ECA Foundation
Fostering harmonisation of GMP/GDP regulations

# GMP Equipment Design Guide

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# Introduction

There are numerous pharmaceutical manufacturing processes, ranging from dry granulation and tableting to fermentation or sterile filling. Adding manufacturing processes from the classical (chemical) production of active pharmaceutical ingredients increases their number considerably. To some extent, however, pharmaceutical requirements are also observed when producing medical devices such as implants. The equipment used for these processes is as varied as the processes themselves. The product itself can place multiple requirements on the production equipment, too. For the design of equipment, it makes a big difference whether the product to be produced needs to be sterile or not, or whether it is a highly effective product. In the latter case, not only do GMP design criteria have to be observed, but also requirements for personal protection. A product or intermediate may, however, also be sensitive to oxygen or moisture. Obviously, all this affects the design of equipment. There might also be the rare case that the requirements of the authorities are not the same in different countries. The production method for WFI (water for injection) for example, was regulated differently in Europe than in the USA or in Japan until recently. In Europe, production of WFI was limited to distillation. This means that systems producing WFI by means of reverse osmosis would not have been GMP-compliant in Europe.

Consequently, this guidance cannot illustrate the requirements for every possible type of production equipment. Moreover, there are books, seminars taking up whole days and even academic subjects for each individual chapter. The purpose of this text is rather to illustrate the generally applicable requirements for the design of equipment and to explain how the connection between design and the statement "produced in compliance with GMP" can be made. To this end, the guidance contains numerous references and points of contact, a sort of a road map, that offer detailed information on the requirements or ways of proceeding for individual cases.

This guide was developed by a task force that included experts in pharmaceutical technology and engineering. The Task Force initially developed a document in German and it was first published by CONCEPT HEIDELBERG. The GMP-Equipment Guide is an English translation of the Guideline developed by this Task Force.

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All references to "he", "him" or "his" should be read as "she"/ "her" respectively "they" / "them" or "their" where appropriate.

# GMP Equipment Design Guide

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# 1. Introduction: What does GMP-compliant design of equipment mean?

In principle, the vague requirement "GMP-compliant design" can be broken down into four obvious requirements for pharmaceutical manufacturing equipment:

1. The equipment must not adversely affect the product quality.
2. The equipment must be easy to clean.
3. The equipment must comply with applicable technical rules.
4. The equipment must be fit for its intended use.

These four points are still so vague, however, that they need further explanation.

The equipment must not adversely affect the product quality. In other words, there must not be interactions between the product contact surfaces and the product that adversely affect the quality. The equipment may not release substances nor may product components be adsorbed. Furthermore, no chemical reactions may take place on the surface and the equipment may not emit substances that are harmful to the product quality - key words here being lubricants, rust or abrasion. Probably, abrasion will never be 100% avoidable, just as the material exchange between the inner surface and the product will never be zero. The question is rather what is tolerable without adversely affecting the product quality. This depends on the type of material and consequently on the type of substance that can be emitted as well as on the type of product.

The equipment must be easy to clean. This universally valid sentence can be found in almost all GMP regulatory documents of all countries and authorities. It covers two objectives. Surfaces (in most cases the inner product contact surfaces) ought to be smooth. It is much easier and more effective to clean equipment with smooth surfaces by wiping or rinsing than if the surface is scratched or cracked. On the one hand, these scratches are a good place for bacteria to survive and to resist cleaning and even disinfection and sterilisation, while on the other hand, product residue may remain in those scratches and gradually merge into following products. This is called cross-contamination. The potential survival or retention of microorganisms in cracks or scratches plays a role especially in the manufacture of sterile medicinal products. The problem is that microorganisms, unlike chemical impurities, can multiply. A handful of bacteria turn into many millions after half a day and this signifies the microbial contamination of the product manufactured in the equipment. And even if no viable germs get into the product, in the end their metabolites or cellular components may nevertheless cause great problems. These substances are called endotoxins and they may cause fever if administered parenterally. 0.8 µm is the generally accepted value for the surface roughness (smoothness). Sealing points, this means small gaps between the seal/gasket and the point being sealed, can also be problematic.

More serious than surfaces which are too rough are areas in the equipment that are hard to reach. Most equipment is cleaned by rinsing or the process is automated by means of CIP (cleaning in place). So-called dead legs cause problems in this context. These are areas in the equipment which are not wetted by the cleaning agent (spray shadows) or which cannot be reached by it. There is less throughflow in dead legs. Hence, it is harder to clean them and during thermal sanitisation it takes longer until these "branches" have also reached the required temperature. Therefore, the 3D/6D rule is often used for specifications in calls for tender and tests, but not always in the completely correct way. In order to explain this further, the rule's origin will be briefly addressed. The rule for the

prevention of dead legs (in a WFI system) is mentioned for the first time in the draft of the FDA "Guides for Large Volume Parenterals" (LVP), 21 CFR 212.49, in 1972. This requirement was taken up in the FDA "Guide to inspections of high purity water systems" in 1993 - only now it was called the 6D rule. This document is used by FDA inspectors as guidance for GMP inspections. The dead leg rule reappeared in an ISPE guide in 2001. The ISPE baseline guide "Water and Steam" now talks about the 3D rule. Further mentions can be found in WHO TRS 929 (1.5 D), WHO TRS 970 (3D) and in ASME BPE. This is a standard of the American Society of Mechanical Engineers for BioProcessing Equipment (2D). This means:

- There is a 1.5D, a 2D, a 3D as well as a 6D rule (now obsolete).
- The rule has been described for hot storage water systems but it is also used for all cleaning in place (CIP) systems.
- A rule of thumb became the industry standard.

But how does it work in practice? Is one rule more binding or better than the others?
One should bear in mind that the 3D and the 6D rule cannot be compared directly as they have a different point of reference. In the case of the 3D rule, the length L of the dead leg is measured from the tube wall of the main tube and put in relation to the diameter of the parting tube. In the original 6D rule, the length L of the dead leg is measured from the main tube's centre line.

As a rule, "3D or shorter" has proven itself suitable for water systems and is considered state of the art. But the following also applies: the higher the risk for the product, the shorter D should be. 1.5 D is state of the art for biotechnology applications today, but this may also mean that a piece of tube in an older clean steam system may remain 6D without posing a GMP risk.

In general, areas in equipment that are difficult to clean need to be avoided, irrespective of whether sterile or non-sterile medicinal products are being manufactured. In the first case, these areas are breeding grounds for microorganisms, while in the second case, areas that are not cleaned of product can cause cross-contamination of the following product. Both cases have to be avoided. In most cases, the risk of the microbial contamination of a sterile product is a lot higher. But the contamination of a non-sterile product such as a tablet with highly potent (e.g. cytotoxic) active ingredients can be just as serious.

The equipment must comply with applicable technical rules.

Real, legally binding GMP regulations are very vague, especially as far as technical matters are concerned. On the one hand, the authors are usually not engineers and, on the other hand, and as already described, the manufactured products and the equipment used are so different that it is almost impossible to formulate generally applicable and at the same time concrete requirements. Furthermore, the GMP requirements must always be changed when technological progress occurs. Therefore, the following applies: equipment has to comply with the state of the art; the requirement of good cleanability still applies even if new cleaning agents or processes should become available. Compliance is also recommendable from a legal point of view. If a product liability case (a patient has suffered harm because of a product) has to be resolved in court, the judge will maybe ask an expert whether the production equipment complied with the state of the art at the time.

Consequently, the question is, which technical rules have to be followed or where the actual state of the art can be looked up. This obviously depends on the type of equipment. In a few cases, pharmacopoeias or authorities' guidelines with an indicative and thus non-binding character might be helpful. And it is always good advice to know the relevant ISO standards or (in Germany) the VDI guidelines. Interest groups often publish documents containing further information. Examples are the ECA, ISPE, PDA or EHEDG. The pharmaceutical industry also uses standards from the food industry, particularly in relation to cleanability. It is important to know that these rules are seldom binding.

They are used very often, nevertheless, as this saves the demonstration that the approach chosen in each case complies with the rules and leads to the same or to a better result.

The equipment must be fit for its intended use. This is one of the most important and nonetheless least generally tangible requirements. It only means that the product being manufactured with the equipment complies with the pre-specified quality standards and consequently has the effect the patient needs (and that has been proven beforehand in a clinical study).

The suitability of the equipment is proven by means of its qualification, which plays an important role in process validation. Here, the following also applies: qualification is product-related. Equipment suitable (qualified) for product A is not automatically equally suitable for product B. This suitability has to be proven again and again and regularly by means of a requalification. Sometimes it is necessary to carry out tests from the initial qualification once more, but analysing equipment data and assessing equipment changes and deviations can suffice. This means that the pharmaceutical company must prove by means of qualification that the equipment is fit for its intended objective or use. Naturally, this demonstration is product-specific. The pharmaceutical company does not have to carry out the qualification itself. In many cases, the qualification is sold together with the equipment as package. But according to pharmaceutical legislation, the pharmaceutical company remains responsible. The production of proof gets more complex the more custom-built the equipment is. Consequently, equipment bought off the shelf is much easier to qualify than unique equipment because the tests remain the same and the qualification documentation can be compiled using copy & paste. The topic of qualification is elaborated upon further in the following chapters.

Calibration is an important part of qualification and of the recurring measures intended to maintain the equipment's qualified state. Here, the requirements are again specified by the product's requirements. For products reacting very sensitively to temperature, the measurement of temperature must be much more exact than for less sensitive products.

There is even a fifth requirement which, however, cannot be influenced by the equipment supplier.

The equipment must comply with the application dossier.

This does not mean compliance with GMP regulations (GMP compliance) but compliance with the documents that have been submitted to the authority or authorities granting the authorisation in the context of the marketing authorisation (regulatory compliance). Each medicinal product needs a marketing authorisation in order to be allowed to be placed on the market at all. Apart from the results of the clinical, pharmacological and toxicological studies, this marketing authorisation also consists of a chapter on quality. This contains details on the production process and partly on the production equipment. Usually, this information is rather general, but there are also cases in which a technical drawing of a part of equipment or a P&ID with all details is part of the documentation. This can be the case for example if technical details are used to answer questions from the authorities within the framework of the authorisation procedure. These documents will automatically become part of the marketing authorisation. Usually, it is the task of quality assurance to ensure regulatory compliance. This is also one of the reasons why change control plays such an important role in technology. It also explains why the pharmaceutical industry in general has so little interest in technological changes (or in technological progress). This is because every technological change first leads to questioning each of the five points mentioned. In the worst-case scenario, it has to be proven in the course of the change that this is not the case (the change does not lead to the equipment adversely affecting the product, it does not lead to the equipment being more difficult to clean etc.). If possible, and for understandable reasons, the relevant QA department ideally wants to avoid a change in the application dossier. Changing the submitted regulatory documents (the marketing authorisation) can be a very expensive and time-consuming issue.

# 2. Overview: General GMP rules, standards, interest groups and state of the art

As mentioned previously, there is no generally applicable set of rules that defines all aspects of a GMP-compliant equipment design or that could show the requirements in detail with figures quoted. The following overriding binding GMP documents are mentioned as worth reading:

- EU GMP Annex 1 – Manufacture of Sterile Medicinal Products
- EU GMP Annex 2 – Manufacture of Biological Medicinal Products for Human Use
- EU GMP Annex 11 – Computerised Systems
- EU GMP Annex 15 – Qualification and Validation

But there are also some other helpful documents containing useful information. These documents are usually papers from interest groups or technical standards, and only rarely guidelines prepared by the authorities. It is important to know that such documents are not binding and that the information contained therein are proposals. Inconsistencies are possible, therefore, but many of these papers are also considered to be state of the art. And compliance with the state of the art in turn is a GMP requirement. Consequently, it will be more advantageous than disadvantageous to adhere to the guidance documents.

Making no claim to be exhaustive, the following institutions or papers are considered to be helpful:

### ISPE

The International Society for Pharmaceutical Engineering is a membership of engineers. It is active in different technological subject areas and has published numerous documents on a range of topics. The documents are fee-based, directed at the USA and can be ordered here: www.ispe.org. Examples include:

- GAMP®5 A Risk-Based Approach to Compliant GxP Computerized Systems
  This document is considered to be **the** document on the validation of computerised systems. It refers not only to highly complex controls, but also to simple systems.
- ISPE Baseline® Guide: Volume 4 – Water and Steam Systems
  This volume contains information on the design of water systems.

Further ISPE baseline guides address the manufacturing of oral solid dosage forms, of sterile drugs or biopharmaceutical manufacturing. There is also a baseline document on qualification and commissioning.

### PDA

The Parenteral Drug Association also is a US-American association. The PDA is a bit less focused on technological aspects than the ISPE and concentrates on questions concerning the sterile or aseptic manufacture of medicinal products. The PDA publishes so-called technical reports on single subject areas. These reports are also fee-based. The following reports are interesting in relation to design requirements:

- Technical Report 49: Points to Consider for Biotechnology Cleaning Validation
- Technical Report 66: Application of Single-Use Systems in Pharmaceutical Manufacturing
- Technical Report 69: Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations

The PDA's technical reports can be bought at: www.pda.org.

## ECA

The European Compliance Academy is a European foundation which puts the focus on the areas of quality assurance and GMP compliance. The ECA is structured into single working and interest groups. These groups develop SOPs and guidelines etc. Most ECA documents are available free of charge. Sometimes documents are reserved for the members of individual interest groups, but often membership is available free of charge. Closest to the topic "equipment" are the groups dealing with validation, visual inspection and computer validation. The ECA's first point of contact is the website www.gmp-compliance.org.

## ASME

The American Society of Mechanical Engineers is very interesting. With the paper *ASME PBE* (bioprocessing equipment) it publishes a document that is considered a standard in the USA and offers detailed information on the construction of equipment (sterile/biopharmaceutical); for example, on the suitability of different stainless steel qualities as well as on still acceptable tempering colours when welding pipework or containers. Further information is available here: www.asme.org.

## EHEDG

The European Hygienic Engineering & Design Group (EHEDG) is a consortium of equipment producers from the food sector, food producers and universities which addresses the hygienic (cleanable) design of equipment. The EHEDG's ideas are also now being taken up by the pharmaceutical industry or by equipment suppliers producing equipment for the pharmaceutical industry. The EHEDG offers publications with partly explicit technical requirements (in relation to cleanability) as well as a database with equipment that the EHEDG has tested in relation to cleanability and certified. Cleanability is the prerequisite for the cleaning validation, the aim of which is to prove that none of the previous product (above a defined limit) can remain in the equipment and thus get into the following product (or batch).

www.ehedg.de

## ISO Standards

The ISO standards are considered state of the art and are often used for this reason. One special exception is ISO 14644 (standard for clean rooms and associated controlled environments) which is the only standard referenced in a GMP document (EU GMP Annex 1) and thus has a binding status. Helpful standards are for example:

- DIN ISO 14644: Clean rooms and associated controlled environments
- DIN 31051: Fundamentals of maintenance
- The standards of the DIN 58950 series of standards are applicable to steam sterilisers for pharmaceutical products.
- EN ISO 14159 Safety of machinery - Hygiene requirements for the design of machinery.

## VDI

The Verein Deutscher Ingenieure (Association of German Engineers) issues guidelines which are considered to be industry standards. They are available from Beuth Verlag (www.beuth.de). Especially noteworthy are the parts of Guideline 2083 addressing clean room technology. Apart from information on clean rooms, ventilation and barrier systems (e.g. isolator), part 17 contains information on the compatibility of materials for clean rooms. The parts of series 6022 can be helpful where ventilation systems are involved. They address ventilation technology. Part 2 of Guideline 3516 is also interesting.

It describes the procedure for the computer validation of small systems (such as pH meters, data loggers or barcode readers).

## PIC/S

PICS (Pharmaceutical Inspection Co-operation Scheme) is a cooperation of regulatory authorities in the field of GMP. The participating countries come from all around the world (Europe, America, Asia, Africa). PIC/S' goal is to harmonise GMP inspections and to facilitate a mutual recognition of GMP inspections. To that end, PIC/S publishes standards and checklists (aide memoires) for inspectors which are freely available. Some of these documents also contain applicable technical formulations. At this point reference should be made to:

- Inspection of Utilities (PI 009) – one of the few documents addressing media systems.

The documents are available free of charge here: http://www.picscheme.org.

## WHO

Though the WHO is the World Health Organisation, its GMP guidelines are not binding. Nevertheless, the WHO is an interesting source. This is because on the one hand, many guidelines are a harmonised "best of" of the GMP regulatory documents of different countries and on the other hand, some of the documents contain helpful technical data.

- Good Manufacturing Practices for sterile pharmaceutical products
- Good Manufacturing Practices: water for pharmaceutical use
- Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms
- Pharmaceutical products containing hazardous substances [interesting regarding the aspects of containment]

## ICH

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is a group of authorities and representatives of the pharmaceutical industry. ICH's goal is a global harmonisation of GMP requirements. There are fewer technical documents to be found here. However due to the document ICH Q9 describing risk management methods, and thus also risk analyses, ICH is nevertheless interesting. Risk analysis is applied in order to define equipment design requirements. It is a central document for qualification.

The ICH documents are available free of charge at the following source: www.ich.org.

Apart from the already-mentioned ICH Q9 document, the ICH Q9 briefing pack can also be found here which further elaborates on the issues of ICH Q9 with examples.

## Pharmacopoeias

Pharmacopoeias also have to be considered as state of the scientific and technological art, however they usually contain only a limited amount of concrete technical information. Exceptions are the chapters on pharmaceutical water and its production. These have to be considered as binding. Information can also be found on packaging with product contact and the verification of its suitability. The American pharmacopoeia USP moreover contains many chapters with an indicative character containing helpful information. These are the chapters with numbers exceeding 1000.

## 3. Risk analysis: the key to pharmaceutical success?

Risk analysis is a central or nowadays almost omnipresent element in the producing pharmaceutical industry. It is an element of risk management and is utilised for defining design criteria for the equipment, or for defining calibration or maintenance intervals, as well as for assessing process deviations. But risk analysis does not originate from the pharmaceutical industry. The HACCP (hazard analysis and critical control points) methodology, for example, comes from aerospace and was later taken up by the food industry where it is still applied. The FMEA (failure mode and effects analysis) method is often used in the pharmaceutical industry and comes originally from the military field and was later taken up in aerospace and by the automotive industry. In the pharmaceutical sector, risk analysis was first mentioned in the context of qualification in the EU GMP Annex 15 (2001). It was supposed to define the scope and extent of the validation/qualification activity subject to the product risk.

The ICH Guideline Q9 "Quality Risk Management" has been valid since 2005 and is the central and currently applicable document on risk management. This guideline describes the use of risk analyses, specifies different methods and shows with the help of a matrix which method can be used for which problem. The GMP authorities do not require a specific risk analysis methodology. Risk analysis is only one aspect of the risk management approach. The objective of a risk analysis is to identify risks or critical areas. The risks are meant to be reduced by appropriate measures (= risk management). For the producing pharmaceutical industry, this is supposed to mean a focus on the quality-relevant steps and at the same time facilitation since the effort for less critical areas will be reduced by this focusing. It also means less qualification, testing and/or documentation efforts. By means of risk management the regulatory authorities in the field of GMP also hand over responsibility to the manufacturer who, quite rightly, should know more about his product and consequently about possible risks for the product.

What role does risk management play in the design of equipment? This will be demonstrated with the help of a simple example: the product to be manufactured is sensitive to temperature, meaning the product will decompose if the temperature it is exposed to is too high or if the exposure lasts too long. Consequently, the temperature is a quality-critical value, it constitutes a product risk. One measure is the measurement of temperature. Depending on the difference between process temperature and damaging temperature, the measuring accuracy of this temperature measuring point is defined. The calibration interval will also be shorter than for a temperature measuring point measuring a less critical temperature. The temperature distribution in the equipment may also be relevant. One measure would be temperature mapping as part of the equipment qualification process (see chapter "Qualification").

In other words: a temperature measuring point is not per se quality- or GMP-relevant und does not need to be calibrated according to authorities' requirements up to +/- 1°C and recalibrated monthly. The pharmaceutical manufacturer knows the quality-relevant process parameters and keeps them under control by means of risk management.

It also follows that a risk analysis is not possible without knowledge of the product and the product risks. Here, the equipment producer depends on information from the pharmaceutical manufacturer. Naturally, there are also universally valid risks. Product-carrying parts of equipment should always be easy to clean as otherwise there is a risk of microbiological contamination or cross-contamination. Liquid (aqueous) products obviously pose a much greater risk of microbial contamination than the manufacture of solids. In the second case, product residues remaining in the equipment und the associated risk of carry-over into the next product (cross-contamination) might play a greater role. Consequently, the fundamental requirement of cleanability applies here, too.

Risk analyses can be carried out in different ways. They can be carried out from the perspective of the product or the equipment so that either risks for the product or for the equipment are sought. The first case is considered a GMP risk analysis. But the second case can also make sense, especially if still little is known about the product to be manufactured later. The way to succeed is to take over relevant equipment risks into the product risk analysis later. A philosophical question in this context is to what extent a risk for the equipment that leads to a failure of the equipment and thus to product loss is a risk for the product itself. Such a case could also be declared to be an entrepreneurial risk.

As said before, the prerequisite for the **GMP risk analysis** is product knowledge. It is the basis for the complete qualification carried out later. Only this kind of risk analysis can be asked for by an inspector in a GMP inspection. But this does not imply that an equipment producer for the pharmaceutical industry shouldn't carry out her/his own risk analyses. He can identify critical production steps for the quality of her/his equipment and can take specific measures which either increase the probability of detection (for example by means of further in-process controls) or reduce the likelihood of occurrence (improved production process). An auditor of a pharmaceutical company carrying out a supplier audit at the equipment producer's will welcome this or even ask for it. Unfortunately, this risk analysis carried out by the supplier is not the risk analysis some pharmaceutical manufacturers would like to order with the equipment. As has been stressed already several times, this risk analysis must be fed with specific pharmaceutical product knowledge.

# 4. Demonstration of evidence: URS, FDS -> GMP design -> qualification

Since the revised EU Annex 15 (2015) came into effect, one document has played a much greater role in the chain of demonstration of evidence that equipment is fit for its use: the URS or user requirement specification. The pharmaceutical user (pharmaceutical company) is supposed to put together his requirements in this document. For logical reasons, these should be the product or quality-relevant requirements. In the event that they were not already sufficiently known, an upstream risk analysis is useful (chicken-and-egg problem). Where appropriate, this document prepared by the person responsible for the product will be translated into a technical version by the operating engineer. This version will then be sent to the potential equipment supplier. Further GMP equipment design is therefore not possible without having defined product specific requirements!

Example: a product sensitive to temperature is to be dried by means of vacuum drying.

Risk: In the event of improper drying, the product decomposes/forms by-products.

Requirements in the URS: it must be possible to precisely set the critical process parameters of temperature, vacuum and time according to the process specifications S, Y and Z.

The following could be further requirements in the URS: type of drying (tray dryer, spherical dryer etc.), recording of process parameters, access control for the entry of the drying formula, alarm if process parameters are exceeded, cleanability of the dryer interior (especially in the case of multi-purpose use), etc.

Complemented technically, the so-called "precisely" would become a defined measuring accuracy: it ought to be possible to set the temperature in the drying room to 30 – 80 °C +/- 1 °C. This is supported by an experience report from development stating that the product starts to decompose only at a temperature of 80 °C or higher, but drying ought to be carried out at a maximum of 70 °C. In such a case, the measuring tolerance might even be higher. The same process is applied for the other parameters and requirements. According to the cross-contamination risk, the surface roughness could also be specified in order to guarantee good cleanability. At this point nobody knows whether this will be the case with 0.8 µm. It is assumed however.

As already mentioned, the URS is sent to the potential supplier(s) of equipment in the next step who answers with a FDS or functional design specification. It shows the design criteria the supplier of equipment will use in order to comply with the product, process or customer requirements.

The documented comparison between the two documents is called design qualification. Obviously, it is carried out by the pharmaceutical customer.

The terms "user requirement specification" and "functional design specification" or URS/FDS have different definitions and applications. In this context it is important that the user's GMP requirements and the fact that they are met by the supplier are documented and can be cross-checked against one another as described (DQ). It is up to the customer whether there are different documents for this, and if hGMP requirements and other customer requirements are laid down in the same document or in separate documents.

The requirements from the URS can also be found in the further qualification steps. The IQ (installation qualification) tests for example whether the temperature sensor mentioned is installed. The OQ (operational qualification) would test if the sensor can measure as required and if the calibration is appropriate. If necessary, the surface roughness of the product contact inner surface could also be measured. A test for the following PQ (performance qualification) could be the proof,

that the temperature set is reached in all required areas of the drying room and, if necessary, also in the product or in a placebo product. The process validation at the end would in any case be carried out with product to provide the final evidence that the drying of the product works the way it is supposed to.

But there are further points besides the qualification tests that can be deduced. The pharmaceutical user is obliged to maintain the qualified state of her/his production equipment. One system to do this is the system of maintenance & calibration. In this simple example it is quite obvious that the measuring sensors of the critical process parameters have to be recalibrated regularly. And should the surface roughness have been a quality-relevant requirement in the qualification, this shows clearly what should be a point of maintenance.

In more complex cases, the chain from the requirements to the proof of suitability is to be substantiated analogously in the different qualification steps.

In this context, the following Good Practice Guide issued by the ECA is very helpful: *Integrated qualification and validation – A guide to effective qualification based on customer-supplier partnership*.

This guide offers guidance on how to carry out an equipment qualification project in a GMP-compliant and efficient way today. It also contains specimen documents and templates. Moreover, the guide explains the integration of process validation aspects as early as the planning of qualification as propagated by the FDA.

This guide is available in the member area of the ECA validation group: www.validation-group.org. Membership is free of charge.

# 5. Material selection for hygiene-critical areas

Systems and equipment for pharmaceutical production should not have a negative impact on product quality. In summary, one can state:

- No substances are released from the material of the system
  No manufacturing substances are adsorbed on the surfaces
  There are no chemical reactions on the surfaces

With regard to a suitable choice of material, the GMP guidelines and various ISO and EU guidelines in particular describe generally required material properties (1) (2) (3).

When used as intended, surfaces of machine components must be durable, cleanable and, if necessary, disinfectable. They must resist cracking, chipping, flaking, corrosion and abrasion, and prevent the ingestion of unwanted substances.

Contact with the product and a cleaning and disinfecting agent must not cause corrosion. The material must not emit toxic substances, contaminate the product or otherwise adversely affect the product. There must also be no absorption of product components into the material.

The materials must be temperature resistant within the defined thermal process window (including cleaning and disinfection). The chemical resistance must be guaranteed against all liquids that come into contact with the material (the product to be processed and media for cleaning and disinfection). Polymers must have sufficient microbial resistance.

## 5.1 Material selection

Two types of materials are widely used in pharmaceutical plant construction: plastics and stainless steel. As metallic materials, stainless steels usually have these basic properties. Stainless steels with the material code 1.4301/AISI 304, 1.4401/AISI 316, 1.4404/AISI 316L or 1.4435/AISI 316L have become widely established for pharmaceutical applications. In principle, metal surfaces that come into contact with the product may be modified by surface treatment or coating. However, the surface modification used must also fully meet all the basic material properties mentioned above.

Many guidelines provide more detailed information on material selection and thus help the user to specify the general material requirements mentioned above. As an example, some guidelines are discussed in more detail below.
The EHEDG (European Hygienic Engineering and Design Group) publishes various guidelines for hygienic system design. The main overarching guidance is Document 8 (4). For example, this document provides some background information for the selection of materials for stainless steel, such as the influence of pH value, temperature and chloride ion content on possible corrosion. For plastics, the document lists possible polymers such as POM, perfluorinated plastics such as PFA, FEP and ETFE, PVDF, PC, PEEK, PE-HD, PP, PVC, PSU, PPSU and PESU. Due to its porosity, conventional PTFE should be viewed critically, as this property can result in insufficient cleanability depending on the application. A selection of elastomers is also mentioned: EPDM, FKM, FFKM, HNBR, NR, NBR and silicone rubber can be used in the food industry.

In addition to a comprehensive consideration of metals and polymers, EHEDG Document 32 (5) explicitly requires service life considerations for the materials used. How does the material behave over the period of use with repeated contact with disinfectants? Can cyclical temperature control, for example through superheated steam sterilisation, have a negative impact on the material properties? Material pairings are also important here: in the case of an aseptic screwed pipe connection, for example, seals experience greater linear expansion than the surrounding stainless steel material due

to cyclical temperature control. Are these material differences for the functional integrity of the pipe fitting in the tolerable range or not?

