ensure inspections are efficiently conducted, making good use of the limited resources of regulators.

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1 Introduction

1.1 Overview

Regulatory compliance of Critical Utilities (CU) is important to maintaining overall facility compliance, but due to their hidden nature, CU can become vulnerable to noncompliance. CU consistently receive close scrutiny by inspectors primarily because of the level of associated risk to product. If contamination is present in the CU systems, the risk of product contamination increases significantly since in many cases, one or more of the following are true:

- Water from the CU is used as an excipient directly in product
- Compressed gas is used in direct contact with product
- Water and/or compressed gas are used in cleaning product-contact surfaces
- Clean steam is used in the sterilization of product or product-contact surfaces

Governmental inspectorates have been largely silent for decades on their specific expectations of users during an inspection of CU. An inspection guide was written by the FDA for high purity water systems in 1993 (Guide to Inspections of High Purity Water Systems [1]). This guide, although valuable in earlier years, has led to many discussions regarding non-contemporary water system designs and validation approaches, to name a few issues, and does not provide the depth of scope to prepare organizations for an inspection in today's pharmaceutical industry. In addition, there are no compliance or inspection guides issued by any inspectorate for other CU such as compressed gases or steam.

ISPE sees the need in the pharmaceutical industry for guidance in the CU area (specifically water, steam, and compressed gases) for achieving and maintaining GMP compliance, and for demonstrating that compliance during a regulatory inspection. This Good Practice Guide (GPG) is intended to fill that void by providing knowledge based on the collective experiences of the authors gained from operational and regulatory inspections. To make this Guide internationally useful, the authors have included information acquired from experience with the inspectorates of Brazil, Canada, China, the European Union, India, Japan, the United Kingdom, and the United States.

This GPG is not a regulatory document, and should not be interpreted to reflect inspectorate guidance. Additionally, it is not the goal of this GPG to provide tips on how to pass an inspection; rather the intent is to provide guidance on achieving and maintaining compliance, and to assist organizations in preparing the documents, personnel, and meeting rooms to help ensure inspections are efficiently conducted, making good use of the limited resources of regulators.

1.2 Purpose

The purpose of this GPG is twofold: to help pharmaceutical organizations achieve and maintain their CU systems in a state of control and to help organizations efficiently demonstrate these systems' GMP compliance to auditors and regulatory inspectors. By making inspections more efficient, our hope is that regulators' limited resources will be deployed more widely, resulting in enhanced patient safety.

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1.3 Scope

CU systems are utilities with the potential to impact product quality or performance in a significant way. The primary CU discussed in this GPG is the water system, as it is highly complex and prone to noncompliance. (Appendix 1 contains examples of typical regulatory citations specific to water systems.) The other utilities covered are Pure Steam, compressed air, and compressed medical gases.

This GPG provides an overview of the processes and documentation needed to implement and maintain a validated utility system, for example, assessing the risks of upstream noncritical parameters (Section 3.3), the value of proactively scheduling water system sanitizations (Section 4.2), and determining a suitable statistical distribution model for monitoring water system data (Section 4.5). Furthermore, Chapter 5 discusses the challenges of legacy water systems.

Topics such as the importance of maintaining up-to-date system drawings (Section 3.4) and sampling water in the same manner as water use during manufacturing (Appendix 3) provide inspection preparation activities specific to CU systems. Also included in this GPG are broadly applicable best practices, such as inspection hosting and an inspection readiness checklist (Appendix 2). These are presented here to make the GPG comprehensive, since they are not covered in other ISPE Guides. However, activities pertaining to CU inspections described in depth by other ISPE Guides (such as the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification* [2], and the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* [3]) are discussed at a higher level in this GPG. The objective of this redundancy is to make this GPG as stand-alone as possible without sending the user searching to find other GPGs with the critical content needed during preparation for an inspection.

It is worth noting that compliance begins with properly engineered systems; however other ISPE Guides fully cover this aspect. As such, this GPG does not address the design of CU systems, but serves as a companion document to these ISPE Guides (for example, *ISPE Baseline® Guide: Volume 4 – Water and Steam Systems* [4]).

Although HVAC is considered by many to be a CU, it is not included in this GPG. Such systems are often considered to be an integral part of clean room operations and subject to additional quality attributes and operational issues, and so tend to be associated with inspections of aseptic processing operations rather than CU. In addition, media supply systems are normally considered as an excipient (except compressed air for oral solid dosage forms manufacturing), but HVAC systems are not. Thus, the viewpoint when inspecting HVAC systems is different compared to the CU systems mentioned in this Guide.

1.4 Key Terms

This section introduces key terms as they are used in the context of this Guide. Refer to Appendix 7 for an expanded listing of definitions.

Critical Utilities (CU)

Utilities that have the identified potential to impact product quality or performance in a significant way.

Deviation (ICH Q7 [5])

Departure from an approved instruction or established standard.

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Drinking Water

Drinking water is not covered by a compendial monograph but must comply with the quality attributes of the US EPA NPDWR[1] [6] or comparable regulations of the European Union (EU) [7], World Health Organization (WHO) [8], or Japan [9]. It may be derived from a variety of sources including a public water utility, a private water supply (e.g., a well), or a combination of more than one of these sources.

Medical Gases (FDA [10, 11])

> *"Compressed medical gases (CMG or medical gases) include gaseous and liquid (cryogenic) forms stored in high-pressure cylinders that are administered as a gas. Types of compressed medical gases include, but are not limited to, oxygen, carbon dioxide, helium, nitrogen, nitrous oxide, medical air, and combinations of these gases."*

> *"The term 'medical gas' means a drug that— (A) is manufactured or stored in a liquefied, nonliquefied, or cryogenic state; and (B) is administered as a gas."*

Potable Water

Water that is suitable for drinking.