Ultimately, this is decisive for the choice of material. For a well-founded material selection, the material itself is decisive, but also whether its chemical-physical properties are suitable for use in hygiene-critical areas. Its intended place of use and the immediate structural and building environment has to also be considered. The trend in material testing is shifting more and more away from the detached actual material properties towards service life considerations in light of risk assessments that have been undertaken. In principle, a two-stage selection process must be carried out. Step 1 defines the basic suitability of the material based on the intended process and step 2 the suitability of the material based on the structural conditions. EHEDG Document 32 also lists elastomers that are suitable in principle along with their basic properties.

## 5.2 Surfaces

The surface roughness of a material is an important parameter for assessing its cleanability. It is generally understood that a very rough surface is less easy to clean than a smooth one. However, which roughness value should be used to adequately assess the surface quality is discussed, for example, in Document 32 from the EHEDG. A comparison of different roughness values in relation to the cleanability done in the food industry shows that no correlation can be determined with sufficiently low roughness values below 3 µm (6), (7). With regard to what is understood to be a sufficiently low roughness value, Document 8 of the EHEDG mentions a roughness value of Ra = 0.8 µm for large-area parts that come into direct contact with the product. However, the document relativises the mere numerical value in that, ultimately, the cleanability in relation to the process must always be guaranteed and therefore, depending on the process, roughness values of Ra > 0.8 µm are justifiable (4).

In its document ASME BPE-2007(8), the American Society of Mechanical Engineers describes in addition to the well-known references to basic material properties, some of which can be found with identical wording in all hygiene-related documents, mainly concrete design specifications. These include, for example, designs such as a hygienic screwed pipe connection or a container lid with several feed-through holes. A chapter is dedicated to the basic properties for stainless steel product contact surfaces, for which Type 316L stainless steel is suggested as the base material for most applications. The document divides the quality of a stainless steel surface into different surface classes from "SF0" to "SF6" depending on the surface roughness value Ra. "SF2" corresponds to mechanically polished stainless steel with Ra = 0.8 µm, while "SF6" denotes electro-polished stainless steel with Ra = 0.6. According to the document, the biocompatibility and possible extractable components of the elastomers and polymers used must be known in addition to their physical and chemical properties.

Conformity with the requirements of Document 21 CFR Part 177 (9) by the American Food and Drug Administration (FDA) should be fulfilled for the materials used. Among other things, this document specifies precise test methods and limit values for so-called "leachables and extractables", i.e. which chemicals can escape from the respective polymer at which temperatures and contact media and can thus migrate into the product.

The ISO 14159 (2) guideline specifies the relevant requirements of the EC Machinery Directive 2006/42/EC for machines placed on the market for the first time in member states of the European Economic Area (EEA). For the selection of suitable materials, this standard specifies, comparable to most hygiene-relevant guidelines and standards with material reference, a necessary consideration of the material with regard to the absorption of undesired components from the process or product and contamination of the product through the release of undesired substances. Both effects can be directly linked to one another due to the fact that adsorption of a substance that has taken place can sometimes be a reversible process and can therefore contaminate the product if this substance is

released with a time delay. Possible scenarios are, for example, adsorption of cleaning components, which are continuously released back into the product to be processed after the end of wet-chemical cleaning.

This effect is not limited to direct liquid media contact, but can also take place via the gas phase. An important example of this can be found in the gaseous decontamination of machines and systems with hydrogen peroxide. To kill microorganisms, a defined dose of hydrogen peroxide is fed into the system as an aerosol or in gaseous form. After a specified dwell time, the system is again ventilated with fresh air in order to get the hydrogen peroxide concentration below a specified limit value as quickly as possible. Some polymers absorb the hydrogen peroxide into their matrix during decontamination and release it into the environment with a time delay after the end of aeration. The atmosphere surrounding the product is enriched with hydrogen peroxide, which in turn can be absorbed by the product. If the product can be attacked by oxidation, this can directly lead to product damage. This effect is often of fundamental importance in the production and filling of active pharmaceutical ingredients and is intended here to illustrate possible contamination scenarios. This material property, which is particularly important in the pharmaceutical industry, is examined in guideline VDI 2083 sheet 20 (10).

## 5.3 Considerations on material selection for the process environment

However, the selection of materials for hygienic production areas is not limited to the machine. The surrounding space must also be considered. Walls, ceilings and floors can become dangerous sources of contamination if the wrong material is selected (11). The EHEDG, for example, also published its Document 44, which deals with hygiene-related room and building requirements, including building material selection (12). Even the filter material of an air filter in air treatment can have indirect product contact due to the fact that possible outgassing products (so-called volatile organic compounds, VOC) or loose fibre fragments of the glass fibre medium contaminate the air to be filtered and thus in turn the product to be processed. Information on the requirements for floors, ceilings and walls can be found in the chapter entitled "Requirements for the process environment: The clean room".

## 5.4 Conclusion: a risk-based approach for the selection of suitable materials

For a targeted selection of materials for hygiene-critical production areas, the entire process must be examined in a risk assessment, for example. What kind of product should be processed? What are the requirements for the purity of the product? How and with which method should it be cleaned? What chemical, thermal and mechanical stability does the component have to show? Is it a static component or is it loaded tribologically (by friction)? What number of cycles is required? Material costs? And finally: does the selected material also conform to existing regulations and guidelines?

In summary, it can be said that all known standards and guidelines regarding the selection of materials for hygiene-critical areas more or less specify this most important basic material requirement: the material used must not adversely affect the processed product AND the production process in its defined quality. For the user, this usually sounds too vague and not very concrete. However, a standard or guideline should not and cannot make a tough decision on the choice of material, since every hygiene-relevant production process is far too individual for that. Nevertheless, by knowing the influencing factors mentioned in the relevant standards and guidelines, an intelligent material selection can ultimately be made.

## 5.5 References

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# 6. Process contact surface requirements: surface specifications and surface treatments

Process contact surfaces may have an influence on the quality of a product and may even adversely affect it. For this reason, it is necessary to take a closer look at the surface treatment procedures and the surface qualities of metallic materials used in the construction of pharmaceutical and biotechnological equipment.

The focus of these considerations lies on the material group of austenitic stainless steels, especially on the CrNiMo steels 1.4404 and 1.4435 [1]. For material 1.4435, conformance with the Basler Norm BN 2 (former company standard of the Basel Chemical Industry) [2] and/or limitation of a maximum permissible content of δ-ferrite in welds is required (see also [2] and delta ferrite [DF] class according to DIN 11866, Annex A (nonmandatory) [3]).

## Excurse: Delta-Ferrite

Technical tenders for pharmaceutical manufacturing equipment repeatedly include the requirement to comply with a specification for the delta ferrite content in stainless steel of less than 0.5% and thus also to the Basel Standard 2 (Basler Norm 2 / BN2). The delta ferrite content has an influence on corrosion resistance - but it was also assumed that the low content would minimise the formation of rouge. But what is the current view on this requirement?

Ferrite is a phase that may precipitate during solidification of austenitic stainless steels depending on the ratios of the alloying elements. The ferritic phase consists of crystals with a body-centered cubic (bcc) lattice in contrast to the face-centered cubic (fcc) lattice of the austenitic matrix. The presence of ferrite in austenitic stainless steel welds may reduce the corrosion resistance in some corrosive environments. However, a minimum ferrite level may be required to maintain specific properties of particular product forms (e.g., castings) or is deemed necessary to prevent hot cracking of heavy wall weldments (e.g., vessels made from plate).

The ferrite level of austenitic stainless steel base metal strongly depends on heat analysis, primarily the chromium to nickel ratio, product form, and final heat treatment. Whereas wrought 316L-type stainless steel materials UNS S31603, 1.4404, and 1.4435 in the solution annealed condition typically show very low ferrite levels of 0 vol. % to 3 vol.%, 1.4408 and CF8M or 1.4409 and CF3M stainless steel castings may contain 10 vol. % to 20 vol.% of ferritic phase in the austenitic matrix. As-solidified austenitic stainless steel welds typically have higher ferrite levels than the base metal. This is caused by rapid cooling that prevents the ferrite to austenite transformation from proceeding to thermodynamic equilibrium.

*Influence of ferrite on the construction of pharmaceutical equipment and systems*

Ferrite in the base metal and welds can have a positive or negative effect depending on the type of application, but generally offers little cause for concern in pharmaceutical engineering. Laboratory corrosion tests in highly corrosive media, e.g. 10 % hydrochloric acid, have shown that increased amounts of ferrite in the weld seam structure can reduce corrosion resistance. [4] Investigations of welds with different delta ferrite contents showed no drop in corrosion resistance up to 3 % ferrite. Only from approx. 5 % delta ferrite, a decrease in resistance to chloride-induced pitting corrosion

could be demonstrated. [5] However, in high-purity water systems, there have been no reported corrosion failures related to delta ferrite content in welds. [6]

*Control of ferrite content in welds of austenitic stainless steels*

In the past, numerous specifications required a low delta ferrite content of max. 0.5 % in the base metal and welds. In welds, this could usually only be achieved by one or more of the following measures:

(a) Postweld solution annealing
(b) Use of weld filler or consumable inserts with increased nickel content
(c) Increase of nickel equivalent by addition of approximately 1 vol.% to 3 vol.% nitrogen to the shielding gas (argon)

These methods and the associated quality assurance measures led to increased production time and high costs. According to the current state of knowledge, ferrite control of max. 0.5 % in welds in the construction of pharmaceutical equipment and systems seems not necessary.

To avoid ferrite contents of more than 5 % in welds of austenitic stainless steels, material 1.4435 with additional restriction of analysis according to BN2 has proven itself [2]. Although this works standard of the Basle Chemical Industry was withdrawn without replacement by its publishers in 2012, all major steel manufacturers have adapted to this restriction and included the material 1.4435/BN2 in their standard range. Orbital welds of tubes made of this material show on average a delta ferrite content of 3 %, i.e. not critical in terms of corrosion for pharmaceutical equipment and systems. Additional measures to reduce the ferrite content in welds, as described above, are not necessary.

*Conclusion*

Worldwide, the material UNS S31603 (316L) is the most widely used material in pharmaceutical equipment and systems. The European materials 1.4404 and 1.4435 are both within the analysis limits of UNS S31603. The material 1.4404 is more in the typical lower range of the main alloying elements chromium, molybdenum and nickel. 1.4435/BN2, on the other hand, contains significantly higher contents of the three main alloying elements and shows lower ferrite contents in welds. However, this advantage is only significant in terms of minimizing the risk of localized corrosion, such as chloride-induced pitting corrosion.

The process contact or product contact surface of vessels, tubing, fittings, and instruments represents the boundary surface between product or process medium to the metallic material. At this point the following aspects are of special importance:

- Risk of corrosion, especially of localised corrosion
- Risk of contamination of the product or process medium, i.e. transfer of substances and particles from the surface of the metallic material in the liquid phase
- Cleanability of the metallic surface in order to prevent cross-contamination and the accumulation of micro-organisms

With this, the main criteria regarding the operating performance of material and surface are defined: good corrosion resistance against aqueous media, a high level of surface cleanliness and prevention of macroscopic dead legs and microscopic cavities and crevices.

The following paragraphs describe different machining methods for process contact surfaces, typical characteristics and their influence on the above-mentioned criteria, and they offer recommendations for different areas of application.

## 6.1 Surface qualities/specifications

Surfaces can be described from a technical and scientific standpoint using three characteristics: topography, morphology and energy level.

- Topography describes only the geometric shape of a surface. Geometrical structures below 0.1 mm are also referred to as microtopography. The surface topography influences the accumulation of particles and microorganisms, biofilm formation as well as the cleaning characteristics. In other words, the deeper the pits and scratches on the surface, the greater the probability that particulate contaminations and microorganisms will accumulate in them and the more difficult it will be to remove them by means of cleaning procedures.
- The morphology of metallic materials describes the chemical composition, i.e. the elements, their oxidation states and binding partners, as well as the crystallographic structure. In the field of metallic surfaces, the morphology defines the chemical reactivity/passivity and especially the corrosion behaviour.
- The energy level of the surface or the surface tension is defined as the energy required per unit area to increase the size of the surface, and it determines a number of physical and chemical properties of the surface. The energy level influences adhesive forces. Consequently, it also influences the tendency to accumulate particles and microorganisms as well as the cleaning behaviour.

In the pharmaceutical and biotechnological engineering of equipment, the consideration of selected topographical and morphological characteristics has been established. In this context, the ASME BPE [7] and the DIN standards for stainless steel components for aseptic applications in the chemical and the pharmaceutical industries [3], [8], [9], [10], [11], [12] should be mentioned in particular. These standards describe the following requirements:

- Visual inspection regarding surface anomalies or indications (defects) and contamination such as oil and grease residues, corrosion products and water stains.
- Surface roughness parameters. The *Ra* value (roughness average) should be mentioned first. It is measured using surface profilometry according to EN ISO 4287 [13] and EN ISO 4288 [14] as well as ASME B46.1 [15]. Surface profilometry is the most common measurement procedure for surface roughness. The metrological effort is small compared to optical methods. The measurement can also be carried out in tubes and bores with an inner diameter of a few millimetres. Since the surface is scanned by means of a diamond stylus, a small scratch with the length of 4.8 mm remains on the surface. On the surface of stainless steels, a scratch with a depth of less than 0.02 mm (20 µm) is irrelevant and acceptable. In fittings and machined components, the accumulated length of all scratches must not exceed 6.4 mm (see also DIN 11865, table 17 [8]).

Table 1 shows the requirements and references to standards that are state of the art in pharmaceutical and biotechnological engineering. Electropolished surfaces are rated as being higher quality in general, i.e. regardless of the respective area of use [6], [16]. In contrast there is only scant scientifically proven data on the importance of the *Ra* value for the operating performance of a process contact surface. Experiences from the pharmaceutical and biotechnological construction of

equipment since the beginning of the 1990s, however, demonstrate that surfaces with *Ra* values in the range of 0.10-0.80 µm[1] show no significant differences with regard to the risk of corrosion, the accumulation of microorganisms and cleanability, provided that the same materials and surface treatments are compared (see paragraph 6.2).

Table 1: Surface qualities according to DIN 11866:2016 **[3]** and ASME BPE-2019 **[7]**

| Standards | Materials (selection) | Process contact surface (selection) | | | |
|---|---|---|---|---|---|
| | | Surface treatment | Visual inspection (standard) | Roughness average | Surface designation |
| DIN 11866 | 1.4435 | Bright finished[(a)] | DIN 11866, table 5 | *Ra* ≤ 0.80 *µm* | H3 |
| | | | | *Ra* ≤ 0.40 *µm* | H4 |
| | | Electropolished | DIN 11866, table 5, table 6 | *Ra* ≤ 0.80 *µm* | HE3 |
| | | | | *Ra* ≤ 0.40 *µm* | HE4 |
| ASME BPE | UNS S31603<br>1.4404<br>1.4435 | Mechanically polished[(b)] | ASME BPE, table SF-2.2-1, table SF-2.6-1 | *Ra (max)* ≤ 0.51 *µm* | SF1 |
| | | | | *Ra (max)* ≤ 0.64 *µm* | SF2 |
| | | | | *Ra (max)* ≤ 0.76 *µm* | SF3 |
| | | Electropolished | ASME BPE, table SF-2.2-1, table SF-2.2-2, table SF-2.6-1 | *Ra (max)* ≤ 0.38 *µm* | SF4 |
| | | | | *Ra (max)* ≤ 0.51 *µm* | SF5 |
| | | | | *Ra (max)* ≤ 0.64 *µm* | SF6 |

(a) *Bright finished*: this option includes a number of surface treatment methods such as mechanical polishing, bright annealing or pickling.

(b) *Mechanically polished*: this option includes all surface treatment methods that meet *Ra (max)* such as mechanical polishing, bright annealing or pickling.

[1] Measurement according to DIN EN ISO 4287 (DIN EN ISO 4287, 2010) and DIN EN ISO 4288 (DIN EN ISO 4288, 1998) as well as ASME B46.1. (ASME B46.1-2009, 2009)

Conformance with the relevant requirements is verified by examination/inspection of the components and equipment at the producers' premises and as part of the installation qualification (IQ). There are also measurement methods for identifying further characteristics:

- Dye penetrant testing (PT) [17] in order to detect imperfections such as crevices, overlapping, folds, pores or lack of fusion
- Scanning electron microscopy (SEM) and light microscopy within the scope of structural examinations in order to find microscopic defects and contaminations [18]
- Determination of the Cr/Fe and $Cr_nO_m/Fe_xO_y$ ratios in the surface area and measurement of the thickness of the chromium oxide enriched passive layer by means of photoelectron spectroscopy (XPS/ESCA) or Auger electron spectroscopy (AES) as a key figure for corrosion resistance [19], [20]
- Corrosion tests, such as the cyclical potentiodynamic polarisation measurements [21] or KorroPad [22]
- Contact angle measurement for determining the surface energy.

The last five methods mentioned are not usually applied within standard tests and acceptances but primarily in the areas of selection of materials, risk assessment, failure analysis as well as electropolishing procedure qualification.

## 6.2 Surface treatment methods

The following procedures are typically applied for the machining of metallic surfaces in the pharmaceutical and biotechnological construction of equipment in order to obtain the surface qualities listed in chapter 6.1, Table 1.

### 6.2.1 Mechanical surface treatment methods

Mechanical surface treatment methods are applied for surface qualities H3, H4 according to DIN 11866 et seq. as well as for SF1, SF2, and SF3 according to ASME BPE.

Non-cutting processing

Rolling of strip and sheet metal or cold drawing of tubes (sink drawing, drawing over a mandrel and plug drawing) are non-cutting processes by which plastic deformations on the component surface take place by means of tool contact. These deformations result in a local flow of the material. On a microscopic scale, the process of *cold forming* results in a shifting of small domains along crystallographic planes. This causes

- hardening due to increased lattice tension up to a level which results in the formation of deforming martensite,
- enhanced homogeneity of the metallurgical structure by cold forming and subsequent heat treatment, and
- smoothing of the surface from plug drawing processes.

Figure 1 shows the inner surface of a longitudinally welded, cold redrawn tube 50.80 × 1.65 mm, 1.4435/UNS S31603 under the optical microscope with approx. 500 x magnification as example of non-cutting processing.

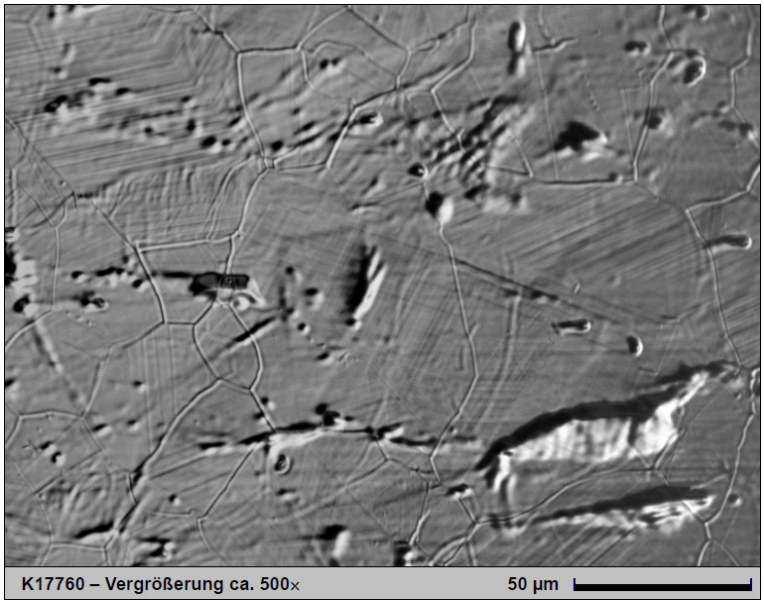


Figure 1: Inner surface of a longitudinally welded tube 50.80 × 1.65 *mm*, cold redrawn tube (plug), solution annealed under hydrogen atmosphere, 1.4435/UNS S31603, *Ra* = 0.23 *µm*; microscopic image (DIC) at approx. 500 x magnification.

Metal-cutting processing

One of the most frequently used procedures in metal-cutting processing is mechanical polishing with silicon carbide or aluminium oxide (corundum) as the abrasive material (K80 to K300). Typically, 0.01 to 0.15 *mm* of material are removed from the surface. In areas of components which are difficult to reach, the inner surface can be mechanically polished by extrude honing. Mechanical polishing allows a uniform appearance and low *Ra* value to be achieved.

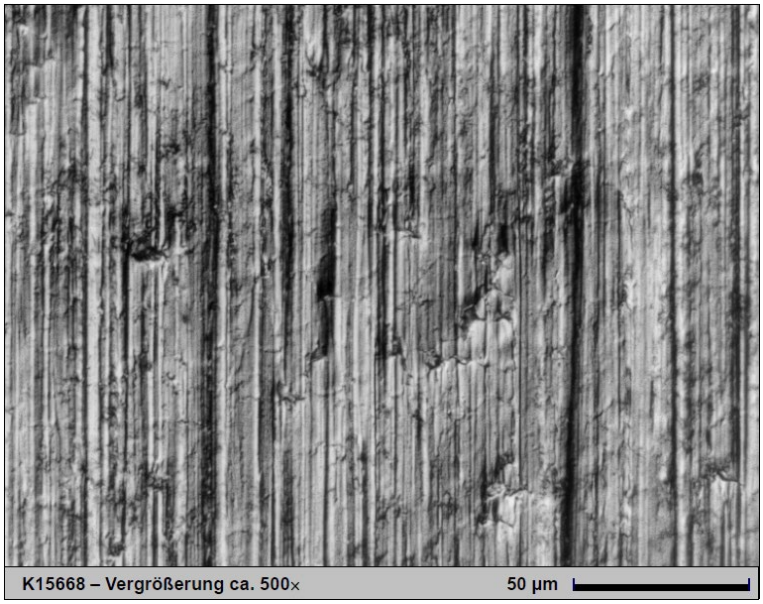


Figure 2: Inner surface of a longitudinally welded and mechanically polished tube 50.80 × 1.65 *mm*, UNS S31603, *Ra* = 0.24 *µm*; microscopic image (DIC) at approx. 500 x magnification.

Mechanical polishing, however, has a negative effect on the size of the real surface (factor 2.5 to 4.0) and on the risk of microscopic overlapping and pockets (see also Figure 2). [23]

### 6.2.2 Chemical surface treatment

Pickling

Chemical pickling is a very effective cleaning method by which contaminations, e.g. scale and heat tint, and a certain amount of metal from the surface (ca. 1-3 *µm*) are dissolved. Metal atoms are oxidised and dissolved by a strong oxidising agent such as nitric acid ($HNO_3$) at a concentration of approx. 20-40% and the addition of agents which form easily soluble compounds with the metal ions, e.g. $[FeF_6]^{3-}$ or $[FeF_5(H_2O)]^{2-}$. A commonly used agent is hydrofluoric acid HF (≈ 4-10%). Chemical pickling involves the removal of metal and therefore is not suitable for surfaces which have been electropolished. These surfaces should not be pickled in general. Consequently, pickling is only applicable for the surface qualities H3, H4 according to DIN 11866 et seq. as well as for SF1, SF2 und SF3 according to ASME BPE. Figure 3 shows the chemically pickled inner surface of a seamless tube 1.4404/UNS S31603.

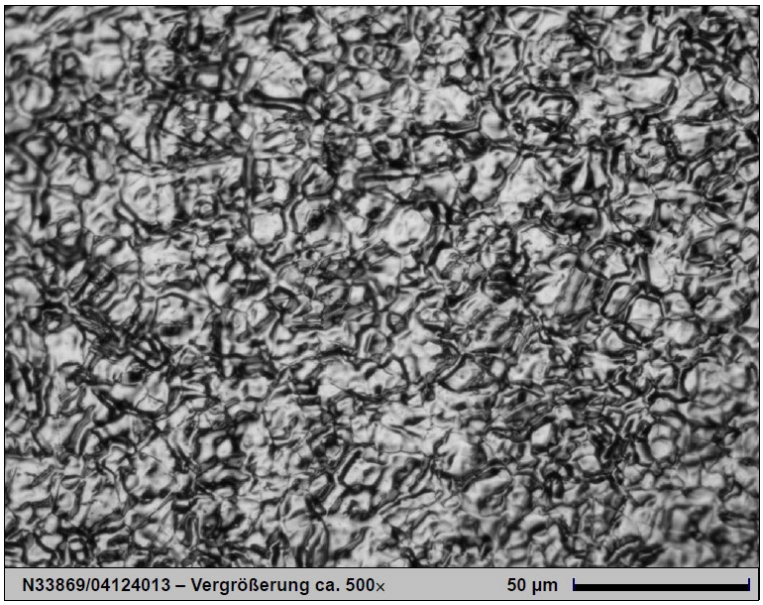


Figure 3: Inner surface of a seamless tube 12.70 × 1.22 *mm*, chemically pickled in $HF/HNO_3$, 1.4404/UNS S31603, *Ra* = 0.40 *µm*; microscope image (DIC) at approx. 500 x magnification.

Pickling of a surface may be required if poor-solubility oxides have formed on the surface during manufacturing and heat treatment processes or if an insufficient inert gas purge during welding has caused an unacceptable level of discolouration in the heat affected zone (HAZ). Pickling is a removal of metal related to general corrosion. Therefore all relevant parameters, i.e. concentration of the pickling acid, temperature and duration, should be maintained accurately to limit the attack on grain boundaries (etching). Excessive attack on the grain boundaries is clearly visible even at low magnification and often results in irreversible damage of the component.

Passivation

A chromium oxide-enriched passive layer forms automatically under normal conditions in air atmospheres. However, formation of the passive layer can be accelerated under strongly oxidising conditions. Such processes are called passivation and are required in numerous *user requirement specifications* for equipment and systems in the pharmaceutical and bioprocessing industry. A commonly used agent is 20 % nitric acid at temperatures ranging from 20–30 °C for a duration of 30 *min* [24], [25]. By means of *passivation* it can be ensured that subsequent to manufacturing processes, such as machining or welding (cast structure), a regular and homogenous chromium oxide enriched passive layer forms on a stainless steel surface even under conditions where sufficient access to air containing oxygen cannot be guaranteed. It should be noted that a clean surface, free of oil and

grease, is a prerequisite for the formation of a passive layer under normal conditions in air as well as in the case of targeted *passivation*. In this sense, *passivation* in nitric acid is not a cleaning process and only removes easily soluble contaminations from the surface such as phosphate and sulphate residues after electropolishing.

Topography and thereby the image under the microscope are not changed by passivation. This means that passivation can be used for all surface qualities according to chapter 6.1, Table 1. A comprehensive overview of passivation procedures can be found in ASME BPE-2019, non-mandatory Appendix E *Passivation Procedure Qualification* [7].

*Passivation* has no negative effects on the surface condition. In practice, reagents and solutions are used occasionally, however, that have a higher cleaning effect than diluted nitric acid but which might attack the surface of stainless steels and consequently have the effect of a pickling acid. This is true, for example, for some electrolytes based on citric acid or oxalic acid.

### 6.2.3 Electrochemical surface treatment

Electrolytic polishing

Electrolytic polishing (aka electropolishing) is a procedure during which the surface of a component made of stainless steel to be electropolished and an electrode made of copper[2] are arranged preferably in parallel and immersed in an electrolyte based on a mixture of phosphoric acid ($H_3PO_4$), sulphuric acid ($H_2SO_4$) and additives. The component made of stainless steel (anode) is connected with the positive pole of a direct voltage source, and the copper electrode (cathode) is connected with the negative pole. At temperatures of about 50–70 °C and a voltage of 2–30 *V*, material is removed from the surface of the stainless steel. A charge quantity per anode surface of 100 *A min/dm²* corresponds to a material removal of about 7.5 *µm*. Figure 4 shows a schematic diagram of electropolishing.

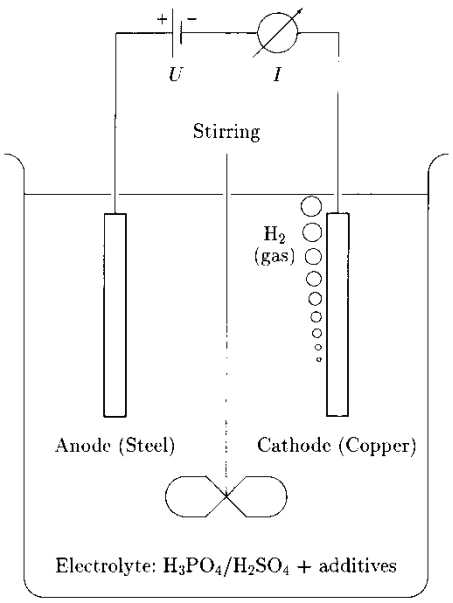


Figure 4: Schematic diagram of electropolishing of stainless steels in a phosphoric acid/sulphuric acid-based electrolyte

Similar to pickling, potential contamination and a certain amount of metallic material itself are removed from the surface. Since the local current density $i_D$, which is directly proportional to the material removal rate is higher at *peaks* than in *valleys* of the surface will be smoothed during the

[2] Or of another metal with good electrical conductivity.

process. Within the defined process parameters and in contrast to chemical pickling, no selective attack occurs along the grain boundaries. By electropolishing, any desired removal can be set without causing damage to the component. Moreover, the process of electropolishing can be supervised and controlled by recording the process parameters (aka essential variables), i.e. applied voltage, current flow, composition and temperature of the electrolyte, duration and agitation of the bath or flow velocity of the electrolyte. Figure 5 and Figure 6 are images of electropolished inner surfaces of seamless tubes. Both examples fully meet the requirements of the surface qualities DIN 11866, HE4 as well as ASME BPE, SF4.