Pure Steam

Steam that is produced by a steam generator which, when condensed, meets requirements for Water for Injection (WFI).

Purified Water (PW)

A classification of water according to compendial standards.

Water for Injection (WFI)

As defined in the US Pharmacopeia (USP) [12]

> *"Prepared from water complying with the quality attributes of "Drinking Water." Purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms."*

As defined in European Pharmacopoeia (Ph. Eur.) [13]

> *"Water for the preparation of medicines for parenteral administration when water is used as a vehicle (WFI in bulk) and for dissolving or diluting substances or preparations for parenteral administration (sterilized Water for Injection)."*

[1] EPA NPDWR: US Environmental Protection Agency National Primary Drinking Water Regulations

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2 Critical Utilities Viewed from a Regulatory Perspective

A Critical Utility (CU) is defined by ISPE [14] as: "Utility that has the identified potential to impact product quality or performance in a significant way." This GPG focuses on water systems (specifically PW, WFI, and Pure Steam); however it is relevant to also address some of the systems/utilities that feed water systems, specifically potable water and pretreated water, as these grades of water are important to overall compliance. Process gases are touched on in this Guide as well, albeit to a lesser extent as they typically do not present the same degree of difficulty in maintaining compliance.

CUs are special in that they can be considered a raw material, and therefore are subject to GxP requirements. However, with the continuous generation and distribution of water and steam, and the constant availability of compressed gases including air, it is not feasible to take the traditional approach of identifying these materials by a discrete lot number, testing the lot, and releasing for production. Continuously produced utilities are typically used before all results are available.

Additionally, since these CU have a broad impact across multiple products and processes at a manufacturing site, they are considered to entail a significantly higher risk to product quality and subsequently, to patient safety.

For these reasons, regulatory scrutiny of CU systems often includes more elements of the quality system that address monitoring, control, maintenance, and calibration than is seen for a noncritical utility system.

2.1 Drinking/Potable Water

Drinking water, also referred to as potable water, must comply with appropriate regulatory requirements (such as defined by US EPA [6], WHO [8], etc.) and is the minimum quality of water to be used in pharmaceutical manufacturing (i.e., various pharmacopeias, and GMPs found in the FDA 21 CFR Parts 210 [15] and 211 [16], and elsewhere[2]).

Since this is the only specifically mentioned water in the GMP regulations, it is clearly important to regulatory authorities that a lower quality of water not be used in pharmaceutical manufacturing and that the users have taken steps to ensure that a lower, potentially unsafe quality of water is not inadvertently utilized. This puts the burden of proof on the users of this water to ensure the quality meets minimum requirements and is suitable for its intended use.

2.1.1 Minimum Water Purity Requirements for API and Finished Product Manufacturing

According to ICH Q7 [5], the minimum water quality to be used for API manufacture and in the pharmaceutical facility in general, is water that complies with WHO Guidelines for Drinking-Water Quality[3] [8].

Depending on the nature of the API processing and its final microbial and chemical attributes, water of a purity level higher than potable quality may be needed. This is particularly important in the latter stages of synthesis or purification, where removal of impurities introduced with the water may not be accomplished by these final API processing steps [5].

[2] Note that at the time of this writing, the EMA document "Guideline on the quality of water for pharmaceutical use" [17] is pending implementation.
[3] Although the attributes specified in WHO Guidelines for Drinking-Water Quality are considered goals and not necessarily mandatory for human consumption, compliance with all attributes is mandatory when used in API manufacture as well as for general pharmaceutical uses [5].

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Most pharmacopeias require the minimum water quality used for API and excipient manufacture to be potable or drinking water. USP General Notices Section 8.230.20 states[4] [12]:

> *"When used in the manufacture of official substances, water shall meet the requirements for drinking water as set forth in the U.S. Environmental Protection Agency National Primary Drinking Water Regulations (NPDWR) or in the drinking water regulations of the European Union or of Japan, or in the World Health Organization's Guidelines for Drinking Water Quality. Additional specifications may be required in monographs."*

This means that if a pharmaceutical manufacturer is in a jurisdiction other than the US, a member state of the EU, or Japan, the drinking water quality used in manufacturing must comply with the one of these jurisdictions' drinking water regulations or WHO drinking water guidelines [8]. Compliance with a different jurisdiction's drinking water regulations, if not one of those four, is irrelevant to USP as well as FDA.

The Ph. Eur. [13] defines the minimum quality of water for use in API manufacture as:

> *"complies with the regulations on water intended for human consumption laid down by the competent authority."*

Ph. Eur. does not explain who a competent authority is; however, it is understood to be the national entity in charge of the subject. It is the manufacturer's responsibility to identify the applicable drinking water regulations of the country in which the product will be marketed and ensure that the drinking water used in manufacturing meets those requirements.

2.1.2 Source Water for Purification Systems

Another important use of drinking water is as source water for an on-site purification system that produces compendial grades of water, such as PW or WFI. When starting with one of the pharmacopeial drinking waters, all unsafe levels of impurities have theoretically been removed. So unless there is a possibility that these impurities could be reintroduced into the water, there is no need to test for their absence in the further purified water. Instead, for finished water (i.e., PW or WFI), general non-specific tests for ionic and organic impurities, that is, Conductivity and Total Organic Carbon (TOC), can be used to broadly define the finished water quality; however, several jurisdictions mandate additional tests (see Appendix 4). It is noteworthy that the microbial content of the water undergoing purification is also monitored, and, depending on the treatments selected, it may be that the levels of culturable bacteria in the non-compendial pretreatment water increase due to certain unit operations, and that this is acceptable.

2.1.3 Source Water Compliance Standards

Similarly to the water requirements described for APIs in USP General Notices, the USP [12] monographs for PW, WFI, and Pure Steam specify using one of the same four regional drinking water specification sets as the source water.

In Europe [13] and Japan [18], a globally accepted source water quality for purification into PW is WHO Drinking Water [8]. However some pharmacopeia require that PW is used to supply the final purification step that generates WFI. (See Appendix 4 for the requirements of the major pharmacopeias.)

2.1.4 Public Water Compliance

When a public drinking water source is used, the responsibility for complying with the drinking water regulations of the region usually falls to the drinking water provider. However, it remains the user's responsibility to ensure that compliance of all drinking water attributes has been achieved for water used at the pharmaceutical facility; this responsibility includes year-round verification as there may be seasonal variability in water supply quality.

[4] "Official substances" is USP's [12] term for monographed drug substances [APIs], excipients, dietary ingredients, other ingredients, or a component of a finished device and other finished product ingredients.

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2.1.4.1 Public Water Provider Certification and Verification

ICH Q7 [5] requires identity testing on manufacturing materials in most cases:

> *"At least one test to verify the identity of each batch of material should be conducted….A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers."*

According to the GMPs, a certificate of compliance for any raw material should never be accepted without verification of authenticity and accuracy. That verification may involve an audit of the facility to view operations and the raw data associated with the certification, with organizations checking some attributes with their own testing. These rules apply to any public drinking water provider including local, regional, or other drinking water authority. If the local water provider refuses to allow a site visit/audit, then the level of risk is potentially increased and the level of monitoring by the organization should increase to compensate.

Also, drinking water compliance applies primarily to the water at the source, prior to entering the delivery piping network. Water may travel great distances during an extended period through piping of unknown integrity resulting in reduced quality at the destination.

It is the user's responsibility to verify that any provided certification of compliance with drinking water regulations is accurate. Therefore, it may be appropriate for the pharmaceutical facility to periodically verify the drinking water's compliance. This includes sampling the drinking water at the manufacturer's site in one or more locations to verify that quality criteria are being met. The number of locations and frequency of sampling should be determined based on a risk assessment.

Not all quality attributes in a set of drinking water regulations are required to be tested annually nor with every sample, particularly where a history of compliance has been demonstrated by the manufacturing firm through analysis of the incoming supply water. The selection of parameters for testing should be based on a combination of risk assessment and the drinking water regulations applied to the manufacturing site. It may be appropriate during a drinking water compliance audit of a water authority's facility and its testing data to observe consecutive years of historical testing data in order to confirm that all attributes have been tested at least at the required frequency.

2.1.4.2 Absence of Reliable Certification or Use of a Private Water Source

There are scenarios where a pharmaceutical facility may have its own private water source for use in manufacturing and further purification. There may also be instances where the documentation supporting a drinking water provider's certification of compliance is absent, incomplete, untrustworthy, or not one of the acceptable standards. In these scenarios, the pharmaceutical facility is responsible for demonstrating compliance to an acceptable set of drinking water regulations.

The potential for variability, or when variability has been demonstrated, in drinking water quality in these situations is a factor in how often testing should be performed. Minimally, during the first year of source testing, the robustness of the supplied water and any treatment needed to bring the source water into compliance should be performed multiple times (e.g., quarterly or monthly, depending on the risk assessment of the water supply) until such time as the quality variability is discerned. Thereafter, an appropriate sampling frequency depends on a further risk analysis. For example, in a situation with a high-risk water supply, the first year may include weekly water sampling. If all data is acceptable, in the second year sampling frequency may be reduced to monthly, and if results are good, may be reduced to quarterly in the third year. However, in a jurisdiction where a manufacturer has existing operations fed from the same water supply with consistently good quality, reduced sampling frequency may occur much more rapidly.

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2.1.4.3 Source Water Pretreatment and Sampling Location

It may be necessary to treat the water in order to comply with the drinking water standards. The nature of that treatment depends on the nature of the noncompliance in the source water. Ideally, compliance with the selected drinking water regulations should be shown with the water entering the purification system. However, it is generally acceptably compliant to obtain samples taken from as far into the water system as the furthest Point of Use (POU); however, sampling may be required at other locations that are deemed high risk due to infrequent usage, or due to the nature of the use of the water dispensed. It is noteworthy that in large facilities there may be branches (not recirculating) of potable water that see infrequent use and could be prone to microbial contamination if not regularly flushed. If there are secondary storage tanks for potable water with their own distribution networks, this risk then increases, and sampling from the POU of these systems should be done.

2.2 Compendial Water Pretreatment

The term pretreatment typically indicates unit operations chosen to prepare drinking water for conversion to a higher quality by a primary treatment method. Pretreatment most often is used to either reduce the contaminant load on primary treatment equipment or to extend the interval between equipment servicing.

Hence, pretreated water is not required to meet drinking water nor PW chemical or microbial standards; it is simply an interim quality that allows for primary treatment equipment to operate under less demanding conditions and at reduced operational costs. Pretreatment is significantly less costly to operate than primary treatment equipment and extends the time between service events for the primary treatment components. Pretreatment systems must receive a similar level of care as compendial systems proper in terms of their maintenance (leaks or other dysfunctions) as they are an integral part of the overall treatment. From a compliance perspective, a poorly maintained pretreatment system is a poorly maintained compendial water treatment system.

Pretreatment systems that are not properly maintained may force primary treatment components to bear the additional load resulting in greater downtime, unscheduled outages, and increased cost. Each type of unit operation selected for use as pretreatment requires Preventive Maintenance (PM) and possibly routine service specific to its function.