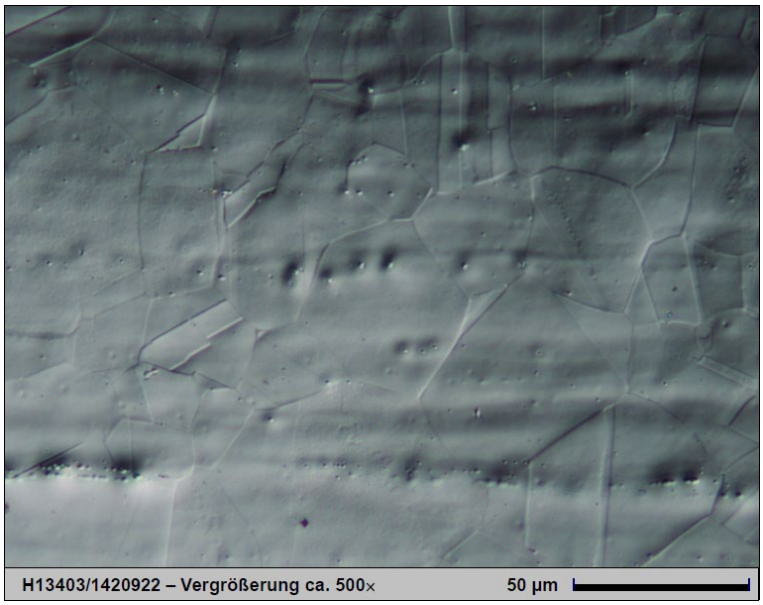


Figure 5: Inner surface of a seamless tube 6.35 × 0.89 *mm*, electropolished according to a qualified procedure with an electrolyte based on a mixture of phosphoric and sulphuric acid (cf. ISO 15730 and ASME BPE, Part SF), 1.4404/UNS S31603, *Ra* = 0.20 *µm*; microscopic image (DIC) at approx. 500 x magnification, grain boundaries and crystallographic twins visible.

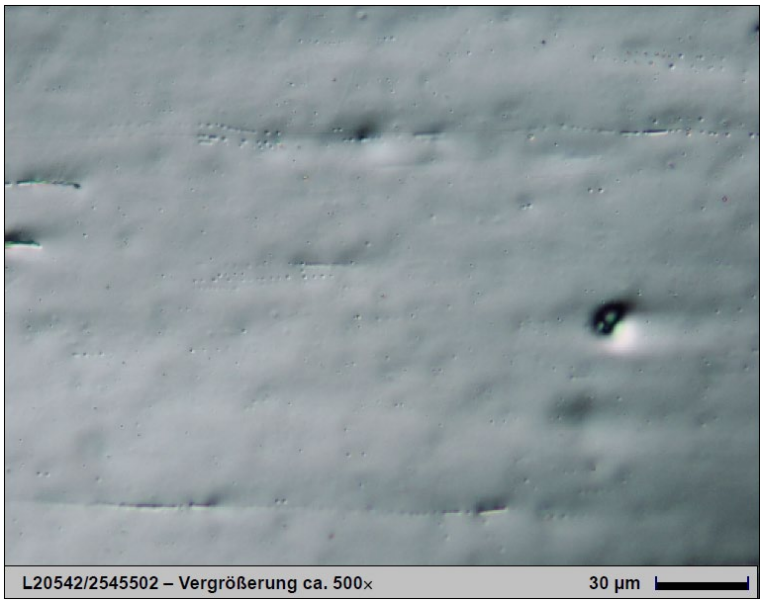


Figure 6: Inner surface of a seamless tube 19.05 × 1.22 *mm*, electropolished according to a qualified procedure with an electrolyte based on a mixture of phosphoric and sulphuric acid (cf. ISO 15730 and ASME BPE, Part SF), 1.4404/UNS S31603, *Ra* = 0.18 *µm*; microscopic image (DIC) at approx. 500 x magnification, grain boundaries and crystallographic twins not visible.

In addition to cleaning the surface and smoothing of the microtopography, it is possible to achieve an optimal Cr/Fe ratio and to form a uniform passive layer rich in chromic oxide by means of electropolishing.

Requirements regarding electropolishing and test procedures for the electropolishing of stainless steels are described for instance in ASME BPE-2019, non-mandatory Appendix H *Electropolishing Procedure Qualification* [7] and in DIN EN ISO 15730 [26].

Anodic cleaning

If a high level of cleanliness of the surface is key without having to fully meet the requirements for an electropolished surface quality, the electrolytic removal of material can be reduced to a value of about 3–5 *µm*. This process can be referred to as anodic cleaning in order to emphasise the difference to electropolishing. Figure 7 is the image of an anodically cleaned surface (centre) in contrast to a pickled surface (left) and an electropolished surface (right).

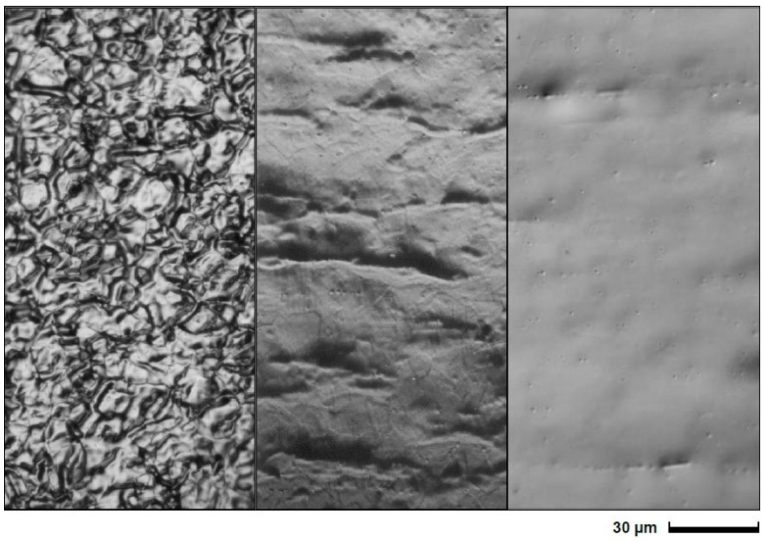


Figure 7: Comparison between differently processed inner surfaces of tubes, on the left: seamless tube 12.70 × 1.22 *mm*, chemically pickled, 1.4404/UNS S31603, *Ra* = 0.40 *µm*; in the centre: seamless tube 12.70 × 1.65 *mm*, anodically cleaned, 1.4435/UNS S31603, *Ra* = 0.24 *µm*; on the right: seamless tube 19.05 × 1.22 *mm*, electropolished, 1.4404/UNS S31603, *Ra* = 0.18 *µm*; all images taken under the optical microscope (DIC) at approx. 500 x magnification.

Anodic cleaning can be applied for surface qualities H3 and H4 according to DIN 11866 et seq. as well as for SF1, SF2, and SF3 according to ASME BPE.

## 6.3 Summary

The requirements for process contact surfaces of metallic materials in the pharmaceutical and bioprocessing engineering of equipment and systems can roughly be classified into two groups:

- According to the current state of the art, the minimum requirements are met by surface qualities H3 and H4 according to DIN 11866 et seq. as well as by SF1, SF2, and SF3 according to ASME BPE. These surface qualities are suitable for process contact surfaces with the exception of WFI systems and product contact surfaces. For definitions see paragraph 6.4.
    - Production and distribution systems for purified water
    - Clean & pure steam systems
    - Distribution systems for CIP and SIP media
    - Nitrogen and compressed air lines (anodically cleaned tube systems for oxygen)
- If the requirements regarding corrosion resistance, surface purity and cleanability are high, the electropolished surface qualities HE3 and HE4 according to DIN 11866 et seq. or SF4, SF5, and SF6 according to ASME BPE should be used. This applies in particular to product contact surfaces.
    - Bioprocessing: fermentation vessels and downstream process (purification)
    - WFI systems
    - Sterile filling systems

As mentioned under 6.1, the *Ra* value seems to have only a minor influence on the operating performance of product contact surfaces. The value $Ra \leq 0.80\ \mu m$ mostly prevails for bright finished (e.g. mechanically polished, bright annealed, pickled) as well as for electropolished surfaces, i.e. surface designation H3 or HE3 in the European area. In regions which are predominantly orientated towards the ASME BPE standard, the surface designations SF1 ($Ra\ (max) \leq 0.51\ \mu m$) for mechanically polished surfaces and SF4 ($Ra\ (max) \leq 0.38\ \mu m$) and SF5 ($Ra\ (max) \leq 0.51\ \mu m$) for electropolished surfaces are typically specified.

## 6.4 Definitions/glossary

*DIC:* Differential interference contrast: a microscopy technique that introduces contrast to images of specimens which have little or no contrast when viewed using bright field microscopy, e.g. highly reflective metallic surfaces. Differences in the optical path length of the observed object are transformed into differences in the brightness of the image.

*Process contact surface*: a surface under design operating conditions that is in contact with, or has the potential to be in contact with, raw materials, in-process materials, APIs, clean utilities (e.g. WFI, CIP, pure steam, process gases), or components (e.g. stoppers) and where there is potential for the surface to affect product safety, quality, identity, strength or purity. [7]

*Product contact surface*: a product contact surface that is in contact with, or has the potential to be in contact with, a product - where product is defined by the owner/user. Examples of product contact surfaces may include the interior surfaces of bioreactors, transfer tubing, chromatography columns, vessels and recirculating segments of CIP systems. [7]

*Austenitic stainless steels*: iron-based alloys with a face-centred cubic crystal structure (austenitic structure) and chromium and nickel as the main alloying elements. The first austenitic stainless steel of the type 18/8 CrNi from the company Krupp was patented in 1912. [27]

*Corrosion:* physico-chemical interaction between a metal and its environment which results in changes in the properties of the metal and which may often lead to impairment of the function of the metal, the environment, or the technical system of which these form a part.

*Localised corrosion:* non-uniform corrosion, independent of the crystal structure (pitting corrosion, crevice corrosion, galvanic corrosion) or dependent on the crystal structure (stress corrosion cracking, intergranular corrosion). In contrast to uniform corrosion, the corrosion reaction takes place locally. [27]

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# 7. Hygienic design - basic aspects

Every machine and piece of equipment placed on the market has to comply with the EC Directive on Machinery 2006/42/EC (Richtlinie 2006/42/EG des Europäischen Parlaments und des Rates vom 17. Mai 2006 über Maschinen und zur Änderung der Richtlinie 95/16/EG (Neufassung), 2006). According to this well-known directive, only machines or equipment complying with this document may bear the CE marking. Within this document, hygienic aspects for machines and equipment were mentioned in the chapter entitled "Foodstuffs machinery, machinery for cosmetics or pharmaceutical products" for the first time as follows: "Machinery and equipment intended for use in hygiene-critical areas have to be designed and constructed in such a way as to avoid any risk of infection, sickness or contagion." This sentence contains in principle every hygiene-relevant aspect which equipment for cosmetics or pharmaceutical products must fulfil. This chapter will substantiate these fundamental aspects.

The following detailed definitions are also described:

**Materials**

- "Materials which come into contact or are intended to come into contact with foodstuffs or cosmetics or pharmaceutical products must satisfy the conditions set down in the relevant Directives." This aspect will be addressed in more detail in the chapter entitled "Selection of material for hygiene-critical areas" of this guide.

**Surfaces**

- All product contact surfaces "must be smooth and have neither ridges nor crevices which could harbour organic materials. The same applies to the joints of neighbouring surfaces".
- All product contact surfaces must "be designed and constructed in such a way as to reduce projections, edges and recesses of assemblies to a minimum".
- All product contact surfaces must "be easily cleaned and disinfected, if necessary after removing parts, easy to dismantle. The inside surfaces must have curves with a radius sufficient to allow thorough cleaning".

**Construction**

- "The machinery must be designed and constructed in such a way that these materials can be cleaned before each use. Where this is not possible, disposable parts must be used."
- "It must be possible for liquids, gases and aerosols deriving from foodstuffs, cosmetics or pharmaceutical products as well as from cleaning, disinfecting and rinsing fluids to be completely discharged from the machinery (if possible, preferably in a cleaning position)."
- "Machinery must be designed and constructed in such a way as to prevent any substances or living creatures, in particular insects, from entering, or any organic matter from accumulating in areas that cannot be cleaned."
- "Machinery must be designed and constructed in such a way that no working substances hazardous to health, including used lubricants, can come into contact with foodstuffs, cosmetics or pharmaceutical products. Where necessary, machinery must be designed and constructed in such a way that continuing compliance with this requirement can be checked."

These pertinent hygiene-relevant requirements of the EC Directive on Machinery 2006/42/EC have been integrated and substantiated into the standard DIN EN ISO 14159 (ISO, 2002): "Safety of machinery - Hygiene requirements for the design of machinery". This standard is considered as the generic safety standard (so-called type B1 standard) for all sorts of machinery and equipment for hygienic production environments. It is outstandingly suitable as high-level guide for all aspects of

hygienic construction, the so-called "hygienic design". Numerous directives and documents have been written in order to describe and substantiate the fundamental hygiene-relevant aspects of machinery in more detail. In this context, the documents of the European Hygienic Engineering & Design Group (EHEDG) in particular have to be highlighted because this group has developed very practical and product-specific recommended actions. EHEDG Document 8 corresponds analogously to ISO 14159 (EHEDG Doc 8, 2004). The individual areas of equipment that has been designed and constructed to be hygienically safe will be described later.

## 7. 1 Equipment-specific definition of the hygiene-critical area

First of all, the hygiene-critical area has to be defined based on a risk assessment. Is it about closed equipment or open equipment such as a batching tank, which has to be opened temporarily to fill in the components? Is it about an isolator? In which hygiene-relevant area or in which clean room class is the equipment installed? This will be illustrated by means of the following examples:

**Closed equipment** such as a batching tank with CIP/SIP joints as a typical closed system is usually not placed in a hygiene-relevant area. The main hygiene-critical area is limited to the part of the equipment coming into contact with the process media such as the inner surfaces of the tubes, valves, sensors, fittings and other components with direct product contact. Nevertheless, surfaces exposed to the exterior which, by definition, are not in contact with the product should be sufficiently cleanable. Moreover, the equipment should be easy to dismantle for maintenance.

**Open equipment** such as an open batching tank usually stands directly in a hygiene-critical zone. Therefore, this kind of equipment is not allowed to affect either the product or the environment. Not only are the product contact components hygiene-relevant, but so too are the parts of the equipment that come into direct contact with the environment.
An isolator, as a special construction of an open production process, may separate the production area hermetically from the environment, but the product is processed openly and in most cases in a sterile manner. This means that the entire production area has to be designed in a rigorously hygienic way, especially since automated cleaning and decontamination procedures are used in most cases.

## 7.2 Aspects of hygienic design – closed equipment

In most cases, this kind of equipment takes the form of media-conducting systems (for instance for fluids or powder) with pipe connections and reaction, mixing or retention containers. The required basic characteristics are presented below.

### 7.2.1 Complete drainability

The equipment has to be designed in such a way that the medium can be removed completely by draining. This requires a sufficiently consistent slope from one degree (for aqueous solutions or steam) to three degrees (for viscous fluids or fluids with particles) towards the horizontal. A drain valve at the lowest point is mandatory.

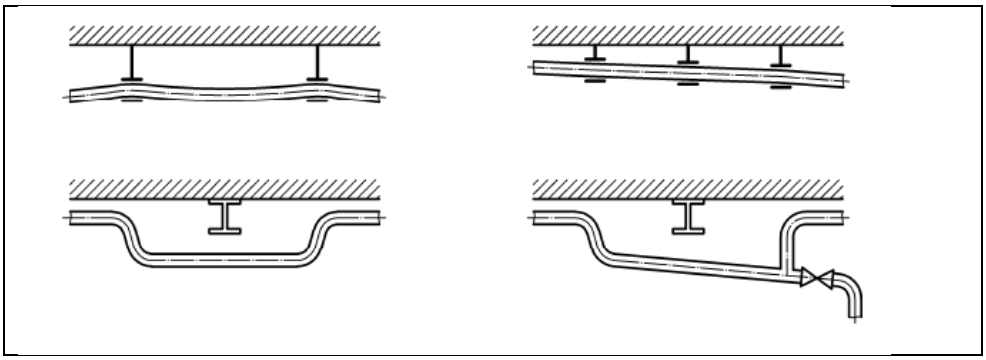

Figure: Drainability of pipework. Left: poor drainability, Right: sufficient drainability.

The design of containers has to avoid areas which cannot be drained completely.

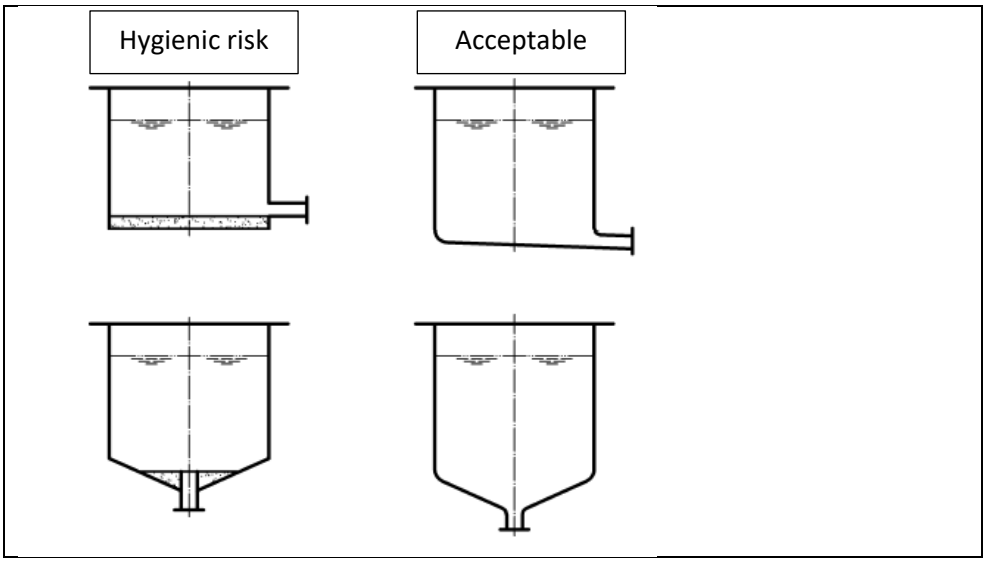


Figure: Drainability of containers. Left: not drainable Right: drainable.

Sensors have to be installed in such a way that the dead leg volume is reduced as much as possible and is ideally drainable.

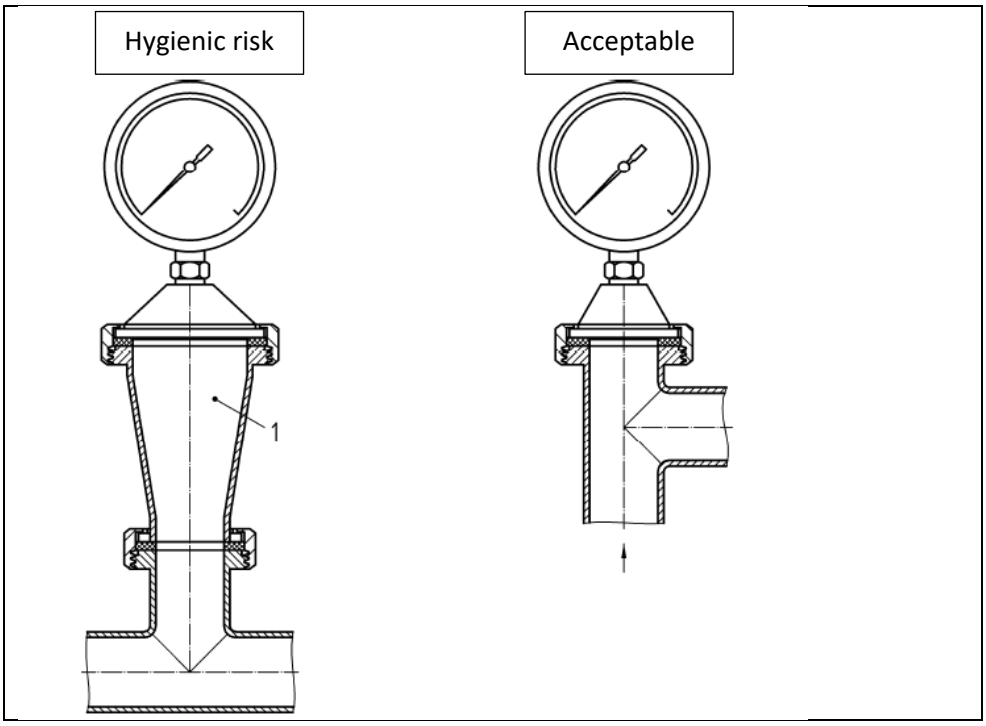


Figure: Sensors: Left: with hygiene risk Right: acceptable

### 7.2.2 Permanent pipe connections

Permanent metal-to-metal connections are usually fabricated by welding. They have to be welded flush and continuously. This also applies to connections made of plastic. Complex size and format components made of plastic, for instance, may not just be screwed. They have to be completely sealed in order to prevent the penetration of liquids deep into the contact surface. This can be achieved by full-faced bonding. Why is this required? If there is contact between two surfaces without a continuous welding seam or sealing, water inevitably penetrates into the gap because of the high capillary forces and therefore evades drying. Tiny contaminants also accumulate in these areas, along with permanent humidity. These contaminations constitute an ideal breeding ground for germs. These germs successfully escape even persistent cleaning since neither mechanical equipment nor chemical cleaning agents can sufficiently penetrate into the gaps. An adequate quality of the welding seam must also be observed. Details can be found in the chapter entitled "Pipework and fittings: detachable and non-detachable pipe connections including welding; welding seam control".

### 7.2.3 Detachable connections

Detachable pipe connections also have to be carried out under strictly hygienic conditions. Details can also be found in the chapter entitled "Pipework and fittings: detachable and non-detachable pipe connections including welding; welding seam control".

EHEDG Document No. 14 also contains detailed information on suitable valve constructions (EHEDG Doc 14, 2014).

## 7.3 Aspects of hygienic design – open equipment

Regarding open equipment, all of the equipment has to be subjected to a risk assessment regarding hygiene since each element may pose a potential contamination risk for the openly processed product. For information concerning cleanability, the standard DIN-EN 1672-2 (6 (DIN EN 1672-2, 2009) from food technology can be helpful.

Shaft seals of an agitator above an open product container can pose a huge contamination risk. A better choice are magnetically coupled agitators. This coupling technique is state of the art in sterile areas. If agitators are installed from above in sterile areas, axial face seals can be greased with WFI. In the case of a non-sterile liquid product, it is also possible to use a dry-operating axial face seal.

Transport rollers of a container pose a relatively small contamination risk for the product. This can be further reduced for instance by organisational measures and by using hygienic suitable transport rollers.
Machines and equipment being installed in a hygiene-controlled zone, e.g. according to the GMP Guidelines, should in general undergo a holistic hygiene-critical assessment. Not only must the product-contacting part of these machines and equipment be cleaned and disinfected regularly, but also the remaining part of the machine exposed to the exterior. The following paradigms are applicable to each cleaning: only those parts that can be accessed geometrically by the cleaning technique used can be finally cleaned. Manual cleaning only covers and cleans visual contamination. What does this mean for the construction of equipment in practice?

### 7.3.1 Accessibility

In the best-case scenario, the surface to be cleaned can be accessed. Where this is not the case, the feature has to be sealed hermetically. A simple example of this is a switch housing. Either it has to be mounted as hygienically safe with sufficiently long spacers on the wall or it has to be fixed hermetically sealed directly to the wall. The same applies to fastenings on the floor. In this case, the required distance to the floor is much bigger than in the case of wall mounting (mop with handle for cleaning the floors versus cloth for cleaning by hand!). For smaller housings, a distance from the wall of at least 5 cm is required. If the housing is bigger, a distance of 15 cm allows for a complete reachability of the wall of the room and at the back of the housing. In a sterile environment - grades A-D - cabinets etc. should be installed flush into the wall.

A minimum of 30 cm has proven to be an adequate distance to the floor. Several suppliers offer commercially available system components in the form of wall spacers and levelling feet according to the requirements on hygienic design.

### 7.3.2 Removable elements

If the construction of elements does not allow for the complete reachability of all surfaces, they should be removable and cleanable separately. Dismantling should be as easy as possible. It should be ensured by means of equipment design that reinstallation is only possible in the correct position. In most cases, a central bolt that is easily accessible from an ergonomic point of view is sufficient for the fixation of the removable element. Asymmetrically positioned guide pins may guide the part to its correct position and may absorb the major mechanical forces. The number of parts to be removed should be as small as possible. The use of contrasting colours for removable and permanently installed mounting elements can be helpful when carrying out a cleaning cycle.

### 7.3.3 Transparency

It is certainly easier to manually clean equipment when all equipment surfaces to be cleaned are directly visible than when the equipment is cramped and its surfaces are not directly visible. Transparent housings and the overall concept of equipment with a lot of space between the individual elements are helpful. Especially in the case of isolators, the "transparency" factor is also affected by the size, geometry and position of installations that can directly influence the primary laminar airflow. It has to be ensured that the primary airflow is deflected as little as possible in the product area.

### 7.3.4 Screw joints

Depending on their design, screw joints may pose a great hygiene risk. The highly popular Allen screw, in most cases countersunk, can definitely not be cleaned hygienically sufficient. Slotted, cross-slotted or Torx screws are not considered as screws that are hygienically cleanable, either. Only a hermetically closed hexagon domed cap nut with rounded flanks is considered as hygienically safe screw fitting. EHEDG Document 13 addresses this topic in detail (EHEDG Doc 13, 1996). The integral part is a washer with elastomer sealing and a metallic stop. On the one hand, the elastomer seal avoids the critical contact of neighbouring incompressible planar surfaces. This prevents the penetration of liquid contaminations that are directly sucked into the crevice of the material pairing because of the adhesive forces and therefore evade cleaning. On the other hand, defined compression of the elastomer without the risk of overstressing is achieved by the metallic limit stop. There are many different hygienic-design screws available on the market. Their purchase price will surely be considerably above the price for standard machine screws. However this should not be about a consideration of costs, but rather about the question of whether the complete machine or equipment has been designed and constructed in a hygienically safe manner or not! This central point should not be neglected when discussing screw joints in the hygienic design of machines and equipment. The principle of hygienically suitable screw joints sealed with elastomer applies similarly to so-called cable glands, as can be seen in the following figure.

Figure hygienic design screw joints. Source: Markus Keller, Fraunhofer IPA

### 7.3.5 Inner corners and angles

The surfaces of inner corners and angles should also be completely accessible during cleaning. To put it simply: "Surfaces of corners that are not completely reachable with my index finger cannot be cleaned entirely." This requires rounded corners and rounded angles with a sufficient rounding radius of at least 3 mm. Cleanability increases steadily up to a rounding radius of 20 mm (DIN EN 1672-2, 2009). Ideally, welds are not carried out in corners but on planar material pairings so that the weld can be post-treated accordingly in order to reach the required surface quality.

### 7.3.6 Horizontal surfaces

Horizontal component and housing surfaces should be avoided. On the one hand, residues of the cleaning liquid might remain after liquid-based cleaning. On the other hand, an agglomeration of dust is not possible on housing tops that have an inclination of 30 degrees or above. The following figure shows the example of a hygienically designed storage cabinet with a roof inclination of 30 degrees in case it is not possible to let the cabinet front reach the ceiling of the clean room.

Figure: Hygienic design of a housing shown with the example of a storage cabinet for GMP-controlled areas. Source: Friedrich Sailer GmbH

## 7.4 Summary

If the fundamental hygienic design principles, outlined above, are considered continuously during design and construction, the machine developed will comply with the requirements of the Directive on Machinery stated in the chapter entitled "Foodstuffs machinery, machinery for cosmetics or pharmaceutical products". As a comprehensive German standard reference work with a high level of details, the following two books by Gerhard Hauser are highly recommended: "Hygienische Produktionstechnologie" (Hauser, Hygienische Produktonstechnologie, 2008) and "Hygienegerechte Apparate und Anlagen" (Hauser, Hygienegerechte Apparate und Anlagen, 2008).