For example, softeners typically need maintenance at a minimum annually for proper operation; however, depending on the water quality and age of the system may require more frequent maintenance. Nonetheless, in addition to regular maintenance, softeners need constant monitoring of salt used for regeneration, often needing additional salt every few days. Failure to maintain salt levels could result in hardness fouling a downstream Reverse Osmosis (RO) system and an unplanned outage.

The pretreatment system water may not meet the requirements of drinking water, but in order for the system to be GMP compliant, it should be operated in a state of control; that is, parameters are maintained within specified ranges. The nature of the parameters to be monitored depends on the technologies deployed in the pretreatment (e.g., hardness testing to verify softener performance).

Proper maintenance and operation of pretreatment equipment help to ensure optimal overall system operation, and help to reduce events that could jeopardize the compliance of the system.

2.3 Purified Water

2.3.1 General

PW is normally used in cleaning operations as well as in the manufacture of APIs, oral solutions, topicals, oral solid dosage products, and medical devices. In most of these cases, PW is a raw material that requires testing to demonstrate quality and compliance.

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2.3.2 Applicable Requirements

PW, as defined by compendial monographs, requires compliance with specifications for chemical and microbial quality. Chemical quality requirements are defined by conductivity and TOC specifications. Microbial quality requirements for PW are usually defined in published standards. Several pharmacopeias specify a variety of other parameters, which are summarized in Appendix 4.

2.4 Water for Injection

2.4.1 General

WFI is typically used in cleaning operations, and in the manufacture of inhaled products and injectable products. It is a raw material, and therefore requires adequate testing to demonstrate quality and compliance.

2.4.2 Applicable Requirements

WFI, as defined by compendial monographs, requires compliance with specifications for chemical and microbial quality. Chemical quality requirements are defined by conductivity and TOC specifications. Microbial requirements for WFI are usually defined in published standards. Endotoxin limits are also applicable to WFI. Appendix 4 summarizes the requirements for most of the major pharmacopeias.

WFI is the product of drinking water that has been pretreated and primary treated to meet the final required chemical and microbial specifications. There is inconsistency worldwide about the allowed treatment techniques and the water that may be used as the feed water to a WFI generation process. Europe [13], North America [12], and Japan [18] allow for the use of non-distillation based techniques for the generation of WFI, and for the use of potable water as the starting material. The Chinese Pharmacopoeia [19] specifies that distillation must be used with PW as the starting material, but is currently considering allowing generation techniques other than distillation.

2.5 Pure Steam

2.5.1 General

Steam is classified as Pure Steam when it is intended to be used for direct and indirect product contact, for sterilization of product or material, or for sanitization of surfaces.

2.5.2 Applicable Requirements

Pure Steam should meet the requirements of the applicable pharmacopeia (i.e., USP [12], Ph. Eur. [13]).

Many pharmacopeias do not include a Pure Steam monograph; therefore, often the relevant WFI monograph specifications are applied. These are, for instance, the requirements for the feed water, a built-in component to retain droplets, and the required test parameters for WFI that may be tested on the Pure Steam condensate. Due to the lethality of Pure Steam, culturing of microbial samples is not required, although endotoxin testing is required.

Pharmacopeias may not define certain parameters such as steam saturation, dryness, and non-condensable gases; however, guidance is provided by the EN285 [20] and the British HTM 01-01 Part C [21] standards. It is recommended to conduct a risk analysis that includes specifics related to these qualities. EN285 may support a decision as to whether or not these parameters are applicable, and to define limits and test procedures.

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The testing for steam quality is most often done at the POU to an autoclave unit and requires specialized test elbows and equipment. If future quality testing is likely, considerations during the design phase should be made to provide the necessary spool pieces.

2.6 Clean Compressed Air

2.6.1 General

Compressed air intended for use in product-impact applications include:

- Steam sterilizer overpressure
- Pressure equilibration after steam sanitization of piping and equipment
- Transfer of product
- Blow down of equipment after clean in place/steam in place for drying
- Air supply to fermenters

In addition, compressed air is used whenever there is air contact with a product-contact surface not cleaned in a subsequent operation, and in all classified manufacturing space into which the process compressed air is exhausted.

Compressed air may be obtained in cylinders based on volume needs, although it is typically produced on site using compressors. This puts it into a category different than most other gases and justifies its description separate from other gases.

2.6.2 Applications

Some pharmacopeias include monographs for medical air. Standards such as “breathing air” (for example, the NFPA 99 Standard [22]) are available. ISO 8573 [23] is sometimes employed by manufacturers as a standard.

In most cases medical grade gases are not required in pharmaceutical manufacturing since medical gases and breathing gases are typically intended for direct use by people or animals. The gene and cell therapy medicines industry along with biotechnology manufacturing utilize medical gases and process air for product contact.

When used in a pharmaceutical process with direct product contact, the purity requirements should be based on product and process needs. These product requirements are usually defined in the manufacturer’s regulatory filings.

When applicable, preparation of a risk analysis is prudent.

It is generally accepted that a critical quality parameter for clean compressed air is the dew point/relative humidity with the expectation that the level of humidity in the air will be non-condensable in the temperature ranges to which the compressed air piping is exposed. Maintaining dryness essentially eliminates the possibility for microbial growth since without water, bacteria are not able to reproduce.

In addition, requirements applied to environmental air can be used to support decisions documented in the risk analysis. This is especially true in cases where the air is used and exhausted within a classified space. As such, a reason for the decision on the maximum allowed amount of particles or microbes in the compressed air may be based on Table 2.1.