## 7.5 References

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2. ISO. DIN EN ISO 14159. *Sicherheit von Maschinen - Hygieneanforderungen an die Gestaltung von Maschinen.* Berlin : Beuth Verlag, 2002.

3. EHEDG Doc 8. *Gestaltungskriterien für Hygienegerechte Maschinen, Apparate und Komponenten.* Frankfurt : European Hygienic Engineering and Design Group, 2004.

4. EHEDG Doc 14. *Hygienic Requirements of Valves for Food Processing.* Frankfurt : European Hygienic Engineering and Design Group, 2014.

5. DIN EN 1672-2. *Nahrungsmittelmaschinen - Allgemeine Gestaltungsleitsätze - Teil 2: Hygieneanforderungen.* Berlin : Beuth Verlag, 2009.

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7. Hauser, Gerhard. *Hygienische Produktonstechnologie.* Weinheim : WILEY-VCH Verlag, 2008.

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# 8. Pipework and fittings, connections, welding & seam control

Pipework, fittings and connections play an important role in the construction of equipment for pharmaceutical and biotechnological systems. The following chapter presents different types and assesses their suitability for different applications in the GMP environment.

## 8.1 Pipework and fittings

Globally, there are three common standards for pipework in the GMP environment:

Seen historically, the tubes in inches came first - in the 19th century - from England. Tubes and fittings according to dimensions of the ASME-BPE are still widespread worldwide and therefore are often perfect in terms of availability, price and delivery time.

Components according to ISO 1127 may be referred to as chemical standards. The chemical industry had requested tubes with special stability for its applications and a corrosion allowance for the wall thickness regardless of the material and the actual operating conditions. This allowance is certainly necessary if acid is transported in the pipework or if the tube is installed in the open air. Sometimes these tubes are deliberately defined as climbing aids in this equipment (tender specification: "climbable construction"). At chemical sites, this thick-walled version was then declared to be the factory standard.

The following table shows an overview of the dimensions of the three standards, including an example of the calculation for the required minimum flow rate in order to achieve a turbulent flow with a 1m/s flow velocity in the tube:

| DN / NW | OD x s mm | ID mm | V* in m³/h at 1m/s |
|---|---|---|---|
| **DIN11866 Row A Metric / DIN 11850 „The German Style"** | | | |
| **6** | 8 x 1.0 | 6 | *0,102* |
| **8** | 10 x 1.0 | 8 | *0,18* |
| **10** | 13 x 1.5 | 10 | *0,28* |
| **15** | 19 x 1.5 | 16 | *0,7* |
| **20** | 23 x 1.5 | 20 | *1,1* |
| **25** | 29 x 1.5 | 26 | *1,9* |
| **32** | 35 x 1.5 | 32 | *2,9* |
| **40** | 41 x 1.5 | 38 | *4,1* |
| **50** | 53 x 1.5 | 50 | *7,1* |
| **65** | 70 x 2.0 | 66 | *12,3* |
| **80** | 85 x 2.0 | 81 | *18,6* |
| **100** | 104 x 2.0 | 100 | *28* |
| **125** | 129 x 2.0 | 125 | *44* |
| **150** | 154 x 2.0 | 150 | *64* |
| **200** | 204 x 2.0 | 200 | *113* |

| [DN / NW] ** | OD x s mm | ID mm | V* in m³/h at 1m/s |
|---|---|---|---|
| **DIN11866 Row B equiv. to ISO 1127 „The Chemical-Fab-Tube"** | | | |
| **6**** | 10.2 x 1.6 | 7,0 | *0,14* |
| **8**** | 13.5 x 1.6 | 10,3 | *0,30* |
| **10**** | 17.2 x 1.6 | 14,0 | *0,6* |
| **15**** | 21.3 x 1.6 | 18,1 | *0,9* |
| **20**** | 26.9 x 1.6 | 23,7 | *1,6* |
| **25**** | 33.7 x 2.0 | 29,7 | *2,5* |
| **32**** | 42.4 x 2,0 | 38,4 | *4,2* |
| **40**** | 48.3 x 2.0 | 44,3 | *5,5* |
| **50**** | 60.3 x 2.0 | 56,3 | *9,0* |
| **65**** | 76.1 x 2.0 | 72,1 | *14,7* |
| **80**** | 88.9 x 2.3 | 84,3 | *20,1* |
| **100**** | 114.3 x 2.3 | 109,7 | *34* |
| **125**** | 139,7 x 2.6 | 139,7 | *55* |
| **150**** | 168.3 x 2.6 | 163,1 | *75* |
| **200**** | 219.0 x 2.6 | 213,8 | *129* |

| DN / NW | OD x s mm | ID mm | V* in m³/h at 1m/s |
|---|---|---|---|
| **DIN11866 Row C / (inch) imperial or ASME BPE or „The International Pipe"** | | | |
| **1/4"** | 6.35 x 0.89 | 4,57 | *0,059* |
| **3/8"** | 9.53 x 0.89 | 7,75 | *0,17* |
| **1/2"** | 12.70 x 1.65 | 9,40 | *0,25* |
| **3/4"** | 19.05 x 1.65 | 15,75 | *0,7* |
| **1"** | 25.40 x 1.65 | 22,10 | *1,4* |
| **1 1/2"** | 38.10 x 1.65 | 34,80 | *3,4* |
| **2"** | 50.80 x 1.65 | 47,50 | *6,4* |
| **2 1/2"** | 63.50 x 1.65 | 60,20 | *10,2* |
| **3"** | 76.20 x 1.65 | 72,90 | *15,0* |
| **4"** | 101.60 x 2.11 | 97,38 | *27* |
| **6"** | 152.40 x 2.77 | 146,86 | *61* |

DN: Nominal Diameter
NW: Nominal Width / Size
V*: volume flow
OD: Outer Diameter
s: thickness wall of pipe
ID: Inside Diameter

** Row in Table here not DIN-conform, value OD shall be used as NW to avoid mix-ups between Row A and B

*Figure: Overview of common tube standards for pharmaceutical and biotechnological systems*

Thick-walled ISO 1127 components are in fact technically inappropriate for 99.9 % of the applications in the GMP environment. However since many major European pharmaceutical and biotechnological sites, for instance in the area around Basel, in the Rhine-Neckar Triangle, in Frankfurt am Main or Leverkusen, have emerged from former chemical sites - and the chemical standard ISO 1127 had been declared the factory standard there - these requirements can often still be found in these sites today.

But especially for constructors of equipment from the food and pharmaceutical industry in northern and in western Europe this was an unnecessary cost burden since many of the essential components for stainless steel such as chromium, nickel and molybdenum are very expensive. In the case of milk processing equipment, this wall thickness from the chemical sector is unreasonable from a professional point of view since milk and many cleaning agents used in this field are not corrosive in a stainless steel tube and the equipment is usually not installed in the open air. With a wall thickness of 2 mm (cf. GREEN box circled in red in the table above for the example DN 50 60.3x2,00 ID 56.3) the components would only get needlessly expensive and heavy.

For design in the SI environment, it is also helpful if it is possible to work with mm instead of inches and if the standard diameter specification matches the inside diameter of the tube. Therefore, the metrical tube standard DIN 11850 was established in 1936 and further developed to DIN 11866 series A (cf. CYAN box circled in red in the table above for 1.5 mm wall thickness for DN50 53x1.5 ID 50).

It must always be anticipated that these three standard types for tubes are used in biotechnological and pharmaceutical companies, for instance along the Rhine. In the worst-case scenario, all three types are installed in one plant since parts from Germany and from the USA have been installed together with equipment already in place at a chemical site. This variety is a great burden for designers, constructors and operators (maintenance and repair).

Many projects are therefore influenced by the conflicting priorities between somewhat outdated factory standards or planning according to the motto "but we've always built like that" and the cost pressure of new construction projects.

### 8.1.1 Dead legs - construction of pipe systems

Parts of the equipment without flow are problematic in relation to cleaning and sanitisation processes. A differentiation has to be made between:

- COP Cleaning out of place Equipment is dismantled for cleaning
- WIP Washing in place Washing when installed
- CIP Cleaning in place Cleaning when installed
- SIP Sterilisation in place (or) Sanitisation in place

Dead legs hinder the efficiency of WIP, CIP and SIP processes since mechanical flow turbulences or temperature influences are difficult to create and control in these areas.

Consequently, these areas have to be minimised by means of construction.

In this regard, the 3D rule is state of the art in most GMP equipment.

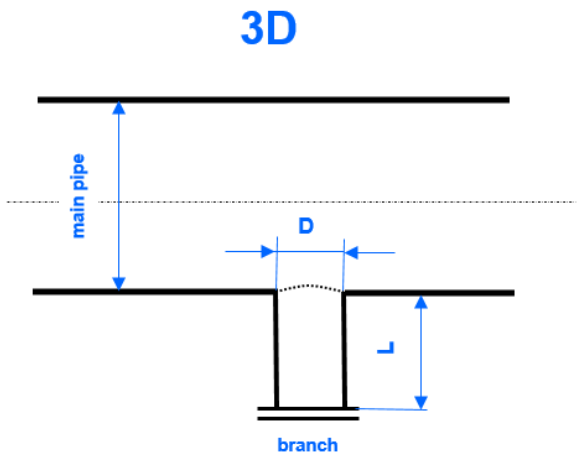



*Figure: 3D rule for dead legs (max. permissible length of branch L ≤ 3x D)*

In (older) literature, the 6D rule can also be found. The rule for the prevention of dead legs (in a WFI system) is mentioned for the first time in the draft of the FDA *Guides for Large Volume Parenterals* (LVP), 21 CFR 212.49 in 1972. This guideline draft was never applicable, however the rule was copied again and again. It can be found for example in the FDA *Guide to inspections of high purity water systems* dated 1993 under the "6D rule". This document may be used by FDA inspectors as a guidance for GMP inspections and is still in use today.

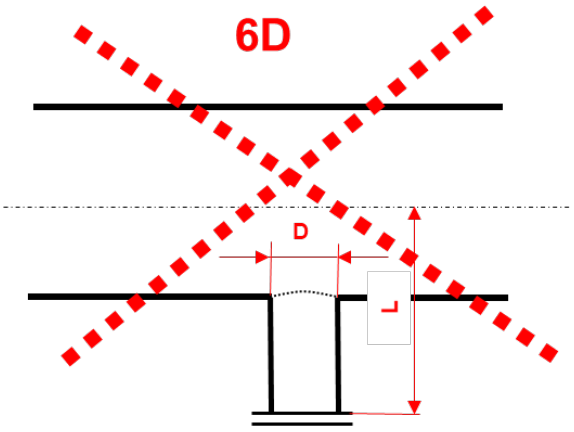



*Figure: 6D rule for dead legs (max. permissible length of branch L ≤ 6x D)*

This is rather unsuitable, however. In the case of a main tube ID 150 mm for instance, the proportion of length L in the main tube would automatically be at least 75 mm. A branch would need to have at least a diameter of 75/6 = 12.5 mm (with an own length proportion branch of 0 mm). Or in other words: according to the 6D rule, DN10 branches would be forbidden on principle in a DN150 tube.

Today, compliance with the 3D rule is state of the art in most pharmaceutical and biotechnological equipment, including for high-purity water systems.

However, in the meantime major efforts are being undertaken to construct according to the 1.5 D rule for expensive products (such as 100 mg product for € 1 million) or, in the case of active substances, products that are difficult to clean (high potency such as hormones, steroids, antibiotics etc.). This may increase the effort & costs in the areas of engineering, tube and valve technology by a factor of 5-20.

The delivery times for applicable monoblock valves, for example, also increase considerably.

The cleanability of the equipment increases with 1.5D, however. In some cases, the product yield can also be increased so that it is nevertheless worth implementing this strict requirement.

### 8.1.2 Detachable connections of pipe systems

Detachable connections generally need to be reduced in CIP and SIP systems.
There are a number of important reasons for this:

- They represent mechanical weak spots
- Points of disturbance/interfering edge in terms of fluid
- Risk of residues when cleaning
- Require a seal/gasket and therefore maintenance and down times[3]
- Hazard point as regard leaks
- Risk of operating error

For some areas, detachable connections are absolutely essential, however, e.g. if instruments have to be dismantled regularly for calibration. Or pumps usually cannot be welded into the system because it has to be possible to exchange them quickly.

The following are the essential standards for detachable stainless steel connections in the European food, chemical and pharmaceutical sectors:

- Dairy coupling DIN 11851 (German industry standard since 1936)
- Clamp DIN 32676 conforms to ISO 2852 ("tri-clamp", since 1974)
- Numerous solutions specific for the manufacturer, e.g.
  (Bioconnect [Neumo], Stericonnect [KST], orbital welding coupling [BBS], W-series [SÜDMO], etc.)
- Aseptic connection DIN 11864 (DIN since 1998, taken over by ASME BPE already in 2002 as "European Hygienic Fitting")

The dairy coupling can still be found in many food processing plants today.


*Figure: Dairy coupling DIN 11851 / Source NEUMO*

The dairy coupling is often used in the food industry. Due to the high viscosity of many products, the pipework must often be opened for cleaning. A dairy coupling can be opened easily and swiftly by means of a C-wrench.

Advantages compared with common flanges with flat gasket are:

- Axial fixing by means of a metallic stop
- Rapid opening/closing possible

[3] The topic of "detachable seamless pipe connections" will be addressed subsequently.

One fundamental disadvantage of the dairy coupling is the gap in the gasket geometry shown in the figure above. This is the reason why this sort of connection is not usually used any more in new biotechnological and pharmaceutical systems. These components are still used in GMP equipment, but only for COP systems (with a low value of product per kilogram). In other words, systems that are regularly dismantled for cleaning.

The clamp according to DIN 32676/ISO 2852 is currently the most often-used detachable connection in the GMP environment. In colloquial speech it is also called tri-clamp, but this is the copyrighted brand name of the company Tri-Clover.

*Figure: Clamp according to DIN 32676/ISO2852*

Essential advantages of this connection:

- Good availability of components since it is the most widely used connection in the pharmaceutical construction of equipment
- No problem with tongue and groove (the parts are exchangeable since they are symmetrical)

But there are also disadvantages:

- Geometrical fixation at the rubber, no metallic stop
- Strain on the pipework may lead to gap formation at the gasket

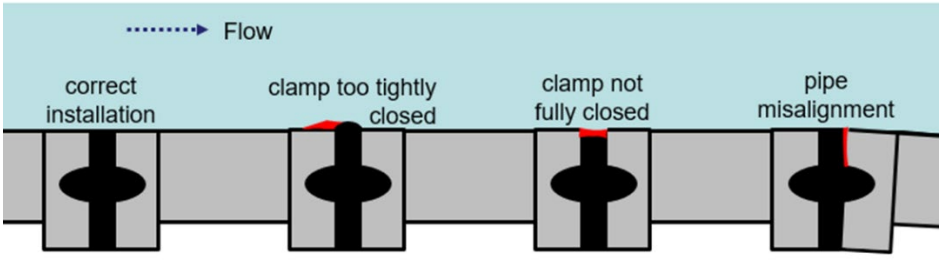



*Figure: Potential errors when using a clamp according to DIN 32676 / ISO 2852*

Clamps are also available as special versions, e. g. clamps that can only be opened with tools or for high-pressure applications.

*Figure: Clamp bracket according to DIN 32676 / ISO 2852 as standard hand, tool or high-pressure version. Source: DOCKWEILER*

The connection according to DIN 11864 has been regarded as superior from a sterile-technical point of view since 1998.

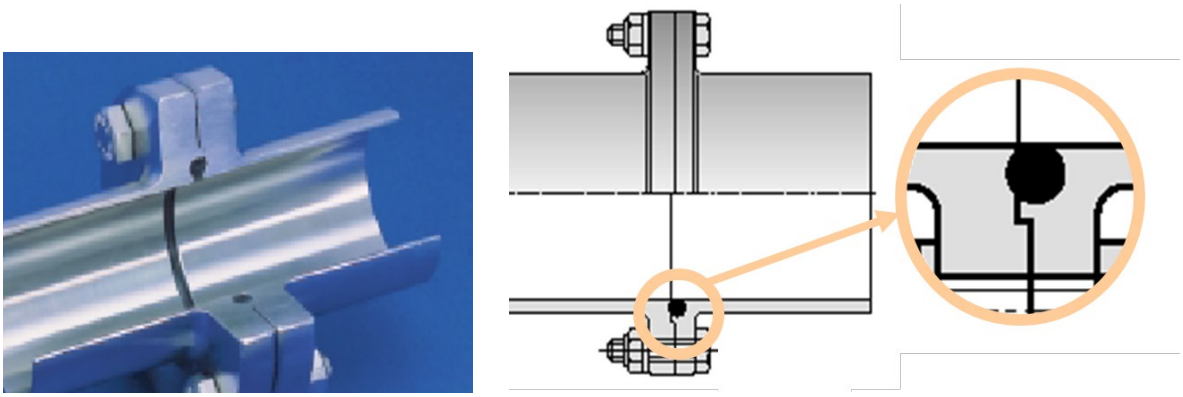


*Figure: Aseptic connection DIN 11864 as a flanged version / Source NEUMO*

Essential advantages of this O-ring connection:

- No dead legs
- Exact metallic stop allows defined gasket compression
- Small mass for fast sterilisation
- Available as flange to be screwed (externally) with clamp or milk pipe C-wrench[4]

[4] Laypersons often think they are able to see from the outside which connection type is used. This can lead to serious errors. Therefore, it is highly recommended in the GMP environment to specify the gasket contour of detachable connections in the PID.

*Figure: Aseptic connection DIN 11864 as a clamp and screw version / Source DOCKWEILER*

The aseptic connection DIN 11864 has the following disadvantages:

- Maximum processing precision required in the construction of tubes
- Execution planning with fixed and floating bearing for the tube has to consider space for the installation and removal of the gasket (so that the tongue of the tongue and groove connection is safely protected from damage)
- The position of tongue and groove have to be considered during planning and assembly

Due to its specific advantages, this type of connection according to DIN 11864 is to be highly recommended for very expensive products and/or highly potent active substances - usually together with the 1.5D-rule already addressed previously.

Between the introduction of ISO 2852 clamps in 1974 and the aseptic connection DIN 11864, there were some proprietary developments from companies processing stainless steel. As a rule, they have pre-empted the advantages of the connection according to DIN11864. However since the solutions were not standardised and only partially commercialised, this led to considerable extra work as regards planning, construction and maintenance.

In general, the elastomer gaskets themselves are a weak point of each connection. Consequently, the search for a technology "without rubber" is understandable.

Developments with metallic "only" designs are available:

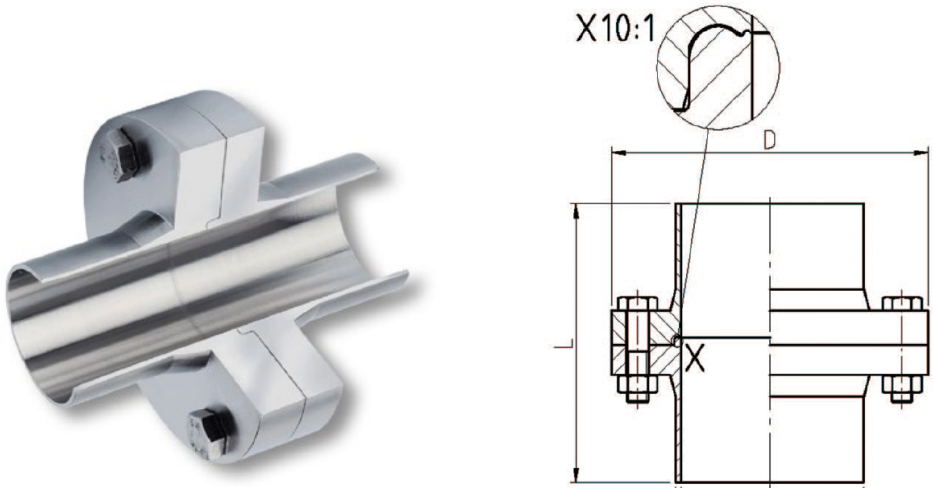



*Figure: Seal-less connection type Bio-Connect-S closed and Doppel-S-Dicht-Kontur / source: NEUMO*

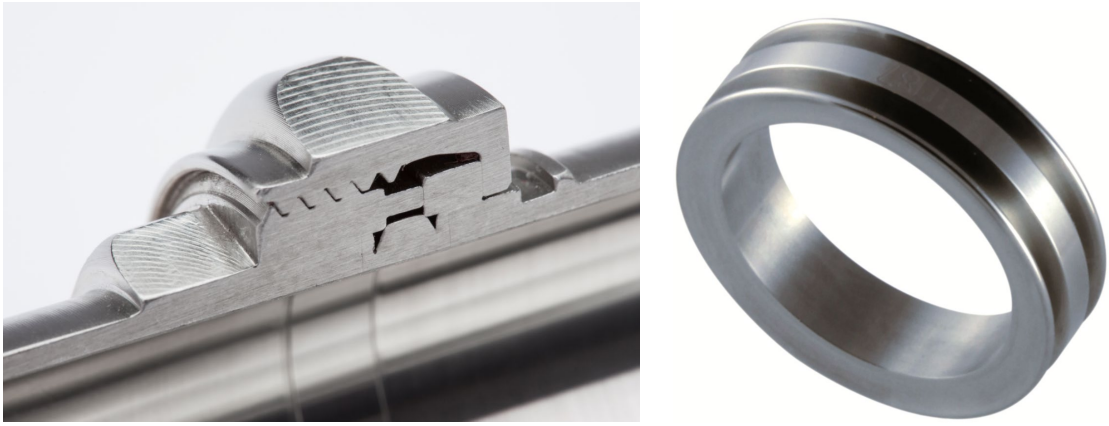


*Figure: Seal-less connection type ZeroCon (pressed and gasket / source: DOCKWEILER*

These seal-less connection types also require maximum precision and cleanliness during pipework assembly in order to ensure the tolerances of sometimes only 100 µm for these connections. Regarding tube systems hanging, for example, on a steel construction which itself has a flexibility of +/- 2 cm (e.g. static layout of the building or influences of weight and temperature), the planning, construction and correct assembly of these types - and of the types according to DIN 11864 - are associated with some effort. It might be that these systems will replace the rubber seal for individual applications (for instance for connections that only have to be opened every 5 to 10 years and/or for applications above 130°C).

For high-purity gases, there are several special coupling systems, some including valve function, non-return-design or pressure relief capability.

## 8.2 Welding technology

The introduction to this chapter takes the form of two sentences from the old DIN EN729-1 (1994): "Quality cannot be tested into the product... Even the most comprehensive and highest developed non-destructive testing doesn't enhance the quality of a welding process."

The following chapter addresses the most important method –tungsten inert gas (TIG) welding[5].

TIG welding can be attributed to the following procedures:

- Metal welding
- Fusion welding
- Gas shielded arc welding
- Butt welding
- Arc welding

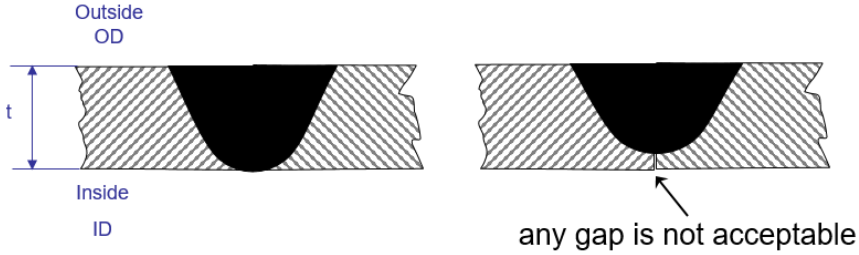
There is no valid ISO or European guideline or standard completely meeting the requirements of the pharmaceutical and biotechnological construction of equipment[6]. That is why ASME-BPE is the usual reference. ASME-BPE defined very useful and clear quality criteria for welding back in 1997 in such a way that they can be worked with on construction sites.

The essential quality criteria for welds are presented below.

The main weld defects are described below:

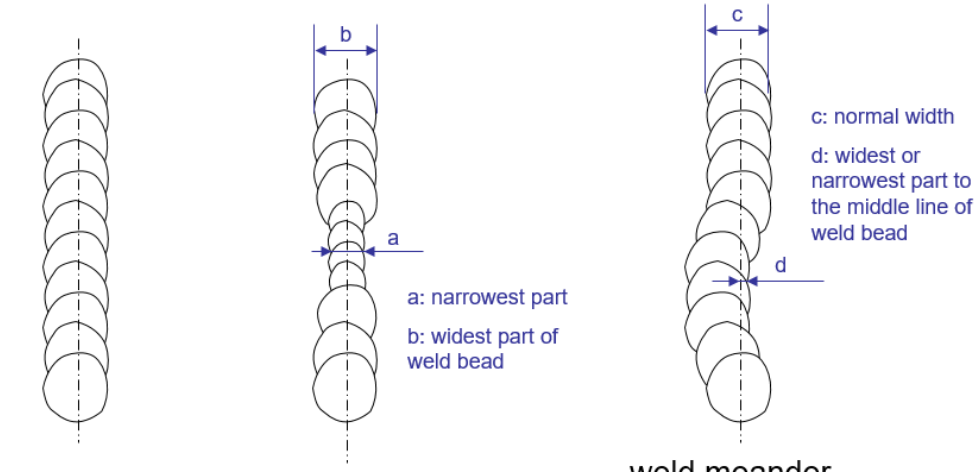
(1) Discolouration on the heat affected zone (HAZ) in the tube = tempering colours
This sort of weld defect was still relatively common when the amount and duration of the pro-purge with protective gas for welding was calculated "by hand" for each welding by means of the volume and the geometry of the component.
This defect almost never occurs nowadays since the introduction of welding machines with automatic measurement of the remaining oxygen and the release of the welding process only at values below 20ppm.

(2) Insufficient penetration/insufficient welding-on of material




[5] Tungsten is used since this material is stable in the arc. Furthermore, only little specific energy is needed to ignite the arc.
[6] The criteria for the highest quality level B in EN ISO 5817 DIN EN ISO 5817 (2014, Fusion-welded joints in steel – Quality levels for imperfections) is still not good enough; e.g. an acceptable convexity of "h≤1mm" is too much for a tube wall thickness of 1.5mm.

(3) Irregular width of welded seam




straight, uniform weld bead

excessive weld bead width variation

a < 50% b
not acceptable

weld meander

d < 25% c
or
d > 75% c
not acceptable

(d shall be 50%)

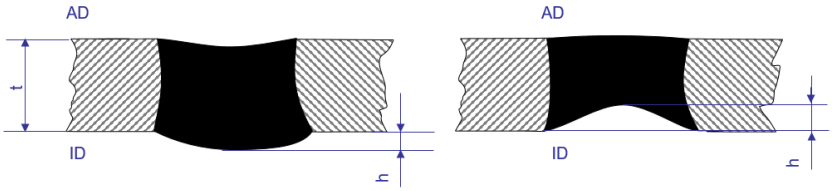
(4) Open cracks, pores & inclusions

Open cracks, pores & inclusions can be checked by means of endoscope pictures and videos. They do not exist de facto if orbital welding machines and tubes that are compliant with the standard DIN 11866 are used.

Therefore, it is not possible to show an image as example.

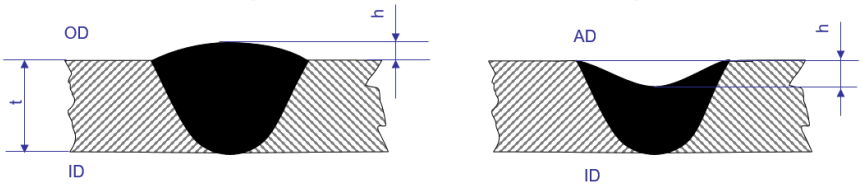
(5) Convexity & concavity

ID concavity and suckback for the clean side



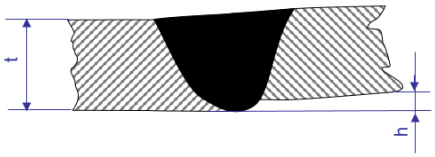

h > 10% t is not acceptable for the clean side

OD concavity and suckback for the dirty side



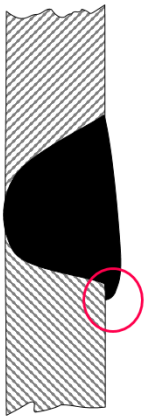

h > 15% of t is not acceptable for the “dirty” side

(6) Tack welding error & misalignment




h > 15% t not acceptable

(7) Overflow of weld deposit



not acceptable,
due to slot generation

The following image shows a welding error still occurring relatively frequently in an endoscope picture.