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Table 2.1: Clean Room and Clean Air Device Classification
(Adapted from EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 1 "Manufacture of Sterile Medicinal Products" [24])

Classification	Nonoperational		Operational		
	Maximum permitted number of particles of tabulated size/m^3				Maximum allowed amount of viable microbes/m^3
Grade	≥ 0.5 µm	≥ 5.0 µm	≥ 0.5 µm	≥ 5.0 µm	
A	3 520	20	3 520	20	<1
B	3 520	29	352 000	2 900	10
C	352 000	2 900	3 520 000	29 000	100
D	3 520 000	29 000	*	*	200
*Annex 1 does not have limits defined for these cases; nevertheless, it is recommended to determine limits according to respective working procedures.					

A risk analysis should consider the need for POU filters or decentralized filters for each production room, whether the use of an oiler or other equipment necessitates the need for backflow prevention, and if air should be exhausted from the room.

To adequately address compliance it may be necessary, confirmed by risk analysis, to monitor and record important parameters from properly defined sampling points using proper equipment, such as instruments to measure particles, humidity, oil, and temperature, as well as a system and procedure to test for microbes. Often the limits in ISO 8573 [23] are applied for humidity and oil content testing.

It is ultimately the responsibility of the user to determine the needs for their product and situations. This should consider and document the requirements of the product and appropriate and applicable regulatory requirements respective limits and tests as necessary.

During the risk analysis, it may be appropriate to evaluate the origin of the compressed air, how it is produced, why compressed air is being used, critical characteristics/quality of the compressed air and why they have been defined (as applicable), which parameters will be tested and why, where filters are installed in the system, which parameters to control, precision of instruments, redundancy of measurements, recording of data, etc.

2.7 Process Gases

2.7.1 General

High purity gases intended for product-impact applications (except clean compressed air) include nitrogen, oxygen, carbon dioxide, and other suitable gases, or combinations of these gases. Often, compressed or liquid gases (e.g., nitrogen, oxygen) are delivered by external manufacturers. Bulk high purity gas supply systems may be equipped with backup bottles for critical uses. Care should be taken when automating these backup systems so that the manufacturer is notified (for example, an alarm is triggered) when the backup bottles have been engaged/used. In such an event, the batch production record should indicate the use of the bottles. Bottles should receive a similar level of scrutiny as other raw materials.

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Common applications for these gases are:

- Blow down for drying pipes and equipment
- Tank sparging (including fermentation and cell culture)
- Incubation
- Tank blanketing and transfer overpressure

Many points mentioned in Section 2.6 for clean compressed air also apply to other gases wherever there is direct product contact (including containers and closures) or contact with a product-contact surface not cleaned in a subsequent operation, and in all classified manufacturing space into which the process compressed air is exhausted. The gene and cell therapy medicines industry along with biotechnology manufacturing utilize medical gases and process air for product contact.

2.7.2 Applicable Requirements

Some pharmacopeias include monographs for medical gases, such as the USP [12] and Ph. Eur. [13], however, the test parameters and limits given in these monographs are intended for gases for use in patients. This is normally the application with the most stringent requirements. See Table 2.2.

Table 2.2: USP [12] or Ph. Eur. [13] Specifications for Oxygen, Nitrogen, and Carbon Dioxide

Test	Oxygen	Nitrogen
	Specifications	
Purity	99% weight/ volume (w/v) O_2	99% w/v N_2
Carbon Dioxide	≤ 0.03%	--
Oxygen	--	≤ 20 ppm
Carbon Monoxide	≤ 0.001% (10 ppm)	≤ 0.001% (10 ppm)
Odor	None Detected	None Detected
w/v: Weight/Volume NMT: Not More Than		

Test	Carbon Dioxide
	Specifications
Purity	99% w/v CO_2
Water	≤ 150 mg/m^3
Ammonia	≤ 0.0025%
Hydrogen Sulfide	≤ 1 ppm
Nitric Oxide	≤ 2.5 ppm
Carbon Monoxide	NMT 0.001% (10 ppm)
Nitrogen Dioxide	≤ 2.5 ppm
Sulfur Dioxide	≤ 5 ppm
Odor	None Detected
w/v: Weight/Volume NMT: Not More Than	

If these gases are intended to be used during a pharmaceutical process such as tank sparging, the compendial requirements may not apply completely. In specific applications (such as nitrogen in API production produced using pressure swing adsorbers) purity requirements may be relaxed based on the needs of the process. A documented rationale should be provided for the parameter limits selected.

Suppliers of gases used in processes should be governed by quality agreements, and included in the organization's supplier qualification and supplier audit programs.

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Gas bottles should be traceable, with the necessary documentation and labeling[5] provided by the vendor.

It is ultimately the responsibility of the user to determine the needs relative to their product and situation. This should be based on a risk analysis considering the requirements of the product and applicable regulatory requirements, and including respective limits and tests as necessary.

During the risk analysis, it is recommended to evaluate:

- The origin of the medical gas
- How it is produced (its source)
- Why the particular gas is being used
- What the critical characteristics/quality of the gas are and why they have been defined (as applicable)
- Where filters are installed in the system
- Which parameters will be tested and why
- Which parameters will be controlled
- What instrument precision is needed
- How the redundancy of measurements will be achieved
- How data will be recorded

Additional points to consider are:

- Monitoring requirements and frequency for process gases, which should be appropriate for the products/processes that they are used to support
- Definition and rationale for managing Out of Specification (OOS) results of any of the monitored parameters
- Definition and rationale of how and when filters are to be replaced

[5] Purchased gases should have an identification number, a material specification, vendor certificates, and should be supported by audit data and receipt testing.

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3 Validation Lifecycle and Quality Systems

This chapter outlines the elements required to maintain the CU systems in a continually validated state, and the requirements of the quality systems to support this validated state. These elements are often reviewed by an auditor during regulatory inspections.