*Figure: Endoscope picture, manufacturer's error: seam: insufficient formation before tacking*
*In the picture, blue and brown tempering colours are visible at one point. This error pattern is typical for a manual tack-weld to fix the position of the tube connection without having a sufficient level of protective gas.*

Weld inspection is today much easier and better than 30 years ago thanks to the good and affordable availability of endoscopes.

Orbital welding of stainless steel tubes with automated machines is state of the art in the construction of GMP equipment. In principle, it is easy to operate the machine. Usually, workmen can learn this within three to six months.

Special cases are always more difficult. For instance if:

- The seam cannot be pre-fabricated in the workshop.
- The seam cannot be carried out by means of a machine (for instance since there is not enough space for the closed welding gun).

For such cases, particularly skilled and qualified personnel is required. To date, there is no "official evidence of formal qualification" for such personnel. Therefore, it is necessary and reasonable to differentiate accordingly regarding personnel and quality control.

Small irregularities compared to orbital-machine welds have to be tolerated in manual welds.

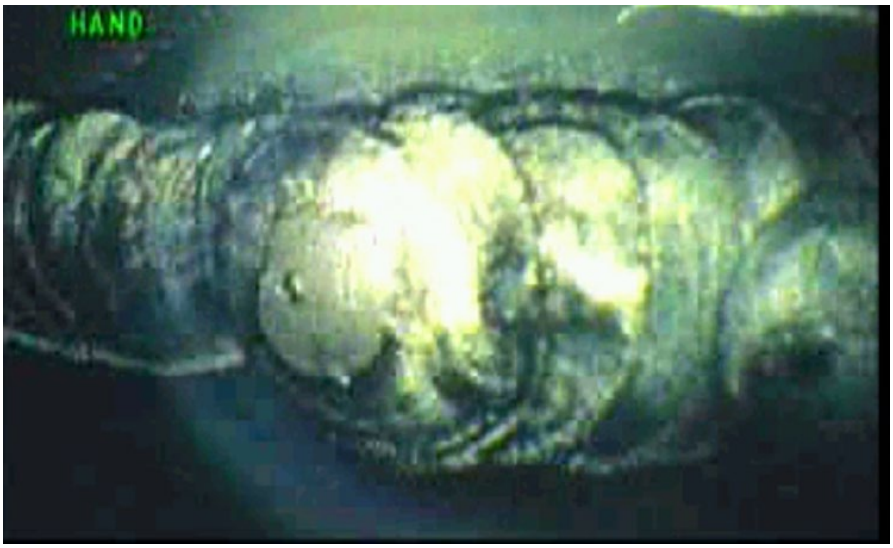



*Figure: Endoscope picture of a manual seam with irregularities as discussed.*

In order to correct a seam, it is usually necessary to saw the defective seam incl. about 1-4 cm HAZ (according to the tube's wall thickness) out of both sides, to re-machine the tube ends, to prepare a fitting tube piece and to insert this by means of two new welds.

If manual seams are marginally irregular, an evaluation has to be carried out as to whether the inner surface will really be improved by removing the problematic manual seam and carrying out the correction according to the above-mentioned procedure.

In an ideal situation, the perfect construction ensures that no manual seams are required. But this might lead to design conflicts: the GMP risk caused by a bigger dead leg has to be considered as greater than the risk associated with the imperfect surface of manual welding.

These test criteria for welds were also presented in order to encourage the person in charge of the system to weld-check the construction. No projects are helped if this check is carried out only at the end by a "qualified welding expert". If this expert detects a defect at the end, this usually means the patients receive their products from this plant either with a delay (weld repair work always has a big impact on schedule and cost).

**Longitudinally welded tubes and seamless tubes**

Longitudinally welded tubes are state of the art in the pharmaceutical and biotechnological construction of equipment.

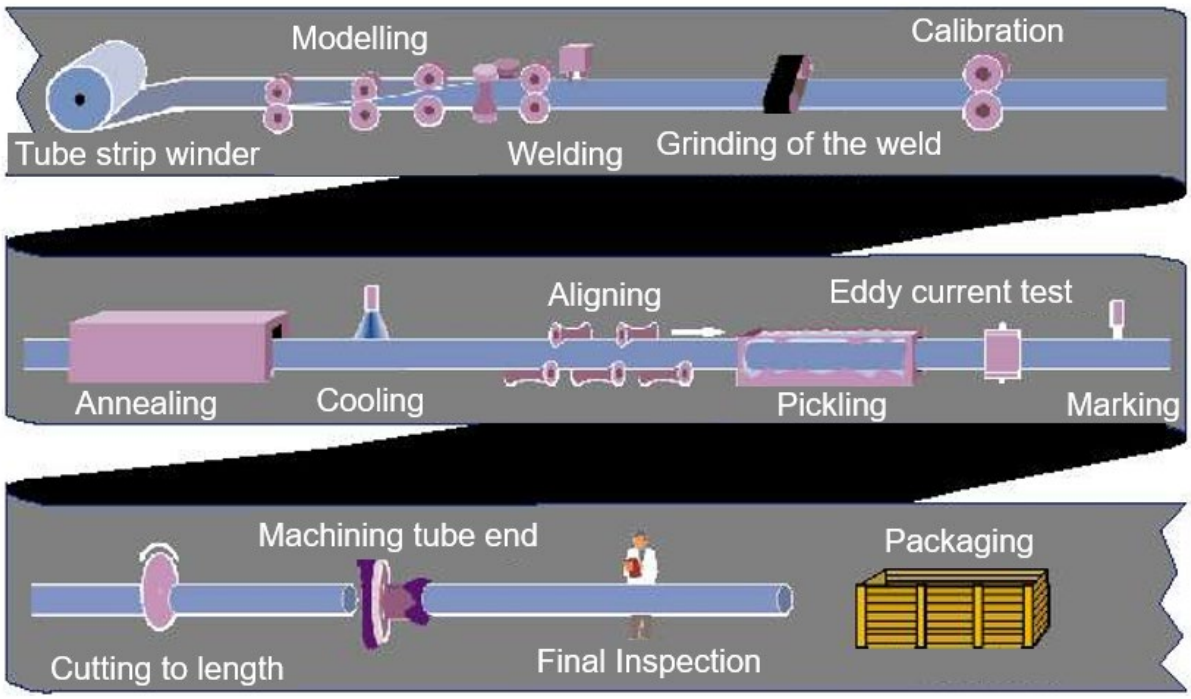



*Figure: Manufacture of longitudinally welded tubes made of foil stock. Source: Dockweiler*

The solidification technology for these longitudinally welded tubes is in general so far developed that they can also be used for critical equipment for very expensive products and/or highly potent active substances. By means of corresponding post-processing, the manufacturers of tubes succeed in making the longitudinal weld virtually invisible.

For special constructions there is also the "seamless tube" requirement. The manufacture of these tubes is much more complex and associated with special risks.

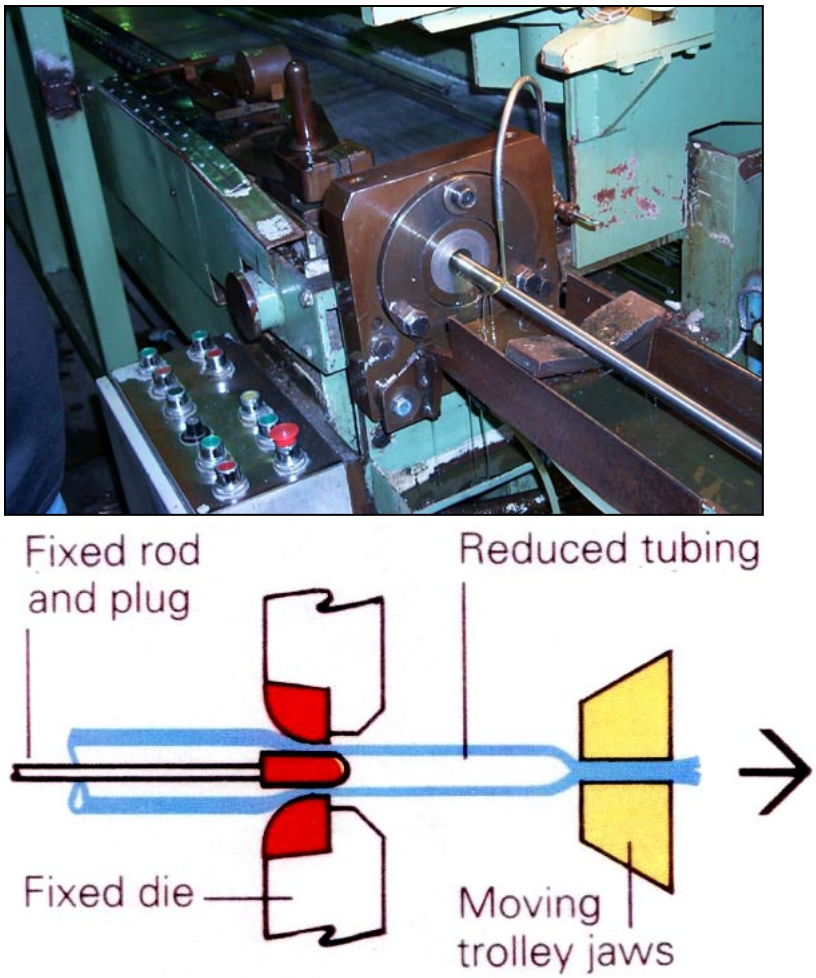



*Figure: Manufacture of seamless tubes by means of plug drawing of the tube. Source: N. Head, Fine Tubes Ltd. U.K. & DOCKWEILER*

These tubes are used, for example, in heat exchangers with double tube sheet (DTS). The focus is not on increased strength, but on the specific production of these components. The tubes in DTS heat exchangers can only be rolled in the inner tube plate. They cannot be welded in. In this case, the rolled-type joint would be disturbed by a longitudinal seam since hardness and deformability would vary widely from the non-welded tube material. This would increase the risk of leaks considerably at the rolled-in part.

## 8.3 Definitions / glossary

- ASME BPE: American Society of Mechanical Engineers Bioprocessing Equipment
- DTS: Double-Tube Sheet
- HAZ: Heat Affected Zone

# 9. Requirements for the process environment: the clean room

The chapters above focus on the equipment itself, mainly on requirements or design parameters for product contact parts or surfaces. In pharmaceutical manufacturing, however the environment of the equipment used for manufacturing also has to comply with requirements that are ultimately supposed to protect the product from contamination.

The following table shows the requirements in ISO 14644 for clean rooms and analogue classifications according to Annex I of the EU Guidelines on Good Manufacturing Practice.

| **Effective standard** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **DIN EN ISO 14644-1** | | | | | | | **EU-GMP** | |
| Clean-room class | Cn=maximum count particles per cubic metre and particle diameter | | | | | | Room classification | Colony forming units CFU/m³ |
| | 0.1 µm/m³ | 0.2 µm/m³ | 0.3 µm/m³ | 0.5 µm/m³ | 1.0 µm/m³ | 5.0 µm/m³ | | |
| ISO 1 | 10 | 2 | | | | | | |
| ISO 2 | 100 | 24 | 10 | 4 | | | | |
| ISO 3 | 1000 | 237 | 102 | 35 | 8 | | | |
| ISO 4 | 10000 | 2370 | 1020 | 352 | 83 | | | |
| ISO 5 | 100000 | 23700 | 10200 | 3520 | 832 | 29 | A / B | <1 |
| ISO 6 | 1000000 | 237000 | 102000 | 35200 | 8320 | 293 | (B) | 10 |
| ISO 7 | | | | 352000 | 83200 | 2930 | C | 100 |
| ISO 8 | | | | 3520000 | 832000 | 29300 | (C)/D/ E/F | 200 |
| ISO 9 | | | | 35200000 | 8320000 | 293000 | incl. employees | |

The grades A, B, C, D are specified in Annex 1 of the EU Guidelines on Good Manufacturing Practice in further detail. The grade is defined by means of the maximum permitted particle concentration and the operational state ("at rest" or "in operation").

| Grade | Maximum limits for particulates ≥ 0.5 µm/m³ | | Maximum limits for particulates ≥ 5 µm/m³ | |
|---|---|---|---|---|
| | At rest | In operation | At rest | In operation |
| A | 3 520 | 3 520 | Not applicable | Not applicable |
| B | 3 520 | 352 000 | Not applicable | 2 900 |
| C | 352 000 | 3 520 000 | 2 900 | 29 000 |
| D | 3 520 000 | Not defined* | 29 000 | Not defined* |

*The particle limits for grade D (in operation) have to be defined by the operator.

| Grade | Air sample cfu/m³ | Settling plates (diameter 90 mm) cfu/4 hours | Contact plates (diameter 55 mm) cfu/plate |
|---|---|---|---|
| A | No growth | | |
| B | 10 | 5 | 5 |
| C | 100 | 50 | 25 |
| D | 200 | 100 | 50 |

It should be noted here that these grades or cleanliness classes are only required for the manufacture of sterile medicinal products. Since there is no separate classification for example for the manufacture of solid dosage forms (such as tablets), grades are often chosen according to Annex 1.

| | |
|---|---|
| A | Sterile area; open product (such as filling operation) |
| B | Environment of grade A; manual operations from grade B in grade A |
| C | Environment of grade B; filling of terminally sterilised products |
| D | Environment of grade C; preparations of terminally sterilised solutions; today often used as clean room grade for the manufacture of solid non-sterile medicinal products |

In order to meet the requirements for cleanliness (number of particles and microorganisms) in the grades mentioned, the air is cleaned by means of HVAC systems and filters. This clean air displaces the "dirty air", so that the required cleanliness is reached after a given time. But this is not enough. There are also requirements concerning the physical room surrounding the manufacture, i.e. the floor, ceiling and walls. Without special components for clean rooms, it would not be possible to permanently ensure the high requirements for cleanliness of grade A, B or C.

The following table shows the usual temperature, humidity and pressure differences for the different clean room areas.

| Area | Temperature | Rel. humidity | Pressure difference |
|---|---|---|---|
| Class A | 20 ± 3 °C | 50 + 20 % | +55 ± 7 Pa |
| Class B | 20 ± 3 °C | 50 + 20 % | +55 ± 7 Pa |
| Class C | 20 +5/-3 °C | 50 + 20 % | +40 ± 7 Pa |
| Class D | 20 +5/-3 °C | 50 + 20 % | +25 ± 7 Pa |
| Class E | 20 +5/-3 °C | 30 to 65 % | Overflow |
| Class F | 20 +5/-3 °C | 30 to 65 % | Overflow |
| c.n.c. areas | 20 ± 5 °C | 50 + 30 % | - |
| n.c. areas | 20 ± 5 °C | No requirement | - |
| Technical areas | 20 ± 10 °C | No requirement or NMT 70% (due to electrical switch units) | - |

The following paragraphs present the individual components and also discuss the state of the art, design versions and details to which attention has to be paid so that the result will comply with GMP. In light of the variety of possible design versions and materials, the question arises as to which version of which component is suitable for which purpose.

**GMP requirements for the components**

As concerns the requirements on premises for pharmaceutical manufacturing, the GMP regulations contain only general statements such as:

- Suitability for intended use
- Sufficient space for production including materials, instruments and personnel
- Design according to the state of the art
- Impermeable components (walls, floor, suspended ceilings)
- No uncontrolled cavities or connections to the environment

The shedding or accumulation of particles and microorganisms or molecular outgassing has to be avoided.

The GMP Guidelines also contain the following requirements for the surface quality of components:

- Smooth, unbroken, impervious surfaces without cracks or inaccessible joints
- No shedding or accumulation of particles possible
- No breeding ground for microorganisms
- Easy to clean and avoidance of inaccessible surfaces
- Proven suitability for the intended cleaning or disinfection agents and frequency of application
- Maintenance, if possible, from outside of the clean room
- This applies analogously for the laying of tubes, other installations and fittings.

## 9.1. Selection and procurement

**Which factors influence the selection of components?**

The process- and product-specific requirements to be deduced from the manufacturing process, the specified clean room classes, the desired flexibility (similar or varying use) und the intended cleaning or disinfection agents are decisive for the selection of components. For the design and definition of the scope of qualification/validation, national and international guidelines also require a risk assessment to be carried out. This leads to special clean room requirements for components in relation to technology and hygiene. The type of use also entails different requirements. Administration, research and laboratory buildings have different demands to production premises. The requirements for production areas and clean rooms used for pharmaceutical purposes have more stringent standards than other buildings, even if these components have no direct contact with the pharmaceutical products. Here, a risk-based assessment of surfaces in the context of proximity to the product and cleanability is required. For the selection and assessment of suppliers, a supplier qualification has to be carried out.

**Differentiation between the requirements for buildings and premises used for pharmaceutical purposes and for other buildings**

- Higher requirements in terms of stability/statics as concerns dynamic loads (such as wind pressure or snow load). The buildings have to safely resist such loads since the interior clean room may not be deformed. The hall roof of a steel construction, for instance, may not be raised or lowered by 1 cm if the clean room ceiling is suspended there. Unavoidable deformations of the building structure - for instance because of changing temperatures – has to be taken into account when designing the clean room, for example by means of suitable compensation structures which have to be arranged outside the critical areas.
- Higher requirements on the smoothness of the floor (in order to be able to install precise wall elements or door seals later or in order not to exceed the silicone seams ability to compensate) and, where applicable, higher requirements on the slope so that during washing processes or leaks a controlled discharge of liquids is possible.
- Higher requirements regarding the tightness of external façades.
  A specific façade leakage is recommended of at least
  <0.3 m3 x h-1 x m-2 with a dynamic pressure of 500 Pa in order to minimise the entry of particles from outside as far as possible (from Report no 6, Partikeltransport durch undichte Fassaden, Dohm Pharmaceutical Engineering, Dr.-Ing. Wolf Ziemer, DI(FH) Mike Urack, Mai 2009, www.dphe.de)
- Higher requirements regarding the tightness of enclosing surfaces of clean rooms (the higher tightness can also become a problem for maintaining the room pressure and has to be taken into account for the room pressure control.)

- Smooth non-porous surfaces, without cracks and uncontrolled cavities and easily accessible for cleaning.
- No retention and shedding of particles or "outgassing" of ingredients ("molecular contamination").
- The materials chosen may not be a breeding ground for micro-organisms.
- Resistance to the intended cleaning or disinfection agents and the cleaning procedure.
- In special cases, the electrostatic charge also is a criterion (for instance if materials in powder form are processed, media transfer in plastic pipes).
- Other installations (tubes, air ducts, electric installations) have to be installed in such a way that they are easy to clean – shieldings up to the ceilings or the observance of minimum distances corresponding to the cleaning procedure (see Figure 2).
- Simple and tight integration of various fittings such as ventilation openings (supply air, exhaust air, overflows), lighting, smoke detectors, sprinklers, etc.
- Buildings and premises used for pharmaceutical purposes are often subject to significant and rapid changes. They should therefore be planned and constructed in such a way that subsequent functional and technical changes can be carried out rapidly and efficiently (for example reserve areas for redundant systems and extensions, sufficient access and removal routes and openings for instruments, space for maintenance and servicing, etc.).

Special operational requirements can also include measures for an ergonomic workplace design fully accepted by the personnel (such as daylight, coloured design of surfaces and so forth).

The following paragraphs describe the design possibilities primarily for the construction of pharmaceutical clean rooms of the GMP grades A-D. The requirements are not as high for non-sterile manufacturing. Solutions for non-sterile manufacturing and also temperature-controlled areas (cold storage rooms, incubation chambers or the like) are not addressed explicitly, but the other solutions can be applied analogously.

## 9.2 Wall and ceiling systems

The most important questions are about the current state of the art concerning ceiling and wall systems, i.e. what can the user demand from competent and experienced suppliers nowadays and what differences have to be kept in mind when assessing offers and alternatives from the selected providers? The following checklist aims to offer help.

| **Checklist wall and ceiling systems** | **Complied with?** | | |
|---|---|---|---|
| **Assessment criterion** | **Yes** | **No** | **N.a.** |
| Well-engineered/proven construction | | | |
| Verifiable tightness, if required | | | |
| Defined building material class according to official or own specification | | | |
| Fire resistance class according to the requirements of the insurer or for fire compartments | | | |
| Size/grid of the elements:<br>axial grid, banded grid, monoblock, easy to change, to supplement and to dismantle | | | |
| Well-designed wall-wall, wall-floor and wall-ceiling joints with the possibility for tolerance and level compensation | | | |

| | | | |
|---|---|---|---|
| If concave fillets are desired, it is preferable to use corner profiles with integrated concave fillets instead of subsequently fitted concave fillet profiles for reasons of hygiene (uncontrollable cavity behind the profile)<br>The radius of the concave fillet has to be adjusted to the cleaning tools intended for use or suitable cleaning tools have to be chosen (rotating floor brushes, for instance, are not suitable for large radii) | | | |
| Seals and expansion compensation towards static walls | | | |
| Size, amount and quality of silicone joints | | | |
| Material and thickness of the panels - usually steel sheets are used with a coating or powder-based paint, stainless steel, aluminium, about 1 mm thick | | | |
| Total thickness, inherent stability and maximum height of the wall elements as well as their load capacity for the direct mounting of small equipment (such as towel dispensers, soap dispensers, etc.) | | | |
| Possibility of installations within the wall elements or variable panelling in order to allow for necessary installations (such as IT cabling, power cabling, return air shafts, instrument connections) | | | |
| Passages through walls and ceilings:<br>• especially fixed pipe bushings taking into consideration the expansion due to temperature changes, electrical installations, etc.<br>• sealable bushings for transfer tubing only needed sometimes | | | |
| Where necessary walls made completely of glass for the separation of special areas (see Figure 3 for an example of an accessible return air duct for aspiration close to the ground) | | | |
| Installation of doors and other elements (clearance and leakage rate, where required drop-down seals, door drives and concepts for failure of the drives, contacts for the control of room ventilation systems for the securing of pressure cascades at open doors, control panels etc.), quality of fittings, accessibility, cleanability | | | |
| Installation of windows and tightness, type of glazing and size of the windows (one-sided/two-sided flush glazing, safety glass, installation of screens, blinds, etc.) | | | |
| Installation quality in ceiling elements: lamps, filters, sprinklers, loud speakers, smoke detectors, etc., flush or protruding | | | |
| Defined load capacity of the ceiling - accessible ceiling for maintenance purposes, suspension grid | | | |
| In the case of raw ceilings with a low height (reconstruction), sufficiently dimensioned and sealable openings facing down (a "crawlable" ceiling will usually not be used - access to - or crossing of - fittings is very difficult and contradicts the GMP concept of "easy" maintenance and inspection) | | | |
| Short installation times and little construction dirt, covering of the elements with foil until completion | | | |
| Effort required for assembly, dismantling and changes | | | |
| Easy to clean and resistant to the cleaning and disinfection agents used (wipe disinfection and fumigation/fogging) | | | |
| Sound absorption value for instance: absorption elements wrapped in foil and fit in the wall or ceiling | | | |

| | | | |
|---|---|---|---|
| Acceptance by the regulatory authority | | | |
| Good acceptance by the personnel | | | |
| Design of airlocks (automatic or manually operated doors, airlock control including locking time and, where required, connection to the control of room ventilation system and the access control and access operation - indicator of status) offered by the supplier as comprehensive solution | | | |

It has already been recognised that uniform lighting and the usually bright surfaces are stressors for work in a clean room. Possible solutions are LED lights, the colours of which can be changed/adjusted, and the colour design of walls and ceilings in the clean room.

### 9.2.1 Wall panelling, coating

The industry offers coatings for walls, ceilings and floors as well as wall panellings consisting of modular panel elements tailored to the needs of the pharmaceutical industry for new constructions, renovations or reconstructions of existing buildings. Already existing walls made of concrete and tiled or plastered walls can be coated or panelled in the same way, e.g. as new walls made of gypsum board or even chipboard.

Bushings for media as well as window and door elements can be integrated into the wall panelling without joints. Wall coatings and floor coverings can be connected without joints and corners or edges by means of a concave fillet (see Figure 1 for an example), vertical or triangle socket.

Figure 1: Concave fillet with wall coating (Source: BARiT Kunstharz-Belagstechnik GmbH, D-73709 Esslingen, www.barit.de)

If existing walls are panelled or coated for the pharmaceutical clean room application, attention has to be paid especially to the following points:

- High-quality moisture-resistant coating resistant to specified cleaning and disinfection agents
- Good assembly or adhesion to the existing underfloor
- Connection to window and door frames - for higher cleanliness classes (C/ISO8 and higher) a flush-mounted installation is considered as standard
- Execution and integration of installations such as lighting, cable ducts, tube bushings, etc.

- Special adjustment works in the socket area, at the connections to the ceilings, if necessary, also at the wear and ram protection if it is integrated into the wall
- Cold storage rooms and freezing rooms have to be tested with regard to the resistance to temperature fluctuations (from approx. +25°C to approx. -20°C) regarding expansion and brittleness. The risks caused by the formation of condensation water must also be considered.

It is quite acceptable to furnish manufacturing facilities with coatings (a nearly jointless execution is possible). Coatings are especially suited for renovations.

A further possibility are wall panellings made of modular panel elements which are attached to the base wall with the aid of special profile elements (see Figure 2 for an example). As regards their appearance and characteristics, they usually also correspond to the standard partition walls made of system components. The joints between the panels are sealed the way it is done with system walls and they also comply with the international GMP standards.

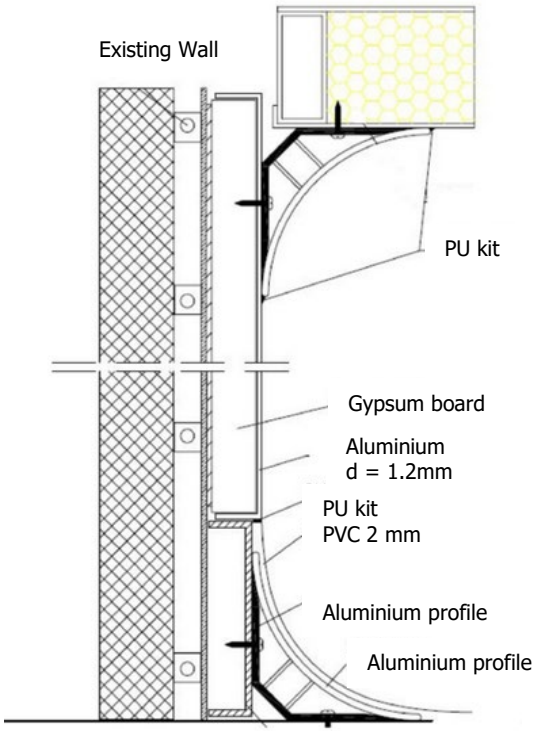



Figure 2: Example of the design of wall panelling
(Source: OCTANORM-Vertriebs GmbH, D-70794 Filderstadt, www.octanorm-reinraum.de)

### 9.2.2 Wall systems

System walls and system ceilings have been the established state of finishing art for some years. The numerous producers of such systems also offer solutions suitable for fire compartments and big, high walls such as storage rooms. System walls and ceilings are flexible in terms of planning and installation and subsequent changes can be carried out rapidly and easily.

The most common application is the "room in the room" solution. This means that a conventional building made of concrete or bricks with pillars and support systems serves as the shell and the clean rooms are fitted out in the interior with system walls and ceilings. In order to be able to use the advantages of an accessible ceiling with installations, the corresponding heights have to be planned for the building shell. Another advantage is the short installation time on the building site and the

ability to change the plans up until shortly before the installation. As they are established state of the art, there are only a few discussions required with the authorities.

Wall systems consisting of metal elements are structured mainly according to three principles:

monoblocks, banded grids and axial grids - with the last two being used the most often. Usually, they are selected based on the desired design version for the enclosed clean room.

In the nineties it was still a pioneering act to use glass walls made of single-pane safety glass, but today such completely transparent systems are offered by several producers. Use has often shown that special bumper buffer devices are not always required since staff act more "cautiously" in the presence of glass. Because they are completely transparent, wall systems made of single-pane safety glass often allow for easier visual communication and daylight illumination, even in rooms situated deeper inside the building.

When cleaning, care has to be taken to ensure no streaks remain. Although they are not a sign of poor cleaning, people tend to equate optical cleanliness with the effect of cleaning.

The following overview contains the most important information concerning the design of the three different versions.

| Version | Design |
|---|---|
| Monoblock | • Compact element consisting of two steel sheet shells, coated or made of stainless steel, with a fully fitted inlay made of the following materials:<br>Polyurethane (PU) foam<br>Expanded polystyrene (EPS, styrofoam)<br>Epoxy resin<br>Mineral wool<br>Gypsum boards<br>Honeycomb made of aluminium<br>Other combinations<br>• Element connections with the "tongue and groove" system (integrated into the panel or with connection profiles)<br>• Defined silicone joint at the butt joint of the elements<br>• Installation elements prefabricated according to plan<br>Door element usually integrated within the frame in the element<br>• Wall panelling partly possible with thinner panels |
| Banded grids | • Banded shells between the wall elements (double number of joints)<br>• Banded shells can be opened on one side without influencing the status of the adjoining room<br>• Access to the cavity possible from one side for subsequent installations<br>• System suited for wall panelling |
| Axial grids | • Lower number of joints<br>• One-sided dismantling of panelling impossible<br>• System suited for wall panelling |
| Glass walls | • Safety glass elements fabricated according to plan<br>• Usually surrounded by a frame (protection against the entry of particles and insects has to be guaranteed)<br>• Cut-out parts and bushings only prefabricated - subsequent adjustments are expensive |
| For all versions | • Usually prefabricated according to drawing<br>• Floor profile for direct installation on the floor (see Figure 3)<br>• Floor socket to compensate an incline |

| | |
|---|---|
| | • Recessed floor connection - for a flush floor connection (see Figure 4)<br>• Ceiling connection with height compensation<br>• Cut-out parts for fittings prefabricated, but also possible for installation with frame |

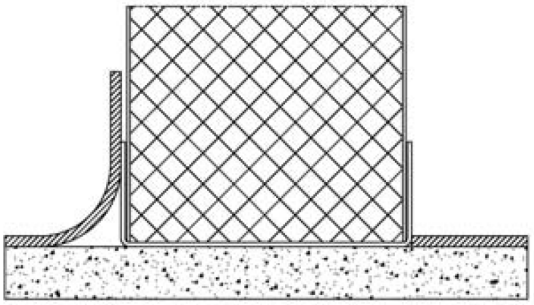


Figure 3: Wall element with simple floor connection (Source: ECOS GmbH, A-3470 Kirchberg am Wagram, www.ecos-at.com)

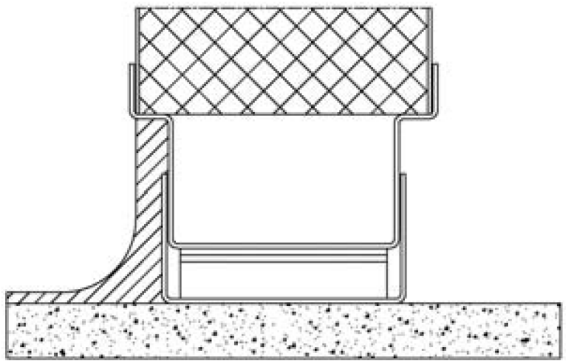


Figure 4: Wall element with recessed floor connection (Source: ECOS GmbH, A-3470 Kirchberg am Wagram, www.ecos-at.com)

### 9.2.3 Ceiling systems

There are different alternatives for ceiling systems:

**Clamped metal cassette ceilings**

This simplest and cheapest alternative can be used readily in clean rooms. The metal ceiling panels, with or without integrated sealing, are clamped into concealed mounted supporting profiles and grouted with silicone. They have a low tare weight. They are mainly used as panelling of installations adjacent to the ceiling. They are not accessible but easy to dismantle (Figure 5).

Figure 5: Clamped cassette ceiling during installation (Source: LSMW GmbH, D-90408 Nürnberg, www.lsmw.de)

**Banded grid ceilings**

Banded grid ceilings with longitudinal or cross-banded grids are the alternatives most often used in pharmaceutical companies. The ceiling panels may consist of different materials: aluminium, stainless steel or coated steel.

Depending on the supporting profile, a suspension grid (usually 1.2 m x 1.2 m) and panel loads from 150 up to 250 kg/m² can be achieved.

If the version has its own node elements for the corner connections, bushings for sprinkler nozzles, measuring connectors for filter leakage tests etc. are possible in these nodes.

Some producers offer grid rail systems for the mounting of LED lighting. With this system, the ceiling elements remain free for other fittings such as filter boxes or filter fan units and the room illumination can be carried out comprehensively in grid dimensions.

**Grid-free monoblock ceiling**

Monoblock wall elements consist of "sandwich" panels filled with insulation material. One disadvantage of this system is its low flexibility. The cut-out parts for fittings (lights, filters etc.) are fabricated according to plan - changes during the installation are possible but require careful work and replacement of some of the elements.

Sometimes, monoblock ceilings are mounted on monoblock wall elements. This reduces the number of ceiling suspensions, but if walls are moved or removed, the load-bearing capacity of the ceiling has to be checked.

## 9.3 Doors and windows

**Clean room windows**

Windows are usually integrated into the double-shelled wall elements as double-pane safety glass and have no protruding parts where accumulations may occur (see Figure 6). Either finished and tight double-pane elements are integrated into the wall (often in monoblock systems) or each pane of glass is inserted and sealed with an installation profile and sealed into each side of the wall (see Figure 6).

Windows with frames are hardly used any more and in clean rooms of class C/ISO8 or higher, they are rather uncommon. One-pane glass with corresponding profiles (no horizontal surfaces, Figure 7) are quite possible and a less expensive alternative.

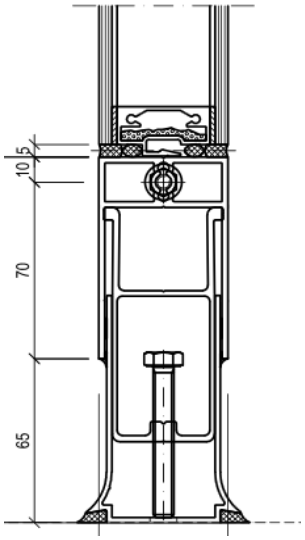



Figure 6: Construction concept: two-pane safety glass integrated into the wall element (Source: Ritterwand GmbH&Co.KG, D-71154 Nufringen, www.ritterwand.de)

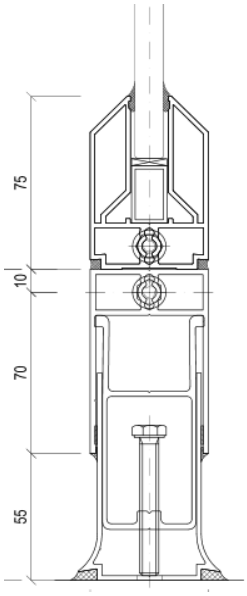



Figure 7: Construction concept: one-pane safety glass integrated into the wall element (Source: Ritterwand GmbH&Co.KG, D-71154 Nufringen, www.ritterwand.de)

**Clean room doors**

Revolving doors, one-wing or two-wing with inactive and active leaf, strike plate, hinges and handles are the most commonly used doors in the clean room area. The frames are usually block frames (flush with the wall element, mostly in monoblock systems) or wrap-around frames (frame profile wraps around the wall element, Figure 8).

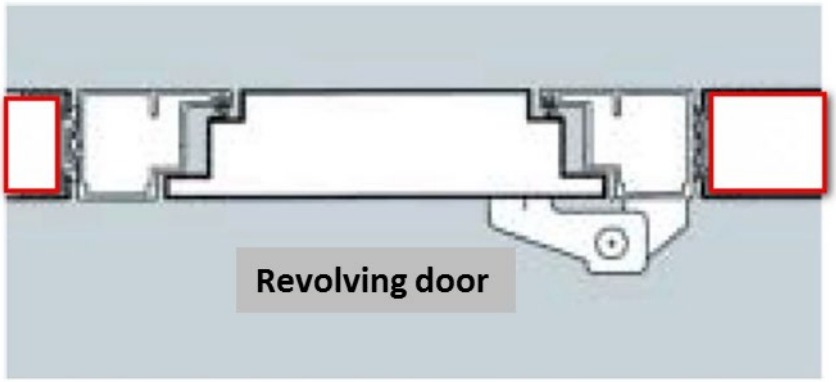



Figure 8: Construction concept: frame of a revolving door (Source: Clean-tek GmbH&Co.KG, D-71272 Renningen, www.clean-tek.de)

The integration of components in the strike plates or frames for a so-called push-pull lock which prevents the simultaneous opening of several doors is to be considered as the technical standard today.

Clean room doors are also available in the appropriate versions for fire-protection requirements within a group of clean rooms. Fire doors are classified as T30 (fire-resistant), T60 (highly fire-resistant) and T90 (fire-proof) doors. The authorities or the fire protection certificate stipulate which version has to be chosen.

Clean room doors can be equipped with drives for automatic opening by means of sensors or with manual control panels and door closers. Monoblock systems often offer the possibility to integrate door closers into the panel. They are not visible from the outside but it should be possible to replace them.

The suitability of the drive for use in the clean room should be proven (for instance by means of a suitability test carried out by an independent institute). The safety requirements of the European harmonised product standard EN 13241 must be complied with. Thresholds or stop rails at floor level are undesirable.

If door leaves are installed flush in the wall element, whether they have one or two sides is not significant and depends on the frame used. A three-dimensional adjustment option for the door leaves is recommended for optimal sealing and integration into the frame. For sterile manufacturing or for similar manufacturing, doors should have smooth surfaces, low-warp frames and easy-to-clean surfaces and seals.

The drop-down floor seal (Figure 9), which is often desired and installed in wings of revolving doors because of its higher tightness, does not comply with this requirement. It causes an uncontrollable cavity in the door leaf which is open on the front sides of the door wing and can only be cleaned if the wing is removed.

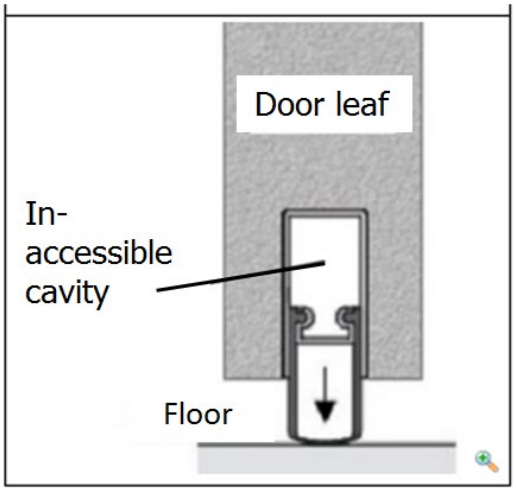



Figure 9: Construction concept: integrated drop-down seal for revolving door leaves (Source: OCTANORM-Vertriebs GmbH, D-70794 Filderstadt, www.octanorm-reinraum.de)

Often it is overlooked that the locking part with bolt, latch and door locks as well as the hinges are weak points. Most doors have uncontrollable and hard-to-clean openings in these areas (strike plate with opening to the complete door frame).

Versions of revolving doors suitable for use in pharmaceutical clean rooms (Figures 10 to 14) are presented below.

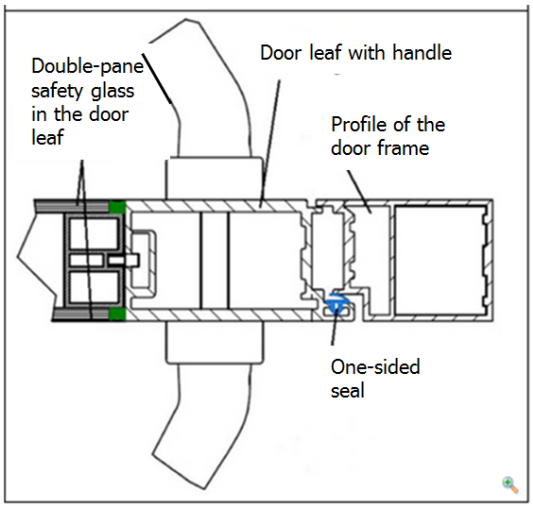



Figure 10: Horizontal section of a clean room door with removable one-sided seal and flush built-in window (Source: OCTANORM-Vertriebs GmbH, D-70794 Filderstadt, www.octanorm-reinraum.de)

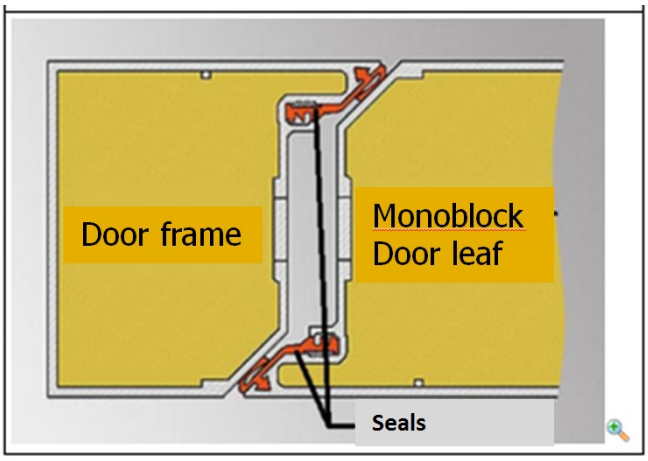



Figure 11: Horizontal section of a monoblock door with frame and removable two-sided seals (Cleangrad d.o.o, www.cleangrad.si)

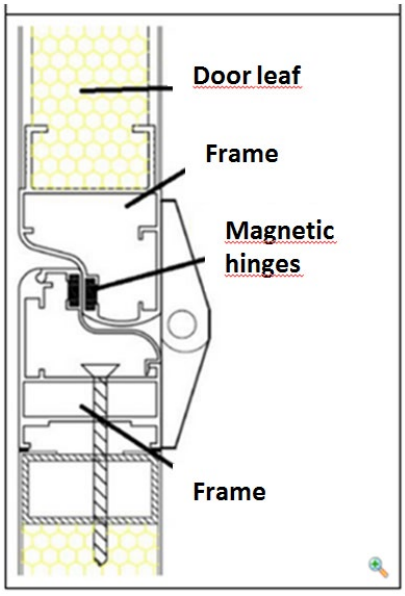



Figure 12: Horizontal section of a clean room door with magnetic frame as sealing area (Cleangrad d.o.o, www.cleangrad.si)

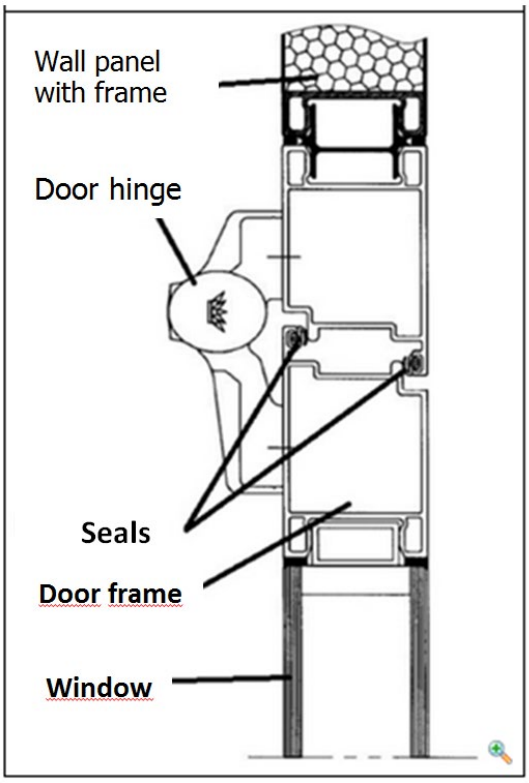



Figure 13: Horizontal section of a clean room door with double seal and block frame (Source: Viessmann Technologies GmbH, D-Hof/Saale www.vitec-hof.de)

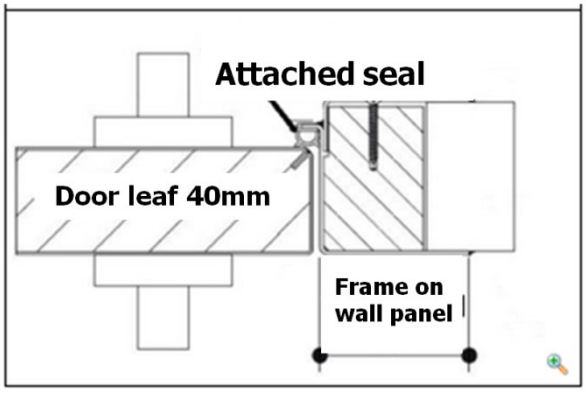



Figure 14: Horizontal section of a revolving door being flush on one side with wrap-around frame (Fa. ems, D-23689 Pansdorf, www.ems-isolier.de)

In GMP grades D and classes E and F (according to WHO for non-sterile production) and in non-classified areas (CNC controlled not classified/controlled (access control) and no clean room classification and NC not classified/corresponds to the general "black" area with access control) easy to clean standard doors with standard locks and corresponding handles can be used.

The translation in an earlier version of the EU Annex 1 regarding sliding doors gave rise to an aversion against sliding doors in the GMP environment in the past. The reason for this was the interpretation that "sliding doors were forbidden". Inspection practice, however, shows that the authorities accept sliding doors and high-speed doors in clean rooms in most cases.

The current requirement in Annex 1 concerning doors no longer differentiates between doors and sliding doors as it says: "Doors should be designed to avoid those uncleanable recesses".

When installing automatic sliding doors, care should be taken to ensure that the drive is installed on the side with fewer requirements for cleanliness. The recommendations for sliding doors are applicable analogously for high-speed doors that open and close vertically.

Horizontal sliding doors and vertical high-speed doors in clean rooms offer a variety of decisive advantages:

- They save space
- They close tightly on 4 sides because of the lowering construction
- The undesired high vortices, air turbulence and pressure fluctuations caused by the opening of wing doors are prevented
- High-speed doors minimise the air exchange and the associated possible air contamination in the clean room

The GMP-compliant design of a motor drive/mechanical drive has to fulfil the following requirements:

- The power should be sufficient to overcome the occurring pressure differences (also in case of an average or when restarting the ventilation technology) (a design only for delta p 15 Pa is inadmissible, generally, it has to be possible to overcome a minimum of 45 Pa without problems)
- The sliding door leaves are fastened to the roller carriage only on the upper side. Thresholds and bottom tracks are undesirable
- The complete drive and the sliding rail are installed to be dust-protected and as tight as possible in a panelling at the side with fewer requirements for cleanliness
- From a technical point of view, it is possible to connect the panelling to the exhaust duct and to aspirate the particles generated in the panelling (abrasion) (= "vacuum" compared to the clean room)
- The panelling of the parts of the drive is easy to open for inspection and cleaning purposes and easily accessible for cleaning

The following control and safety aspects have to be considered or installed:

Safety requirements of the European harmonised product standard EN 13241. Safety can be further enhanced by means of a presence detection system.

- Control units according to clean room standards (for instance with proximity sensor for opening and/or closing (standard: closing automatically as soon as the door area is free and the configurable time X has elapsed))
- Where necessary,a "department store function" is also possible, i.e. the door opens if somebody enters the monitoring area in front of the door; it is recommended that the corresponding areas are marked on the floor
- Alarm function in the event of failures (including visual, acoustic signal and/or notification to the building control system and monitoring system)
- Locking function of the door in the "open" position (according to the process requirements as an emergency or normal operating function and the "pressure cascade/flow of personnel and material" function)
- Mechanism/option to activate by floor cleaning robot
- Mechanism/option for optimal positioning of the door for maintenance or cleaning work in critical areas (drive, seals, fixtures, etc.)

- Emergency stop switch (including technical clarification if activation is also permitted as emergency opening in the case of a need to escape)
- Emergency battery or manual emergency opening
- Regular safety check according to the specifications of the authority, the producer and according to the internal safety requirements
- Monitoring of the door's movement range in order to reliably exclude damage to persons or material because of the door's movement (it is recommended that the corresponding areas on the floor are marked in narrow spaces such as locks for material)

- Mechanism for a lock function including status displays, configurable recovery times (as appropriate, including countdown timer), operation of functions without recovery time if movement is from "clean" to "unclean", if necessary, possibility to control more than 2 doors (in case of large rooms), escape function, if required, notification to the building control system and monitoring system to control the room ventilation system
- As appropriate, connection of the doors to the access control system, including for example magnetic card readers;
  in Germany, in accordance with the works council, expanded personnel and material flow analyses are possible, or the monitoring of quality for instance of external cleaning personnel or for error analyses in the case of failures of the pressure cascade

## 9.4 Floor systems

Clean room floors are usually designated according to the surface covering facing the clean room. The structure of the floor itself - from the tightness and load-bearing capacity to the static requirements - is part of the construction and has special links with the topics of GMP and clean rooms.

According to the guiding principle of "creating quality in every step of the process instead of only testing at the end", the following principles can be defined for competent construction supervision as concerns quality assurance when laying the floors.

| **Checklist floor systems** | **Complied with?** | | |
|---|---|---|---|
| **Assessment criterion** | **Yes** | **No** | **N.a.** |
| Best and defined quality of the screed<br>(examples: cement screed class according to DIN 18560, smoothness according to DIN 18202 - or better in agreement or according to the specification of the customer ordering the clean room),<br>clean, dust-free surface | | | |
| Defined residual moisture of the screed prior to subsequent works (define and document) | | | |
| Exclusively compatible auxiliary materials: bonding bridges, fillers, adhesives; ask in advance for conclusive proof of suitability even for small changes! | | | |
| Experienced contractors and motivated/trained assembly personnel | | | |
| Regular retraining of the assembly personnel, for instance in the manufacturer's covering production plant. A contractor who is able to provide documented proof of the training of his personnel is to be classified as competent. | | | |
| Instructions regarding the further works from the defined surface of the levelling screed, also for fittings and connections | | | |

| | | | |
|---|---|---|---|
| Defined joints, where necessary (depending on the covering and the connections) | | | |
| Keeping of a construction diary with documentation of the processing conditions | | | |
| Quality-securing intermediate testing<br>(examples: peel test according to EN 1372 for PVC web coverings, adhesive pull strength according to EN 13813 for coverings produced on-site etc.) | | | |
| Overall responsibility for the complete floor works from a single source | | | |
| Definition of warranty (warranty is legally regulated only in the consumer business!) | | | |
| Instruction on basic cleaning and its verification | | | |
| Final acceptance by mutual agreement according to previously negotiated parameters and associated specifications (with bandwidth and definitions as concerns statistics) | | | |
| | | | |

### 9.4.1 Construction alternatives

The more precisely the requirements are known and described in the user requirement specification, the more precise the implementation can be. The guidelines on clean room technology contain very different recommendations concerning clean room floors. This makes it even more important to ask the right experts and to specify the requirements.

For the overall construction of a floor for the pharmaceutical industry, additional requirements which are not part of the Eurocode requirements have to be included in the user requirement specification such as:

- Special structural criteria and project specifications (possibly a special surface is stipulated such as cast resin, rubber or the like)
- Moisture protection (incurring humidity during cleaning and/or production)
- Slip resistance (tailored to the clean room shoes used)
- Temperature and moisture at standstill and during production (such as frequency and intensity of the change of temperature and humidity)
- Load capacity according to special project specifications (area and point load, mobile or static, rolling, grinding)
- ESD - electrostatic discharge - safety, electrostatic requirements. The covering must have constant contactivity values (for electronic components, charging because of insulating shoes, wheels etc.) throughout its entire useful life
- Cleanability according to operational requirements (chemical burden)

The following paragraphs present 8 of the most common clean room floors and their frequent alternatives.

**Example 1: Hard aggregate screed**

This floor is suited for storage and heavy transport areas with low cleanliness classes (grade D).

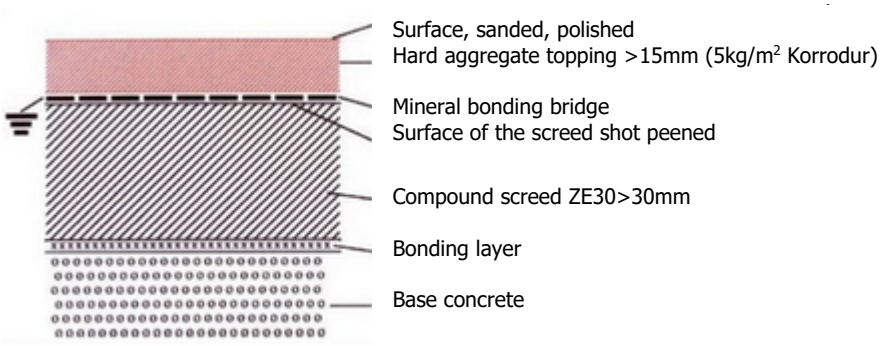



Figure 15: Hard aggregate screed for storage and heavy transport areas (Source: Leonhard Weiss Fußbodentechnik GmbH & Co. KG, D-73037 Göppingen www.lw-fussbodentechnik.de)

**Example 2: Ceramic tile floor**

Ceramic tile floors with synthetic joints were often used in clean rooms in the past. They are also suited for humid operations and heavy rolling loads. When used for permanent wet operation, an insulation layer is required under the levelling screed, however.

**Example 3: Synthetic screed / "Pharma-Terrazzo"**

Floors consisting of synthetic screed which are made by applying filling compound (Figure 16) are the most common clean room floors in the pharmaceutical industry. They are also known under the colloquial name "pharma terrazzo".

The surface can be modified in such a way that slip resistance up to R12 can be achieved. The usual values for slip resistance are R9 and R10 and in wet areas R11 and R12.

It has to be considered that cleanability decreases with increasing slip resistance. This constitutes a compromise between the required hygiene and the workplace safety with regard to a surface suited for wet cleaning or wet production.

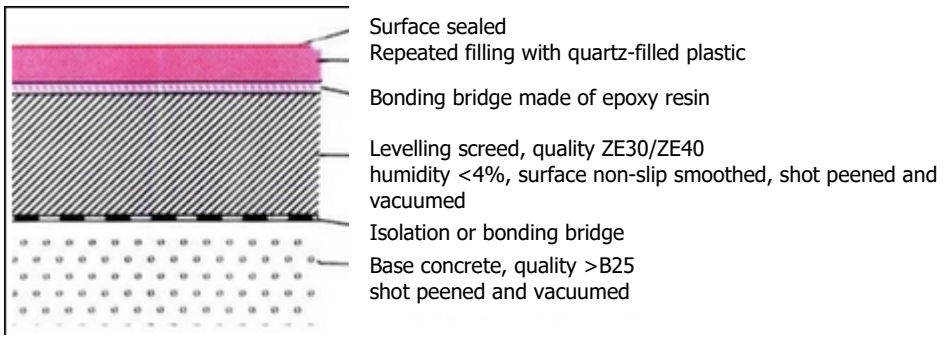



Figure 16: Synthetic screeds made of epoxy resin and quartz mixtures (Source: Leonhard Weiss Fußbodentechnik GmbH & Co. KG, D-73037 Göppingen www.lw-fussbodentechnik.de)

As plastics, polyurethanes and their mixtures are possible apart from epoxy resins. With special formulations or additives such as carbon fibres, metal chips etc., the surface can reach a certain discharge capacity. The layer thickness of the plastic can be adjusted to the desired load capacity by filling or moulding.

**Example 4: Epoxy resin cast floor**

Figure 17 shows the structure of a conductive epoxy resin cast floor.

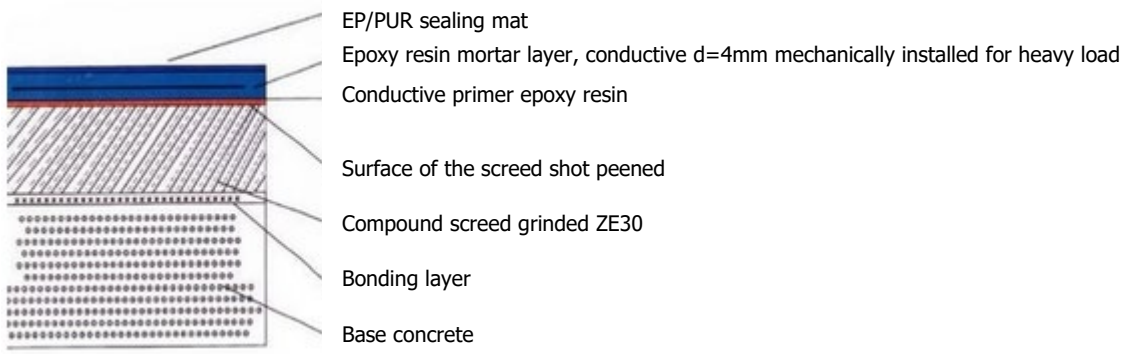



Figure 17: Conductive epoxy resin cast floor (Source: Leonhard Weiss Fußbodentechnik GmbH & Co. KG, D-73037 Göppingen www.lw-fussbodentechnik.de)

**Example 5: PVC tile floor**

Floors made of PVC tiles with welded joints are preferred for areas with dry operations and low load, for locks for personnel or similar applications. Special attention has to be paid to the possible outgassing of plasticisers.

**Example 6: Conductive jointless PVC floor**

For the manufacture of conductive PVC floors (Figure 18), PVC is compressed under high pressure and high temperature. It loses part of the plasticiser during the process. In order to achieve the discharge capacity in the surface, conductive threads are introduced in the mixture. Webs and profiles are welded homogenously and stably without joints. Any desired cleaning procedure is applicable.