3.1 Validation

The topic of validation is well addressed through both the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification* [2], and the *ISPE Good Practice Guide: Approaches to Commissioning and Qualification of Pharmaceutical Water and Steam Systems* [25].

Within the context of this *ISPE Good Practice Guide: Critical Utilities GMP Compliance,* validation documents should be presented to address the request or question specifically. They should show integration with the required elements, including risk assessment, drawings, change control, and calibration and PM programs, to demonstrate that the validated state of this system is controlled and maintained through these ongoing quality processes.

Fundamentally, the presentation of CU validations in an inspection should demonstrate the assessment of risk to establish the validation scope and sampling plans, qualification of the equipment included within the scope, and documented verification of system performance to predetermined acceptance criteria when operated using approved procedures and materials within normal operating conditions. Variables and sampling plans to consider during the validation are derived from the risk analysis and documented in the validation protocol and report. Verification of calibration, PM, document and drawing change control, and equipment change control should be in place prior to the closure of validation to maintain the validated state going forward.

Validation efforts should always be presented with the linkages to these systems in mind so that as an inspector moves through a validation, the anticipated supporting systems described above are also available for review.

While most regulators have not codified what constitutes the requirements for commissioning, qualification, and performance/process validation, enough best practice documents and regulatory guidances exist to establish basic rules for the validation process of CU. Typically in CU, some aspects of the design are commissioned through Factory Acceptance Testing (FAT) and/or Site Acceptance Testing (SAT), or drawing walk downs of installed piping. All other testing is done using Installation and/or Operational Qualification Protocols (IQP, OQP, and/or IOQP), and where required, Performance Qualification Protocols (PQP).

Any new CU installation or significant modification should begin with a validation plan and end with a detailed validation summary report accompanied by a requirements traceability matrix.

3.1.1 Validation Plans for Critical Utilities

The validation plan should describe the system and incorporate a risk assessment process based on product quality.[6] It should lay out what activities will be performed in each stage of testing: commissioning, qualification, and performance/process validation. The intended use of the CU should be clearly defined, so that an auditor reviewing the validation plan can formulate what minimally should be tested. Where the CU installation or modification is part of a larger design or site modification, it may be advantageous to develop a sub-plan for certain CU, such as PW, WFI, or process gas systems in the validation plan. This sub-plan or project plan is desirable because often at the time of initial design, the role of suppliers and supplier documentation in the validation of PW or WFI systems is not known. A sub-plan can prevent the need to completely remodel the more encompassing validation plan, and can provide an abridged package that can be presented to an auditor.

[6] This is outlined in the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification* [2].

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Approval of the validation plan's acceptability should be obtained from the system users' management. Typically, these approvers are production/packaging operations, laboratory management, Engineering, Automation/IT, and the site Quality Management representative.

The plan should describe how commissioning documentation will be used, as well as what testing data will be leveraged from FATs and SATs. Leveraging vendor FAT and SAT documentation decreases the build-to-in-operation time.

The validation plan should define the system deliverables. Typical system deliverables for CU are:

- Validation Plan
- Users Requirements Specification
- System Risk Assessment
- Functional Requirements Specification or Detailed Design Specification
- Testing Protocols
- Procedures
- Training Plan
- Release Requirements

The development of a list of procedures required for the system to become operational can be beneficial early in the lifecycle. These procedures include Standard Operating Procedures (SOPs) for operation, maintenance, sampling and testing plans, trend analysis, and investigations. Some of these documents may form part of subsequent qualification activities.

3.1.2 Commissioning Documentation

Typical commissioning documents include any FAT or SAT. Typically FAT and SAT is only on the vendor-supplied automatic equipment and liquid storage tanks, but can include the distribution system components.

Additionally, some firms prefer to include verification of piping in a commissioning document. A walk down of the piping to verify isometrics and slope should be done; however, that can be done in a commissioning document or in the installation section of the IOQP.

3.1.3 Qualification Documentation

Depending upon the size of the utility, there may be a combined Installation/Operational Qualification (IOQ) or separate IQP and OQP. Splitting the IOQ into distinct protocols still requires that most of the IQ be completed before proceeding to OQ. The depth of OQ will be a function of how much vendor FAT and SAT is going to be leveraged. The goal is to not repeat testing done deemed acceptable, provided there is rationale through risk assessment that the functionality will be transferred to the final installation site, and that the vendor documentation meets good documentation practices. The decision and rationale should be documented and approved in the validation plan.

3.1.4 Performance/Process Validation

Depending upon the utility type, performance verification may be required. Direct impact utilities such as any pharmaceutical grade water also require performance validation.

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Sampling during PQ is performed to demonstrate that compendial parameters are met, including TOC, Conductivity, and microbial requirements. This sampling should be done according to a sampling plan. Guidance for the development of sampling plans is explored in detail in the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* [3].

The same applies to product-contact gases. In aseptic processes, nitrogen and argon are commonly used as head space gases in some parenteral filling operations. Compressed air may be used for cleaning in all dosage form operations. If the gas is a product-contact or potential product-contact gas, some form of performance or process validation should be defined. In the case of gases that disperse into classified spaces (ISO 5, 7, 8 [26] or EU A, B, C, or D [24]), testing of the gases should also verify they meet the particulate counts and hydrocarbon content for the space.

Process verification is not required for ready-to-use bottled gases.

3.1.5 Lifecycle Validation and Revalidation

All CU should be part of the site's periodic review process. This process should review all change controls and Corrective Actions and Preventive Actions (CAPAs) associated with the system, as well as the routine monitoring of sampling results, system performance trends, PM, and calibration metrics. The frequencies should be risk-based, considering the potential for the system to impact product quality. The goal of the periodic review is to assess what has occurred on the CU and determine if requalification, installation, and/or operational qualification testing is required. An evaluation of whether additional qualification is required should be based on the summation of the periodic review.