Damaged spots can be repaired easily with material by means of welding. Depending on the thickness of the layer, heavy stains such as traces from driving can be cleaned mechanically with an abrasive disc.

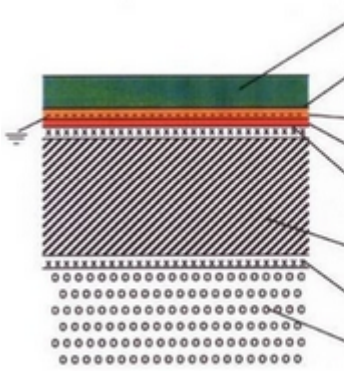



Figure 18: Conductive PVC floor (Source: B. forbo ®) (Source: Leonhard Weiss Fußbodentechnik GmbH & Co. KG, D-73037 Göppingen www.lw-fussbodentechnik.de)s

**Example 7: Conductive (ESD) rubber floor**

The electrostatic behaviour of conductive rubber floors (Figure 19) is suited even for very high requirements regarding the cleanliness class. These floors are characterised by permanently tight welding seams, high elasticity and high slip resistances of R9 to R10.

Studies have shown that rubber floor coverings have an enormously smooth and tight (non-porous) surface. Because of their high permanent elasticity, these coverings allow personnel to stand for long periods and contribute to an ergonomic workplace design.

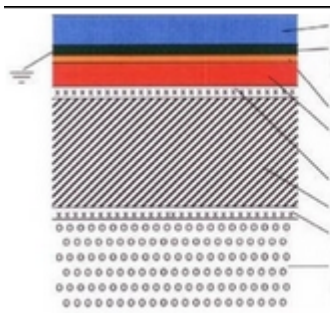



Figure 19: Highly resistant ESD web covering made of rubber (for example Fa. Nora®) (Source: Leonhard Weiss Fußbodentechnik GmbH & Co. KG, D-73037 Göppingen www.lw-fussbodentechnik.de)

**Example 8: Vacuum screed**

The name "vacuum screed" is derived from the production technique: after introducing it, the still damp screed is smoothed by means of suction.

The dry surface is sealed, impregnating it with plastic. Transport equipment must have rubber tyres and the sealing must be refreshed from time to time. This screed is preferably used for low cleanliness classes, storage areas and other ancillary areas.

The great advantage of these floors is that they can achieve a higher cleanability class by means of shot peening and vacuuming for the application of a bonding bridge with an additional surface covering.

### 9.4.2 Approval of floors

The user or her/his planner decides what is approved and with which requirements. In general, experts define the specifications such as the electric/electrostatic characteristics.

The approval of clean room floors regarding fitness for use can for example consist of the following steps:

- Approval according to the contractually agreed testing standards and guidelines for the following characteristics:
  Electric/electrostatic properties
  Smoothness
  Quality of the screed
  Adhesive pull strength
  Slip resistance
  As appropriate, remaining indentation depth
- Consultation of documents (certificates, test reports) where testing on-site is not useful/possible. Examples are:
  Fire protection properties or sound insulation properties
  Grinding loss/abrasion resistance
  Temperature change resistance
  Chemical resistance etc.
- Visual inspections such as:
  Levelling and edge offset at fittings as agreed
  Transitions of the floor and wall connections as per sample/as shown in the drawing
  Cleanliness after basic cleaning as agreed, cleaning results after fine cleaning (and as appropriate disinfection) as agreed/where required according to URS
  Freedom from cracks as agreed, etc.

If the properties can be quantified, the permitted deviation from the set value has to be indicated, and details also have to be provided on statistics, such as the number of samples. Examples are values for the adhesive pull strength of synthetic screed floor or tile floor.

A number of examples are listed below for approval parameters for a GMP-compliant (jointless) ESD web covering made of caoutchouc.

**Technical properties**

- Chargeability/charging voltage of the system shoe + person + floor:
  according to IEC 61340-4-5 or according to ESD-STM 97.1: <10 V (semiconductor industry)
  static electrical propensity according to EN 1815: <1 kV (example taken from microelectronics)
- Earth-leakage resistance according to EN 1081: 106 to 9 x 107
- Insulation resistance according to VDE 0100/part 610: >5 x 104
- Fire classification according to EN 13501-1: Cfl s1
- Adhesion surface covering on levelling screed: as agreed (as appropriate QA of producer)
- Remaining residual indentation according to EN 433: < 0.05 mm
- Abrasion according to EN ISO 4649/5 N load: < 180 mm3

**GMP characteristics for clean rooms**

- Tests: "smooth and unbroken": visually, optical means as appropriate
- Tests: "impervious": visually but usually access to expert certificate
- Resistance to the effects of defined cleaning or disinfection agents

### 9.4.3 Critical clean room interfaces

A) Protection of the floor during the construction phase
Often the floor is provided with protection during the construction phase directly after production. The composite plastic-cardboard (from the roll or as web) used as packaging material for beverages is a well-proven example. It can be used as watertight material so that wet cleaning is possible (the clean room broom cannot be used on the building site!). The use of normal cardboard or wood or fibreboards for this purpose is strongly discouraged (because of the abrasion and since damp mopping is not possible).

B) Repair procedures during operation
The clean room can be damaged by various mistakes.
If the floor is of good quality, it is possible, for example, to repair the damage caused by a hammer that has dropped from the height of 2 m or the scratches from dirty pallet truck rollers rapidly and without voiding the clean room status during ongoing production. Ideally, the producer of the clean room hands over repair kits to the operator's building technology unit and trains them in their use. It can also be worthwhile from a psychological point of view if the clean room personnel carry out these repairs themselves.

C) Silicone seams
These are time-consuming and technically complex. When they are created, the clean room's optimum illumination should already be working to ensure excellent visibility of the relevant areas. In general, silicone seams in clean rooms are also to be regarded as maintenance joints. The durability of silicone seams ranges from 3 months to 20 years, depending on the quality of material and production and on the strain put on them. They are not suitable for compensating vibrations or dimensional tolerances exceeding 1 mm.

D) Equipment forms a clean room boundary
Pass-through autoclaves, freeze dryers and many other systems form a clean room zone boundary in themselves. These have to be planned and built in such a way that the interfaces are optimised mechanically and electrically, as concerns ventilation, but also for maintenance and repair. In practice, this may mean for example that access to an enclosed technology area has to be planned from above via the clean room ceiling.

E) Setting-up of tubs in the clean room
If equipment is placed on the floor in a tub, the tub should immediately be sealed in such a way that no liquids can get into the area between the tub and the floor.

F) Leaks
Leaks above or in the clean room can cause huge damage and downtimes. In recent years, nearly all clean room construction projects have been affected by leaks at least once during the construction phase. A corresponding risk analysis has to be carried out before building the clean room. Critical areas have to be protected for instance by means of seals, tubs, slopes and drains in the floor.

G) Concave fillet floor/wall
A mechanical and chemical burden is put on them. Cracks and leaks can lead to moisture from the cleaning agent entering these cracks and causing microbial growth there. In practice, this

problem is made worse in the following way:
- during the construction phase there are often 2 trades that pass responsibility back to the other
- cleaning is carried out by often changing or external personnel

## 9.5 Areas of application of the components for different cleanliness classes

The following table suggests the application of the described components in the different cleanliness classes in the pharmaceutical industry. The classification is carried out according to the surfaces facing the clean room. A risk assessment with regard to cleaning, disinfection and proximity to the product can also lead to another result, however.

The cleanliness classes listed in the table are based on Annex 1 EU Guidelines on Good Manufacturing Practice and ISO 14644. Classes E and F are taken from the WHO guidelines on non-sterile manufacturing. They contain microbial limits. The CNC and NC concepts are proposals currently being discussed (controlled not classified, not classified).

| **Grades according to the EU GMP Guidelines** | **A** | **B** | **C** | **D** | **E CNC** | **F NC** |
|---|---|---|---|---|---|---|
| **Equivalent ISO classification (defined particle limits in the operational state "in operation")** | **(5) 4.8[7]** | **7** | **8** | **(9)[8]** | **-** | **-** |
| Explanation of the symbols:<br>• x: recommended<br>• o: optional but recommended, non-compulsory (result of risk assessment)<br>• -: not defined, not required | | | | | | |
| **1. Walls** | | | | | | |
| Wall bushings - number as low as possible | x | X | X | X | O | O |
| All bushings to be sealed elastically | X | X | X | X | O | O |
| In areas with low-turbulence displacement flow (unidirectional airflow - laminar flow) the vertical wall surfaces shall not pose a flow barrier and hinder the airflow and they shall not lead to turbulent flow | X | O | - | - | - | - |
| Surfaces smooth, tight, non-porous, non-absorbing or outgassing and resistant to the cleaning and disinfection agents used | x | x | x | x | X | - |
| Monoblock/double-shelled system walls with defined requirements concerning socket and ceiling connection | X | X | X | O | O | - |
| Double-shelled system walls with defined requirements concerning socket and ceiling connection | X | X | O | O | O | - |
| Wall panelling made of one-shelled system wall elements | O | O | X | X | O | - |
| Wall coatings | O | O | O | X | X | X |

[7] *The ISO class 4.8 is reached by defining the limit for particles >5.0µm.*
[8] *For the EU GMP grade D, no particle limits are indicated. In general ISO class 9 prevails for this.*

| **Grades according to the EU GMP Guidelines** | **A** | **B** | **C** | **D** | **E CNC** | **F NC** |
|---|---|---|---|---|---|---|
| **Equivalent ISO classification (defined particle limits in the operational state "in operation")** | **(5) 4.8[7]** | **7** | **8** | **(9)[8]** | **-** | **-** |
| Explanation of the symbols:<br>• x: recommended<br>• o: optional but recommended, non-compulsory (result of risk assessment)<br>• -: not defined, not required | | | | | | |
| Stud partitions made of gypsum board, smooth, coated and cleanable | - | - | - | O | O | X |
| Connection to floor and/or ceiling with concave fillet<br>• Connection with concave fillet is generally the preferred form. Recent studies have shown that an efficient cleaning is also possible with "corner connections", whereas concave fillet and unsuitable cleaning equipment can rather lead to poor cleaning results. The efforts for concave fillet are higher (costs, time) in conventional floor systems | O | O | O | - | - | - |
| Avoidance of horizontal surfaces above critical zones (manufacturing area). Absolutely required fittings should be covered up to the ceiling and sealed | x | O | O | - | - | - |
| Expansion joints and connections of different materials have to be sealed elastically | x | x | x | x | O[9] | O |
| **2. Ceilings** | | | | | | |
| Branded grids ceiling system | X | X | X | O | O | - |
| Monoblock ceiling system | X | X | X | O | O | - |
| Clamped metal cassette ceiling with sealed joints | - | - | O | X | O | - |
| Clamped metal cassette ceiling without sealed joints | - | - | - | - | O | X |
| Ceiling connections have to be sealed elastically | x | x | x | x | O | O |
| Accessible ceiling for maintenance purposes | - | X | X | X | O | - |
| All fittings and bushings to be sealed elastically | x | x | x | x | O | O |
| Surfaces smooth, tight, non-porous, non-absorbing or outgassing and resistant to the cleaning and disinfection agents used | x | x | x | x | O | O |
| Maintenance openings with airtight connections | -[10] | - | O | x | X | X |
| **3. Lighting** | | | | | | |
| The illumination intensity has to be adapted to the needs of the process. Workplace-related laws must be taken into consideration | x | x | x | x | X | X |
| Surface-mounted lights shall not hinder the air flow | x | x | O | - | - | - |

*[9] Recommended in cases of pressure control to reduce the amount of leaked air.*
*10 In grade A and B, maintenance openings in the ceiling have to be avoided.*

| Grades according to the EU GMP Guidelines | A | B | C | D | E CNC | F NC |
|---|---|---|---|---|---|---|
| **Equivalent ISO classification (defined particle limits in the operational state "in operation")** | **(5) 4.8[7]** | **7** | **8** | **(9)[8]** | **-** | **-** |
| Explanation of the symbols:<br>• x: recommended<br>• o: optional but recommended, non-compulsory (result of risk assessment)<br>• -: not defined, not required | | | | | | |
| The exchange of illuminants shall take place outside of the clean area | x | O | O | O | O | - |
| **4. Ventilation installations** | | | | | | |
| Bushings for supply air and exhaust air (with or without filter) must be installed vibration-free and sealed | x | x | x | x | X | X |
| Aspiration close to the ground with cleaning option | X | X | X | O | O | - |
| Diffuser elements (perforated sheets, anemostats and the like) must be installed as flush as possible or with tight connection to the ceiling. The air control blades may not shift during cleaning (wipe cleaning) | - | x | x | x | O | O |
| The connections for the filter test (differential pressure, aerosol feeding for filter leakage test) shall be accessible without removing the air guidance elements | X | X | X | O | - | - |
| **5. Floors** | | | | | | |
| Surfaces smooth, tight, non-porous, non-absorbing or outgassing and resistant to the cleaning and disinfection agents used | x | x | x | x | O | O |
| Abrasion resistance and slip resistance | x | x | x | x | X | X |
| Electrically conductive to prevent electrostatic charge (high charging with very dry air) | x | x | x | x | X | X |
| Area and point load for the operating material used (pallet storage - area load; lifting trucks or mobile containers - point load) | x | x | x | x | X | X |
| Closable and disinfectable floor drains<br>Optional: replace floor drains in grade B with closable connections in the wall. The liquid medium is disposed of with a pump (bilge pump) | - | o[11] | x | x | X | X |
| In the case of wet cleaning, the slope of the floor must be in the direction of the drains | - | O | x | x | X | x |
| Floor covering CrNi steel sheet, polished (observe slip resistance!) | O | O | - | - | - | - |
| Synthetic screed, cast resin and cast floors | O | O | O | O | O | O |
| Synthetic tile floor with welded joints | O | O | O | O | O | O |
| Jointless ESD web covering made of compressed PVC or caoutchouc | O | O | O | O | O | O |

[11] *Floor drains are not permitted in grade A, in grade B they are to be avoided.*

| Grades according to the EU GMP Guidelines | A | B | C | D | E CNC | F NC |
|---|---|---|---|---|---|---|
| **Equivalent ISO classification (defined particle limits in the operational state "in operation")** | **(5) 4.8[7]** | **7** | **8** | **(9)[8]** | **-** | **-** |
| Explanation of the symbols:<br>• x: recommended<br>• o: optional but recommended, non-compulsory (result of risk assessment)<br>• -: not defined, not required | | | | | | |
| Web or tile covering made from PVC with joints | - | O | O | O | O | O |
| Ceramic tiles cemented | - | - | - | O | O | O |
| Hard aggregate screed and coated vacuum screed | - | - | - | - | O | O |
| **6. Doors** | | | | | | |
| No thresholds on the floor | x | x | X | X | O | O |
| Doors and fittings (hinges, handles, windows) are to be produced preferably without horizontal surfaces or uncleanable recesses and cavities | x | x | x | O | O | - |
| Installed in the wall system flush on both sides | x | O | O | - | - | - |
| Emergency exits and accesses to maintenance areas to be secured | - | x | x | x | X | X |
| Use of sliding doors | - | - | O | O | O | O |
| Use of high-speed doors | - | - | O | O | O | O |

## 9.6 Definitions / glossary

ESD: Electrostatic discharge; conductive floor
CNC: Controlled Not Classified
NC: Not Classified
ZE: Cement screed

# 10. Electrical engineering, measurement and control technology in the GMP-regulated environment

In the GMP-regulated environment, equipment of electrical engineering, measurement and control technology must fulfil GMP requirements as well as the process control technology (PCT) measurement and control functions. These GMP requirements refer to the intended operation and to design and accuracy requirements. This equipment can for instance have direct contact with the product and this influences the selection of the materials of construction and the design (such as good cleanability). But it can also directly influence the process flow and the quality of the process and product by means of the controlled parameters. Here, the focus is placed on the accuracy of measurement and reliable functioning.

These aspects have to be taken into consideration by the planning engineer or design engineer during selection and procurement so that the GMP-compliant routine operation or the routine operation in accordance with the requirements, and last but not least the product quality, can be assured. It is for instance possible to use redundant systems for quality-critical product parameters (such as the use of two pH probes in biotechnology production).

The following paragraphs explain the requirements as regards technical design, selection of the measurement procedure, maintenance and calibration which have to be taken into consideration in the GMP-regulated environment. The explanations are examples since it is not possible to cover the whole range of measurement and control equipment.

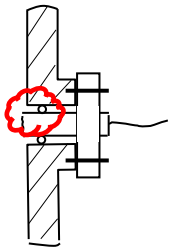
## 10.1 Technical design

When selecting PCT field devices (temperature, pressure, conductivity, level sensors etc.), the same design requirements generally have to be taken into consideration as for the pipework and equipment in which they are installed. In addition to the basic requirement that the product quality may not be adversely affected by the materials used, the design is influenced in particular by the individual requirements concerning cleanability and sterilisability. Therefore, at least the following design criteria need to be considered and defined:

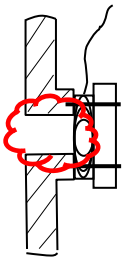
- Selection of materials (metallic, non-metallic material)
- Surface quality (polished, passivated, electropolished, surface roughness)
- No dead legs
- Drainability
- Connections (type of connection to the pipework or equipment; welded, screwed, clamping connection such as hygienic connection according to DIN 11864 or DIN 32676)
- Type of gasket/seal
- Lubricants and auxiliary materials (such as proof of suitability for liquid filling in pressure measuring systems if there is a risk of product contact)
- Location of installation
    - If required, design requirements have also be considered for non-product contact surfaces due to the environmental conditions (such as high clean room requirements)
    - Measurement equipment which has to be maintained or calibrated regularly or which has to be read off on-site must be positioned in an easily accessible place
    - Maybe it is possible to relocate the read-off position and/or access for maintenance from the clean room to the technical area?
- Installation position

- To be considered, as the case may be, in order to guarantee the correct functioning (prevention of measurement errors) and to prevent product deposits due to dead legs not flowed through or shadow areas.

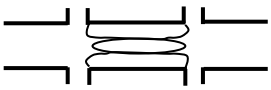
Today there are already numerous suppliers offering measurement equipment specially targeted to hygienic design. Such measurement equipment is characterised by the lack of dead legs and easy rinsability. The following figures are examples of different versions of a pressure measuring system and show critical design elements. The solution shown in Figure 2 is certainly the least suitable, whereas Figure 3 shows the ideal solution with straight throughflow and almost without a dead leg.



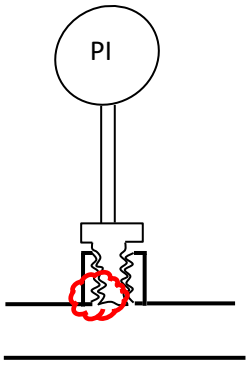
Picture 1, membrane diaphragm seal at the end
Source: gempex



Picture 2, membrane diaphragm seal, flanged
Source: gempex



Picture 3, in-line diaphragm seal
Source: gempex




Picture 4, membrane diaphragm seal at the end
Source: gempex

Explanations:

For picture 1: The narrow ring-shaped dead leg reaching to the O-ring seal is difficult to clean. The dead leg should be reduced by relocating the O-ring at the height of the tubular cross-section.

For picture 2: In general, a connection piece is a dead leg per se. The dimension of the connection piece is decisive, however. The cleanability decreases with a smaller diameter and a longer connection piece. The flange connection (version with flat gasket) is generally problematic since there is no defined sealing surface. When fixing the flange, misalignment and small cracks can possibly occur between the gasket and metal contact.

For picture 3: Ideal design. Measurement equipment is completely flowed through because of the open cross-section, with almost no dead leg. Attention must be paid, however, to a hygienic design of the flange connections.

For picture 4: In principle OK, since the installation runs largely level with the pipework which means that the cross-section is flowed through unhindered. Due to manufacturing tolerances, there is however always the risk that liquids may enter the threaded part.

## 10.2 Selection of the appropriate measurement procedure

For each measuring task such as pressure, temperature and flow measurement, the suitability of the measurement procedure needs to be considered. The selection of a measurement system compliant with the requirements presupposes that, apart from the general suitability for use, the technical application limits such as temperature, pressure, process material and explosion protection requirements are also included in the planning. As regards cleanability, all advantages and disadvantages should be considered. Not every measuring procedure, for instance, is suitable for use in hygienic equipment. One example is the oval rotor flow meter which cannot be recommended for use in CIP equipment (cleaning in place) because of its poor cleanability.

The following table lists constructive advantages and disadvantages of different measuring procedures in terms of cleanability, shown using the example of selected flow measurement procedures. In general, similar criteria apply as previously shown for pressure measurement, although in this case the procedures chosen determine the design.

| *Measuring procedure* | *Advantages* | *Disadvantages* |
|---|---|---|
| **Magnetic-inductive flowmeter** | | |
| Indicating electrode (galvanic) | Nearly no narrowing of the pipework's cross-section | Indicating electrodes having direct contact with the product.<br>Additional sealing of the lining required |
| Capacitive pick-up | No pressed-in electrodes. No installation in the product chamber.<br>Nearly no narrowing of the pipework's cross-section<br>**Good cleanability** | |
| **Oval rotor flow meter and other mechanical volumeters, turbine meters** | | |
| | In principle especially suited for products with lubrication properties | **Poor cleanability** due to mechanically moved built-in parts |
| **Thermal mass flow meter** | | |
| Bypassing | No installations | **Poor cleanability** of the bypass |
| In the pipework | | **Poor cleanability** due to installations in the product chamber |

| *Measuring procedure* | *Advantages* | *Disadvantages* |
|---|---|---|
| **Coriolis mass flow meter** | | |
| Two tubes | No internal gaskets | Does not run dry in every position. When cleaning/rinsing there is no guarantee that both tubes are equally clean |
| One curved tube | No internal gaskets.<br>**Good cleanability** | Is not fully drainable in every position |
| One straight tube | No internal gaskets.<br>**Good cleanability** | Metrologically still inferior to the two-tube systems. Older versions involve more installation effort |

The measuring procedure or measuring principle not only affects the design, but also the reaction behaviour and the accuracy. Temperature measurement set up on the outside of the tube is the ideal as regards design, contamination risk and good cleanability. The measurement is slow and the absolute value is affected by many external influences, however, and therefore is not suitable if rapidly changing temperatures or high precision requirements are involved. The same applies to temperature measurements with a resistance thermocouple (e.g. PT 100) which is introduced into a sleeve welded into a tube. The design is ideal, but there are constraints with regard to reaction behaviour and accuracy.

## 10.3 Maintenance and calibration

Critical measurement equipment is measurement equipment whose measuring value significantly influences the product quality (measuring of CPPs - critical process parameters). The metrological requirements (measuring range, measuring accuracy) on the measurement equipment must already have been defined during selection and procurement and in accordance with the process requirements. Especially as concerns measuring tasks in the area of sterile technology (temperature measurement), it has to be clarified beforehand that the measuring uncertainty of the entire measuring network complies with the requirements and that no tolerances are exceeded because of error propagation.

The following figure shows the links between measuring error (uncertainty) and measuring value in the context of warning and action limits. The ISPE baseline guide: "Sterile Product Manufacturing Facilities" describes the facts in detail. The following example is influenced by the baseline guide.

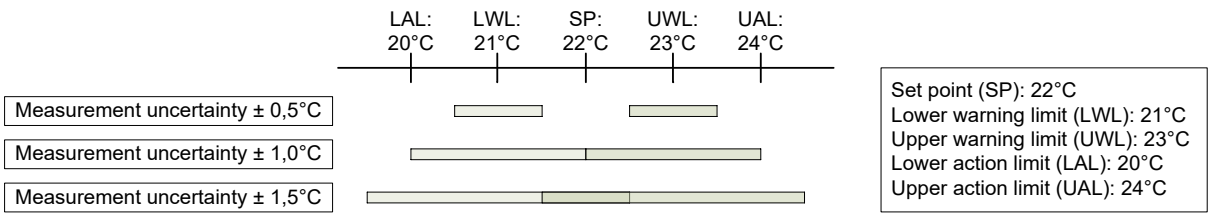



Figure: Measuring value and measuring uncertainty
Source: gempex

In the example above, the measuring uncertainty may not exceed ±1.0°C. This guarantees that the temperature is within the action limits when reaching the warning limits, even considering the measurement uncertainty.

With a measurement uncertainty of ±0.5°C there is still a leeway of 0.5°C of exceeding the warning limits. If the warning limit is reached with a measuring uncertainty of 1.5°C, it is not guaranteed that the real value is still within the action limits.

The correct functioning of critical measurement equipment has to be verified by carrying out regular calibrations. In general, it has to be ensured that the calibration always includes the complete measurement chain from the sensors to the display. There are two possible approaches:

- Comparison measurement: setting the physical measuring value and comparison with reference system. The sensor must possibly be removed.
- Isolated calibration (if the measurement chain cannot be calibrated together): external calibration certificate of the sensor and electrical simulation of the input signal on the remaining measurement chain by means of a calibrator.

Furthermore, attention has to be given to ensuring that the calibrated area covers the complete working range of the measurement equipment, especially if the technical equipment is used for different processes with different working ranges. In these cases, always the lowest and highest operating points in relation to all processes have to be selected. Where applicable, three-point calibration is required to prove linearity, or even more points depending on the measuring range.

Calibration is a mere comparison of the corresponding measurement equipment with an appropriate reference standard that can be traced back to certified standard values or physical basic values. In the GMP and especially in the FDA environment, a NIST (National Institute of Standards and Technology) traceable standard is requested. Calibration does not include adjustment which is carried out if the indicated value's deviation from the so-called true value (reference) is too great. If adjustment is required, it is important from a GMP point of view that the existing difference is documented first (as basis for a potential deviation assessment) and then the difference after adjustment.

Another important aspect in connection with accuracy requirements and calibration is the fact that the components of a measurement chain in principle have an accuracy guaranteed by the manufacturer that has to be considered and calculated for the complete measurement chain. The calculated accuracy for the standard version of a PT 100 (temperature) measuring network, for instance, is usually ± 1.7K. This means that the guaranteed accuracy is ± 1.7K even if the deviation between the indicated and true value is set to 0 in the course of a calibration and subsequent adjustment. If the instrument for example indicates 120°C, this could in reality also be 118.3°C, which would still correspond to the manufacturer's guarantee but could be disastrous in the context of sterilisation.

## 10.4 Definitions / glossary

| | |
|---|---|
| Action limit: | Defined limit - requires corrective action and further investigation if values fall short of the limit or exceed it. |
| CIP: | Cleaning in place |
| CPP: | Critical process parameter;<br>a process parameter whose variability has an impact on a critical quality attribute and, therefore, should be monitored or controlled to ensure the process produces the desired quality |
| Electropolishing: | Removal technique. The surface is smoothed by means of anodic removal of a metal surface in acidic electrolytes |
| Adjustment: | Setting the measuring value indicated from a measuring instrument to the smallest possible deviation from the "true" reference value (reference instrument) |
| Calibrator: | An instrument for the calibration of electrical measuring instruments |
| Calibration: | Measuring process for the reliably reproducible determination and documentation of the deviation of a measuring instrument |

| | |
|---|---|
| Passivation: | (Concept of surface technology) The spontaneous formation or targeted production of a protective layer on a metallic material which hinders or significantly slows down the corrosion of the base material |
| PCT: | Process control technology |
| Warning limit: | Specified limit that allows for an early warning of a possible variation from normal operating parameters. This must not necessarily give rise to corrective measures but requires further investigation |

## 10.5 References


- DIN EN 1672-2:2009-07 "Food processing machinery - Basic concepts - Part 2: Hygiene and cleanability requirements"
- DIN EN ISO 14159:2008-07 "Safety of machinery - Hygiene requirements for the design of machinery"
- ASME BPE 2019; from the American Society of Mechanical Engineers new developed standardisation of semi-finished tube/tube parts and fittings made of austenitic stainless steel alloys with different application classes for piping installations for the pharmaceutical / biotechnological construction of equipment (dimensions, materials, surface finishes etc.)
- EHEDG Guideline Doc. 8 "Hygienic design principles"
- EHEDG Guideline Doc. 37 "Hygienic design and application of sensors"
- 3-A Sanitary Standards Inc., Various resource papers and e- learning modules
- NAMUR Recommendations (NE) and Worksheets (NA); Sensors
- ISPE Baseline Guide: Sterile Product Manufacturing Facilities 2011
- ISPE Baseline Guide Vol. 5: Commissioning & Qualification
- ISPE GAMP Good Practice Guide; A Risk-Based Approach to Calibration Management, Nov. 2010

# 11. Requirements for automation and control systems

In the age of digitalisation and Industry 4.0, it is hard to find any instrument or machine today that is not equipped with high-quality control and data collection. Collecting data, converting them into graphics, analysing them and forwarding them directly via an app to the smartphone or PC is very common nowadays.