If the periodic review identifies risks as a result of system changes that were not fully mitigated through appropriate documented testing, then a revalidation plan should be developed and executed to prove that the system remains in a state of control.

3.1.6 Decommissioning and Retirement

Prior to the decommissioning process, the replacement utility should be in place and properly qualified to the site procedure. Decommissioning CU typically is finalized by demolition of the replaced equipment. Change control should be written and organized to ensure that the replacement utility is in place and properly qualified before beginning the decommissioning process of the existing utility. It may be advantageous to establish a separate change control for the replacement utility, which is closed out before opening the change control to retire the old utility. Decommissioning activities should document the revision or cancellation of associated records, such as maintenance records, PM records, calibration records, drawings, library files, and SOPs. In addition, calibration of critical instruments should be completed prior to demolition, in order to confirm that the system met requirements at the end of use as well as to close the calibration period.

3.1.7 Procedures

Typically, a CU minimally has the following procedures:

- SOPs
- Sampling and attributes testing procedures
- Maintenance procedures

They should be governed by the site's procedures for change control, training, CAPA, deviation and investigation, and validation/qualification. All procedures pertaining to the system should be documented in the IQ test procedure.

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3.2 Change Control

ICH Q10 states [27]:

> *"Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company should have an effective change management system."*
>
> *"The change management system ensures continual improvement is undertaken in a timely and effective manner. It should provide a high degree of assurance there are no unintended consequences of the change."*

The main purposes of a change control process are to:

- Ensure timely and effective changes with a high degree of assurance that there are no unintended consequences of the change.
- Use quality risk management to evaluate proposed changes.
- Evaluate proposed changes to the applicable marketing authorization. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements.
- Ensure the change is technically justified by the evaluation of the appropriate expertise and knowledge from relevant areas.
- Confirm that the change objectives were achieved and that they had no deleterious impact on product quality by performing an evaluation of the change after implementation.
- Provide the traceability that all documentation (SOPs, maintenance plans, Process and Instrumentation Diagrams (P&IDs), floor plans, automation test plans) reflect the future state of equipment following change execution.

As outlined in the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification* [2], some companies often use an Engineering Change Management (ECM) system designed to capture changes that occur during initial qualification phase (commissioning, IQ, and OQ) prior to releasing the system or equipment for PQ and subsequent product use. The company's quality system change control is used to capture any changes outside this scope. The ECM may also be applied at the site level during subsequent lifecycle management of changes to noncritical aspects, components, or functions (as determined and documented by a system risk assessment). It is important to ensure that if this approach is used, the boundaries are clearly documented.

The main types of change control are:

- Document Change Control

  Consists of the initiation of a document or modification of approved documents including SOPs, method of analysis, format/labels, qualification and validation protocols, stability protocols, validation master plan, policies, and guidelines

- Facility/System/Equipment Change Control

  Consists of the planned modification/installation, major maintenance, removal/decommissioning of equipment, utility, facility, and automation

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The following sections should be part of a proposed change:

- **Subject:** Describes the details about the change and the documents, facility, and procedures where change is required.
- **Proposed Change:** Explains what is changing.
- **Scope:** Describes the department, equipment, document, and process name, along with the extent of change, i.e., what the change is about.
- **Reason for Change:** This section describes why the change is proposed. It may include the implication from other changes, GMP requirements, changes in regulations, addition/deletion of equipment, adoption of new processes, test methods, protocols, gap analysis during scheduled revision, CAPA, customer complaints, validation.
- **Existing Procedures, Equipment, Facility Documents:** This describes the current state.
- **Risk Assessment:** Describes the impact of the change on aspects such as products, processes, stability, regulatory, validation, qualification, training, packaging materials, documents, and parameters, and should be analyzed using a centralized approach (i.e., not confined to the particular system undergoing the change). The analysis should focus on evaluating and, if possible, quantifying the risk. (Section 3.3 discusses risk management techniques that may be applied.) Ensure stakeholders from affected departments are involved in the assessment.
- **Dates:** Included here are the proposed implementation date of the change, the actual implementation date, and the change control closure. Any extensions should be properly documented and evaluated.
- **Effectivity Check:** Confirm that the change objectives were achieved by developing a target or measure of the change to prove that there was no deleterious impact on product quality.
- **Attachments:** Attachments should be identified, and approved properly.

3.3 Risk Management

ICH Q9 Quality Risk Management (QRM) [28] as well as ISO 14971 [29] serve as industry references for risk management. Per ICH Q9:

> *"Two primary principles of quality risk management are:*
>
> - *The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and*
> - *The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk."*

A compliant manufacturing facility continually assesses and manages risks to product quality with respect to the CU from design, installation, ongoing maintenance, and routine monitoring. An effective QRM approach can facilitate a better understanding of potential risks and provide regulators with a greater confidence of a company's ability to mitigate risk and accept any identified residual risks.

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The QRM process is used to:

- Identify and assess the risk associated with:
  - The normal operation, for example identification and further risk management of starting material (such as source water) attributes or critical process parameters
  - The failure or potential failure of an operation, a system, or a process
- Determine control strategies to mitigate the identified risks and implement these strategies with the goal of minimizing risk to the ultimate user of the product or output. The aim of QRM is to reduce risk to an acceptable level; however, it is not always possible to eliminate risk entirely. Some residual risk may need to be accepted and will depend on factors associated with each case.
- Document and communicate information about risk and risk management between the decision makers and others throughout the QRM process.
- Review or monitor events for effectiveness of implemented control strategies.

The *ISPE Baseline® Guide: Volume 7 – Risk-Based Manufacture of Pharmaceutical Products* [30] describes commonly used approaches to risk management that could also be applied to CU systems. These techniques allow complex systems to be broken down and Critical Control Parameters (CCP) and Critical Quality Attributes (CQA) to be established. There are a variety of risk analysis techniques that can be used to evaluate the system or process, such as:

- Failure Mode Effect Analysis (FMEA) [31]
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

The following are examples of risks to consider or often overlooked when reviewing CU systems across the lifecycle of the system:

- A risk review of a CU may identify the need to monitor upstream noncritical parameters that can indirectly impact product quality or reliability. Monitoring these noncritical parameters ensures both the quality of the water and its continuity of supply. For example, alert and action limits should be established for both the water softening (reliability) and deionizing (quality) steps.
- As outlined in Chapter 2, the quality of the municipal feed water should be fully evaluated. Variations in hardness, alkalinity, Total Dissolved Solids (TDS), as well as the impact of seasonal variations (e.g., spring runoff or lake turnover effect), are all factors that can impact the efficiency and performance of the utility system on an ongoing basis and can help identify any control strategies that apply to each plant.

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- The accumulation of rouge in stainless steel piping is a well-known phenomenon in high purity process systems. An evaluation technique like FMECA may identify the detectability, probability, and severity of the rouge to determine the risk to patient and product. This could help identify an appropriate control strategy that could factor in the risks of treating the rouge, such as chemical contamination or surface degradation. A monitoring and derouging program may improve the detectability and reduce the risk to an acceptable level.

The implementation of the ICH Q3D guidelines on 'Elemental Impurities Risk Assessment' [32] has also placed renewed focus on the quality of water used to manufacture drug products and its impact on product quality. A review of these guidelines and their potential impact on the ongoing quality monitoring of the organization's water systems is recommended. Additional waterborne impurities for risk consideration are listed in Table 3.1.

A more in depth analysis of system attributes and trends can be executed as part of an annual review of the water system, a critical component of any risk management program. System review and trending is further discussed in Section 4.5.

Table 3.1: Examples for Impurities to Consider in Risk Mitigation

Impurity	Discussion
Chlorine/Chloramines	Chlorine/Chloramines must be monitored primarily for downstream equipment protection as it will rapidly degrade Thin-Film Composite (TFC) membranes in Reverse Osmosis (RO) systems, contribute to chloride stress cracking in distillation systems, and degrade Electrodeionization (EDI) units
Total Organic Carbon	TOC is measured as a reflection of the available food source for microbial organisms
Microbial Contamination	Microbial contamination is a direct measurement of water quality and can have a direct impact on non-sterile products lacking downstream microbial control, and a significant impact on sterile products
Endotoxins (for WFI)	Endotoxins are a measurement of degraded proteins of the outer portion of Gram negative organisms. Endotoxins in sterile products can cause direct harm to patients, resulting in fever and unanticipated immune responses
Conductivity	Conductivity directly measures the chemical purity of the water based on the absence of ionic species
pH*	pH is a direct measurement of the hydrogen ion concentration and represents the acidity or alkalinity of the water
*The testing of pH is a requirement for China and Mexico, as outlined in their respective pharmacopeias. Refer to Appendix 4.	

3.4 Drawings and Documentation

From a regulatory perspective there are no direct references to drawings as being explicitly required; however, they are understood to be part of the system design and qualification documentation.

EudraLex Volume 4, Annex 15: Qualification and Validation [33] states:

> *"IQ should include, but is not limited to the following:*
>
> *Verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications."*

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The PIC/S Aide-Memoire, Inspection of Utilities [34], also specifies that pharmaceutical water systems documentation, which includes drawings, is required to be up-to-date.

CU systems present a high level of risk to product; therefore, there are high expectations regarding the level of documentation and risk management. Drawings are one form of this documentation.

3.4.1 Context of Drawings

Drawings are clearly understood to be important during the design, construction, and verification of a system (refer to *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification* [2]). The importance of the system drawings is seen throughout the lifecycle of the system for multiple reasons, including training, change control, and operation.

There are several categories of drawings important for different reasons. These must be kept current and should include any changes made. In order of importance (from a regulatory perspective):

1. Process Drawings

    a. The recommendation is that manufacturers use fully detailed and developed P&IDs, and use these drawings to support their operations and inspections hosting.

    b. Process Flow Diagrams may be used as an alternative to P&IDs; however, caution is recommended as this creates a situation where the same content is covered on multiple drawings and both locations for that content must be maintained.

2. Isometric Drawings and Distribution Piping Layouts

3. Electrical and Controls Drawings/Documents

As part of maintaining the system validated state, manuals, detailed equipment layouts, and general arrangement drawings should be maintained as current and may be requested during an inspection.

When executing a system change (either planned or a corrective maintenance), one of the important activities is to update the master drawing set to reflect the system change. Failure to do so is a failure to maintain the validated state of the system (documentation of the system). All documentation related to a validated system should be suitably controlled.

3.4.2 Master Set Drawings

The owner should maintain and control master drawings for their CU systems. The drawings should be an accurate reflection of what is installed in the field, and as stated above, should be updated to reflect system modifications and changes.

3.4.3 Piping and Instrumentation Diagrams

There are several GMP activities that are dependent on having accurate drawings. These activities are listed below in order of importance from a regulatory perspective including recommendations for content on the drawings:

1. System Sampling and POU

    a. Drawings should reflect the system POU and sampling points. They should be accurately represented on drawings, both in quantity and in the location with respect to each other in the process flow. All sampling points may not be routinely sampled. Refer to the *ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, and Process Gases* [3] for sampling recommendations.

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