In the GMP-regulated environment, in contrast, there is an increased demand for validated computerised systems, for data protection and data integrity. Especially with regard to automated equipment, the question of delimitation arises - what exactly has to be validated and to what extent? When must an exclusive control (automation) be assessed as critical? What can be handled in the course of the qualification of devices and what must be done in a complex validation according to GAMP®5?

This is surely not the place to address all possible systems and delimitations in detail. The aim of these explanations, however, is to reach a better understanding of the different requirements and to have guidance to hand on how to delimit systems and which minimum requirements have to be fulfilled. The implementation of the individual steps of qualification and validation will not be addressed. These are deemed to be known.

## 11.1 Qualification or validation

A qualification in the traditional sense typically includes the elements of DQ (design qualification), IQ (installation qualification), OQ (operational qualification) and PQ (performance qualification). Within the framework of OQ (operational qualification) especially, manual functions (manually operated actuators, on/off switches, correct direction of rotation) but also automated functions - ranging from simple controls and alarm circuits to sequence controls and step chains - are tested or, to put it more accurately, confirmed in their correct functioning. Particularly, controls and step chains are typical processes of automation supplemented additionally by topics such as data collection, display and evaluation for instance on local displays (HMIs = Human Machine Interfaces). It is not uncommon that these automated systems are additionally connected to higher-level controls and guidance systems in order to collect all data and information at a central place and let them flow directly into a production record (such as PCS or MES).

A frequent question in the manufacturing environment is about the rules and guidelines according to which such automated systems have to be qualified or validated. It should be noted that the basis for a potential (computerised system) validation is always a qualified infrastructure - i.e. qualified machines and instruments. The quality assurance measures carried out within the typical mechanical and electrical operation tests represent the basis of a validated overall system. Consequently, the following is generally applicable: the higher-level PCS is validated while the basic infrastructure (automated machines and instruments) is qualified.

Not so simple, however, is the approach to the borderline case, when equipment is either defined as "computerised" or as an "automated" system. Will it be validated or qualified according to the respective requirements?

How is a machine control dealt with for example when recipes can be started via its HMI? Is it validated according to GAMP® 5 or qualified according to Annex 15 of the EU Guidelines on Good Manufacturing Practice or to the ASTM standard? A pragmatic solution has to be found. If the equipment is a stand-alone system and therefore also a completely automated machine with HMI and touch panel, surely a complete validation and operation according to GAMP® 5 requirements is not required. All considerations and tests to be carried out for reasons of data integrity regarding e.g. user

administration, data security (reliability, process data, configuration data, audit trail data) and archiving can also be carried out within the framework of equipment qualification.

However if this system is connected to a higher-level PCS, it has to be verified in the end which quality-relevant data are stored in which subsystem. If the PCS serves only as a monitoring system without collecting, managing and evaluating data, the systems can be dealt with separately. The more quality-relevant functions are moved to the PCS (such as data back-up, archiving) the more the original approach to treating the systems independently of each other has to be reconsidered.

## 11.2 Delimitation of the subsystems

The data flow of quality-relevant signals and controls can be used to define the lead system. Where are data collected, stored, visually displayed or output? This also determines the validation or qualification procedure. If this is only done by the machine or instrument, the necessary measures can be covered by means of qualification. If it is done by the higher-level system (such as PCS), the validation approach according to GAMP®5 has to be selected.

When validating higher-level systems, interfaces and transfer points to the infrastructure, the machines and instruments must also be subjected to a risk assessment and clear responsibilities must be defined for the sub-areas so that the complete range of required quality assurance measures is covered in the end. These framework conditions and delimitations have to be described in the validation plan.

All control elements and control units which can be regulated and set directly via the HMI connected with the equipment are considered, assessed and tested in the equipment qualification. The interface between process units (PUs) and the PCS are dealt with in the PCS validation.

In the case of a system in which the PCS has a higher-level and controlling role, the following functions can be assigned to the different systems, and therefore also to the different quality assurance measures by means of examples and from the point of view of qualification:

| Function | Description |
|---|---|
| User login HMI | Partly relevant for qualification as access takes place only by means of the overlayed PCS. Only access by the local administrator has to be verified in the qualification. |
| Graphical representation | Not relevant for qualification. Verification is carried out within the scope of the PCS validation. |
| Authorisation concept (HMI) | Not relevant for qualification as access takes place by means of PCS roles; only the local administrator can access the configuration of the PU control. |
| Data output and data storage | Not relevant for qualification; it is carried out within the scope of PCS validation. |
| Time synchronisation | Must be carried out in qualification. |
| Interfaces | Description by PU supplier in communication matrix. Validation within the PCS project. |

| | |
|---|---|
| PU internal functionalities | Individual control level, interlocks and step chains: description by PU supplier; testing by means of FAT/SAT of PU supplier. Verification within the scope of qualification. |
| Back-up / restore plan | Partly required in qualification. After each change of the PU controls configuration, an image has to be created. Dynamic data are saved in the PCS, however. |

This allocation has to be redefined for each project since the connection of different equipment is handled very differently. Furthermore, it is not always completely possible to integrate subsystems into higher-level systems.

## 11.3 Special feature - configuration management

Apart from the common topics verified within the operational qualification such as

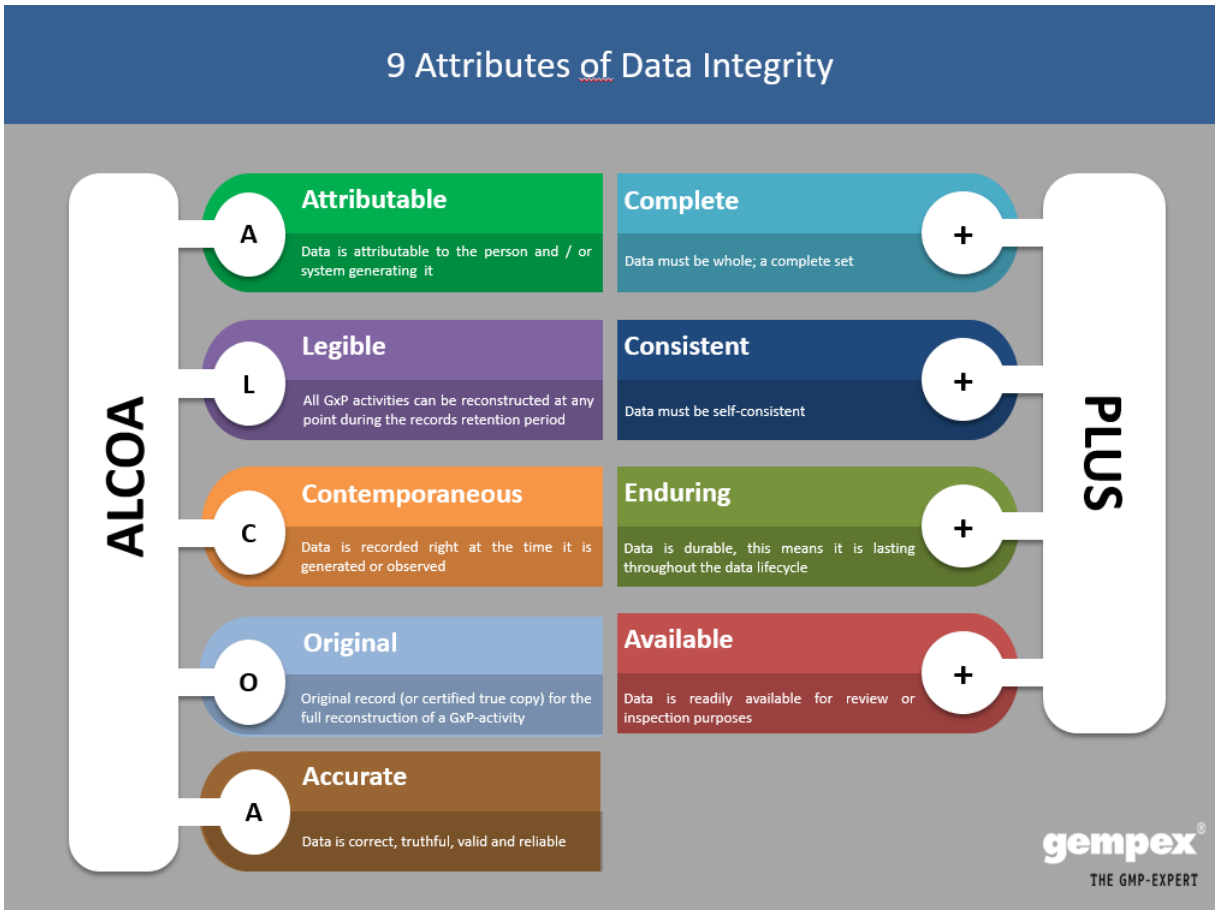
- manual functions
- circuits and control loops (loop test)
- alarms
- sequence controls
- process working areas
- and others

special emphasis should be placed on the topic of configuration management. Regarding this, it is important to know that apart from the usual parameter settings such as set and alarm values, maximum and minimum levels stored in a PLC (programmable logic controller), there are a significant number of further parameters affecting the mode of operation and thus the process and the product quality. For instance, there are also stored control parameters for typical PID controllers or standard machine settings in a permanently installed EPROM (memory chip). These parameters have to be stored in such a way that they can be re-entered at any time in the event of machine failure or that it is possible to fall back on the old configuration in the event of a malfunctioning software update (fallback scenario). The established standard is that, with each change in the configuration, a back-up is immediately made and stored in a database. Before carrying out a software update, the old configuration is stored and after installing the new software the new configuration is also stored. This means that at the end of each configuration at least two copies exist, one from the initial phase and the other from the end of the operational phase.

## 11.4 Data integrity

Even though the authorities have started to focus on the topic of data integrity only in recent years, the corresponding requirements have existed since the beginning of the GxP regulations.
Good documentation practice is applicable for paper-based records, and nowadays for electronic data and electronic records as well.

The concept of data integrity describes all measures required to ensure that data are retained completely, consistently and correctly. These requirements are applicable during the complete lifecycle of data, beginning with their generation, recording, processing, use, storage and archiving up to their controlled destruction. For the evaluation of data integrity the authorities refer to the ALCOA(+) principle. This is an acronym used to summarise the fundamental properties of GxP-compliant data.




Source: gempex

Regardless of whether the system is validated or qualified, the subjects of user management, data security and archiving have to be considered.

In general, at least three user groups have to be set up in a system control. The group of administrators for configuring the system, a supervisor group with rights to set operating parameters (set values, alarm limits) and an operator group having only reading and basic operation rights (such as acknowledging alarms). Further roles and rights might be established according to needs and complexity. Users with modification rights have to log into the system with their own assignable user name. Only then is it possible to set up a correct audit trail.

The measures required for data security depend primarily on the infrastructural connections. When carrying out the qualification or validation, the relevant data must be defined and the back-up procedure described in detail. It is standard that an image of the complete system is created before each system change (see also configuration management). This file saves the system's configuration data. A back-up of the dynamic data (data from the running process) has to be created regularly on the basis of a risk-based approach. Highly critical systems should be designed redundantly (potential data loss "zero"). For non-critical systems, a weekly data back-up is quite sufficient. It should be obvious that the reliability of data back-up and data recovery ("initial restore") has to be demonstrated (completeness and integrity of the data transferred) in connection with qualification and validation.

The retention periods for batch or product-relevant data depends on the nature of the product. Applying the Product Liability Act, documents should generally be retained for 10 years. The AMWHV (German Ordinance on the Production of Pharmaceuticals and Active Substances) requires not less

than 5 years and at the same time at least one year beyond the expiration date. The MDR (Regulation on Medical Devices), in comparison, requires a retention period of at least 15 years for medical implants after the products have ceased to be marketed.

The back-up procedure should therefore be used to prepare a potential archiving of the data. Depending on the system, the backed-up data can be archived by means of standard relocation procedures (such as tape back-up systems). It should be noted, however, that after the system has been decommissioned, this data must be accessible in readable form for a further 10 years. Without a system it is no longer possible to simply reimport the data. To ensure readability, the data must either be migrated to the subsequent system or the system must be archived completely or the data archived in a neutral readable form.

The operator needs to have procedural instructions for all these processes - authorisation concept, data back-up, data archiving and data recovery. The functioning of the procedures described has to be demonstrated in the course of qualification or validation.

## 11.5 Integration of FAT and SAT in the validation

Usually, a FAT (factory acceptance test) and a SAT (site acceptance test) are carried out on automated systems. In most cases, these tests are based on standard test documents provided by the supplier. To be included in the validation of a system, the test points and the test scope defined for this purpose in the supplier documents have to correspond to the result, i.e. the requirements from the functional risk analysis. The missing tests have to be listed in the user's IQ/OQ test protocols and also be carried out in the corresponding test phase. Functionality tests already present in the FAT/SAT documents must also be referenced in the traceability matrix. The test results of FAT and SAT are finally assessed when carrying out the IQ or OQ. In principle, the integration or use of the results from the FAT and SAT is possible within the framework of the qualification and validation of automated or computerised systems, provided the scope and depth of testing have previously been agreed upon with the user's quality unit. By applying this procedure, multiple tests can be avoided and standardised supplier documents can be fully integrated into the validation. A corresponding passage can also be found in Annex 15 of the EU GMP Guidelines.

## 11.6 Definitions / glossary

| | |
|---|---|
| ASTM | American Society for Testing and Materials |
| DQ | Design qualification |
| FAT | Factory acceptance test |
| GAMP | Good Automation Manufacturing Practice |
| HMI | Human machine interface |
| IQ | Installation qualification |
| MES | Manufacturing execution system |
| OQ | Operational qualification |
| PID controller | Proportional, integral, differential controller |
| PCS | Process control system |
| PQ | Performance qualification |
| PU | Process units |
| SAT | Site acceptance test |
| PLC | Programmable logic control |

## 11.6 References

ASTM E2500 – 13: Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment, 2013
EU Guidelines to Good Manufacturing Practice, Annex 11: Computerised Systems, 2011
EU Guidelines to Good Manufacturing Practice, Annex 15: Qualification and Validation, 2015
ISPE GAMP®5: A Risk-Based Approach to Compliant GxP Computerized Systems, 2008
ISPE GAMP®: Records and Data Integrity
NAMUR Interessengemeinschaft Automatisierungstechnik der Prozessindustrie e.V.

# 12. Documentation in the lifecycle of GMP equipment

Documentation has special importance in the GMP environment. It serves as proof that something has really been done and it serves the traceability of the measures implemented. If errors arise or there are deviations in production, the documentation is needed for cause analysis, for assessing the effects and for future error prevention. Regarding this, the focus is not only put on the operator's documentation. Special requirements are also placed on the technical documentation of rooms, equipment and devices beginning with the planning documents up to the documents required after completion for the smooth operation of technical equipment.

The technical documentation also plays a decisive role for qualification since it documents the construction of equipment which can later be retraced by means of this documentation. Therefore, all relevant documents have to be presented on time and the planning engineer has to consider when procuring technical equipment that the documents have to be prepared at an early stage and that they have to be complete and always up to date. It goes without saying that these documents have to comply with the customary GMP requirements on Good Documentation Practice (see chapter "Formal aspects").

Which documents will be needed in general in which phase, from planning to operation, is presented below. As the actual extent of documentation is mainly determined by the nature of the project (such as completely new construction or only procurement of an instrument) the explanations can be understood as indicative. Documents such as operator requirements and/or risk analyses are specific GMP documents and will not be dealt with in more detail.

## 12.1 Documentation in basic engineering

As concerns medium and larger-scale projects for a new construction, reconstruction or extension, a distinction is usually made according to Good Engineering Practice (GEP) between the following construction phases:

- Conceptual design
- Basic design/engineering
- Detailed design/engineering

It occurs often that in the early phase of conceptual design, various solutions are still examined and compared and therefore documents generated in this phase are not of crucial importance for the subject of GMP and qualification. Only when an alternative solution is chosen and considered in more depth and then followed up in the basic engineering is the corresponding documentation brought into focus.

Documentation in connection with basic engineering is important since key basic GMP requirements are already being defined at this stage, depending on the product to be manufactured and the purpose of use (GMP classification). The documents prepared during this (planning) period are in general included in the design qualification (DQ) as rough test documents and are as such subject to a design review. Rough test documents are all technical documents on which the carrying out and the results of a test are directly documented (in most cases by hand). Naturally, in this planning phase they cannot have the level of detail usually required for the implementation. But they should already contain all important GMP requirements. This is also verified in the course of the DQ and directly confirmed on the documents.

The following documents typically belong to basic engineering and are relevant for GMP (the list is not exhaustive and depends on the respective project):

- Flow and/or block diagrams of the process (simplified) or process flow diagrams, P&IDs (simplified), lists of machines and devices (important parts of equipment, especially the long lead equipment)
- Data sheets, technical specifications (for example specifications for machines and devices, but also data on measurement equipment) with important information that is required according to GMP and other information, as far as is known during the planning period
- Layout/design drawings (sketches, as far as these are known)

As already stated, an initial design review is carried out on the basis of these documents and is confirmed by means of a date and signature on the documents. Further design reviews can follow if significant changes regarding GMP-relevant aspects occur during planning. DQ usually ends with the release for implementation/construction by engineering. This release document is decisive regarding the qualification documentation. Important intermediate results can be included. With conclusion of the DQ phase the change control obligation starts. This means that changes have to be documented, followed up and released.

## 12.2 Documentation in detail engineering & implementation

In detail engineering, the documents already prepared in basic engineering are elaborated in more detail. They form the basis for the subsequent execution or implementation of the technical measures (design, construction, connection). These documents, too, are subject to a design review within the course of the design qualification and are revised as concerns compliance with GMP and the operator requirements.

After realisation of the technical measure, the documents from the detail engineering phase form the basis for the installation qualification (IQ). Consequently, "compliance with the situation on-site" (correct installation) is assessed on the basis of different drawings (for instance P&IDs). Material certificates (metallic materials) are used in order to ensure the correct material specification. For material certificates - in connection with parts lists - traceability is important. This means that which part of equipment or workpiece the certificate belongs to must be clearly recognisable. This applies equally to the certificates of conformity for plastics, greases and lubricants (e.g. seals/ gaskets, filter materials, filter aids).

Treatments of the surface of metallic materials are often only documented with a general manufacturer's declaration, if not otherwise stipulated with the supplier at the beginning. Measurements of the surface roughness and the results are documented with the help of measurement reports (photos and measurement values). Again, traceability has to be guaranteed.

The following documents typically belong to the detail engineering phase and are relevant for GMP (the list is not exhaustive and depends on the respective project):

- List of actual machines and devices with details on the relevant specifications
- Possibly also URS + company policies
- List of product or media contact pipework, flexible tubes and detachable connections
- List of product or media contact fittings
- List of measurement points with technically relevant data / specifications
- P&IDs (in detail, according to DIN EN ISO 10628 and DIN EN 62424)
- Isometries
- FAT/SAT protocols
- Material certificates (metallic parts)
- Certificates of conformity (plastics, greases, lubricants)
- Proofs of surface treatment
- Measurement reports as regards surface roughness

- Welding certificates, test protocols for welding seams
- Spare parts lists
- Cable diagrams, wiring diagrams, circuit wiring diagrams (electrical engineering)
- Function charts
- Calibration records
- Proof of cleaning
- Product contact surfaces

## 12.3 Important documents for qualification

The importance of the technical documentation specifically for qualification has already been highlighted. The most important documents that are particularly important for qualification will be highlighted and discussed once more below. In the framework of a technical project, particular attention should be paid to these. These documents may be checked in the course of an inspection by the authorities or a customer audit.

**P&ID** examined and approved as a central document
It should follow the common standards (DIN EN ISO 10628 and DIN EN 62424). The P&ID presents the sequence and relationship of all components such as pipework (with slope), devices, containers, fittings and measurement points. All components have to be unambiguously marked on-site as in the R&ID. The marking has to guarantee the correct linking to other documents such as the list of machines and devices. When testing on-site is carried out, coloured markings in the rough test document (diagram) are recommended. The P&ID is the central IQ test document for process engineering equipment.

**Isometry** with documentation and testing of welding seams
According to the pipework list, indicating the welder (reference to the welding certificate), type of welding, number of welding seam, material numbers of the components (reference to the material certificates 3.1), testing (visual and endoscopic, x-ray). Isometries are especially important for quality-critical pipework, such as for the distribution of ultra-pure water, but also as concerns the reliable cleaning with CIP (cleaning in place) in equipment. Then it has to be possible to retrace the course of the individual pipework in detail.

**List of devices and machines** with process engineering data (including the manufacturer and type)

Specification of the material with indication of the type of material certificate and specification of the surface quality (with test certificate) and

*List of product or media contact pipework, flexible tubes and detachable connections* (type and gasket) detailing nominal width, nominal pressure, material and type of material certificate and specification of surface treatment and quality.

*List of product or media contact fittings*

Detailing construction type, nominal width, nominal pressure, material and type of material certificate and specification of surface quality.

For a cleaning validation, the *product contact surfaces* must also be detailed. They can also be specified in the lists mentioned above.

**FAT/SAT protocols** from the factory acceptance tests (FAT) and the site acceptance tests (SAT) if these are integrated as a basis for the qualification. These technical test documents created by the

producer or supplier already contain a variety of the points to be tested within the installation qualification and the operational qualification. If it has been agreed beforehand with the later user and if pre-tested, these documents can be used to avoid the duplication of testing (no repetition required within the qualification).

If FAT/SAT test results will be used in a later qualification phase instead of testing, this has to be recorded beforehand in writing, for example in the validation master plan.

**List of measurement points** at least with technically relevant data (measuring range, accuracy, etc.). Ideally, this includes the specification of the surface quality, the materials and the type of material certificate of the product contact surfaces of installed measurement equipment. Quality-relevant measurement points (definition of risk analysis) have to be revised and calibrated regularly.

Regarding this, *calibration records* which have to be created during the planning phase and at the latest before the operational qualification (this means after the completed IQ) are very important.

**Cable diagrams, wiring diagrams, circuit wiring diagrams** help electrical engineering and process control engineering (PCE) to show that everything has been connected and tested correctly.

**Function charts** describe the functions of equipment or of a device taken as a basis (e.g. functions of a PLC - heating/cooling) and are the base document for the operational qualification.

**Ground plans**, especially with information on the flow of personnel and material and with information concerning a zone concept, are the basis for the revision and qualification of areas with higher requirements such as clean room areas. *Plans on the course of ducts* for the presentation of the ventilation installation and the *detailed construction drawings* for the design of the interior of clean rooms should be mentioned as additional supporting technical documents.

As a result of the qualification, the checked diagrams, drawings and lists documented with the technical installation are available. They can also contain documented tests, e.g. if special requirements concerning the installation of measuring instruments (inlet runs of flowmeters) and of other components (3D rule for valves or no dead legs) have been complied with. The technical documents used and processed within a qualification are rough test documents within the meaning of GMP.

## 12.4 Operating documentation

Upon completion, the technical equipment is handed over to the operator and starts routine operation. Not every document prepared during the planning and execution phases will be needed later (e.g. foundation plans for concrete). They are archived as project-specific documentation. Technical documents, however, which are necessary to operate and maintain technical equipment are handed over to the operator as operating documentation after having been updated following qualification. The operator has to keep the documents updated. The following are typical important documents for the operation (the list is not exhaustive):

- Technical data sheets and specifications
- P&IDs
- Ground plans
- Drawings (e.g. design drawings)
- Spare parts lists
- Parts lists specifying the materials and the corresponding certificates
- Protocols within the scope of commissioning (as appropriate also FAT/SAT protocols)
- Operating and maintenance instructions

Some of these documents originate from the planning office, while others must be asked for at the supplier's when ordering the individual components. It has to be agreed at an early date that the documents are supplied since they are rarely supplied automatically and often only for an extra charge.

In general, the operator has to prepare and maintain additional instructions with concepts for operation, cleaning, maintenance and calibration for the equipment. This also includes a list with all maintenance and repair works on the basis of the specifications in the documentation of the individual components. All of the equipment documentation has to be kept updated. It has to be updated in particular after a technical change within a change control procedure.

## 12.5 Material certificates

According to the applicable GMP requirements (e. g. Annex 15 EU GMP), the qualification has to contain a verification of the materials used for construction. This is to ensure that the equipment is made with the materials the pharmaceutical manufacturer has asked for (the equipment's material may not adversely affect the product). As not every pharmaceutical manufacturer has the necessary means to perform a revision of the material or to identify it, the material certificates come into play here. A differentiation is made between:

### 12.5.1 Material certificates for metallic materials

The certificates issued for metallic materials disclose the composition of the metal melt, more specifically the concentration of the alloying components. There is a

Test report type 2.2 according to DIN EN 10204:

Statement of compliance of the material with the order, with indication of the results of a non-specific inspection.

Inspection certificate type 3.1 (formerly 3.1b) according to DIN EN 10204:

Statement of compliance of the material with the order, with indication of the results of a specific inspection.

These certificates/test reports should be asked for especially in the case of product contact surfaces in critical and late process steps (near the end product). An inspection certificate 3.1 should always be supplied if possible and available as this is the only way to guarantee that the certificate can be traced back to each component. For components made of plastic, this is often impossible, however, so certificates are usually accepted in which the producer himself confirms compliance with the requirements.

### 12.5.2 Material certificates for product or media-contacting plastics (e.g. seals/gaskets)

These are certificates of conformity from the producers confirming compliance with certain standards or regulatory requirements. Regarding plastics and elastomers, these are in particular requirements coming from the food sector guaranteeing food suitability.

There are certificates of conformity according to CFR 21 177.2600 Food (US FDA) or EHEDG or EU certificates of conformity. These certificates confirm that the materials contain no ingredients that could adversely affect the product. The conformity means in general that the material is not toxic if swallowed. Such a certificate of conformity can obviously not guarantee general compatibility with the product, the process media, etc.

For substances that could enter the product unintentionally (e.g. diaphragm seal fluids, lubricants) stricter requirements apply concerning biocompatibility. On the one hand, the classification according to USP applies and on the other, the DIN EN ISO 10993 standard. Here, the conformity (e.g. USP Class VI) is also confirmed by the producer (supplier).

The US American pharmacopoeia therefore also makes statements on the pharmaceutical suitability of plastics and subdivides them into six biocompatibility classes. USP Class VI is the strictest class and is equated with the pharmaceutical marketing authorisation for polymer materials. In order to obtain a classification in Class VI, the material has to be tested in external test laboratories. For this, animal experiments used for determining the acute toxicity (irritant effect when swallowed or inhaled) are carried out, the intracutaneous reactivity is tested (tissue test), or an implantation test is carried out. This requirement often is specified needlessly. In this regard, it is important to be aware that not only is money wasted, but that this needless specification is to be blamed indirectly for unnecessary animal experiments.

As concerns biotechnological production, it may also make sense to specify that the materials are ADI-free. This means that no materials of animal origin were used for the construction of the equipment (ADI free = raw materials contain no animal-derived ingredients). Accordingly, such materials are also free of BSE and TSE (BSE = bovine spongiform encephalopathy; TSE = transmissible spongiform encephalopathy).

The pharmaceutical manufacturer has to clarify herself/himself if the plastic used reacts or interacts chemically with the pharmaceutical material. In biotechnology, the leaching-out of plastic materials is also critical, i.e. there is a need for clarification over which substances could migrate from the plastic into the pharmaceutical material. To this effect, producers of equipment carry out studies which in a sort of worst-case scenario test with the aid of model solutions which substances can be extracted from the plastic at all (determination of the extractables). Leachable studies with the pharmaceutical material test which substances really leak under real conditions. The results of the studies must then be assessed from a toxicological point of view under consideration of the process, product, application, etc. The pharmaceutical manufacturer determines by means of risk analyses if leachables and extractables studies are required.

## 12.6 Formal aspects

Apart from indicating which technical documents are important during which phase for which purpose, this chapter addresses the formal requirements, namely the requirements of Good Documentation Practice.

Each planning document used for qualification has to contain on each page a clear allocation to the corresponding part of the equipment or to the corresponding equipment and to the underlying main document (with its version and date of creation). This applies particularly to documents with test entries. Notwithstanding this, and according to Good Engineering Practice, each technical document should contain an unequivocal identification (number or name), a status of revision and a date of processing. It should be possible to identify the person responsible and the tester at least by means of initials. In this case, there should be a list of initials for correct allocation.

Usually, these requirements are complied with by the technical documents having a standard legend.

The management of the document, i.e. the handling of revisions and the updating of individual drawings and lists is as important as the labelling. Professional engineering companies and/or suppliers often have a project quality plan (PQP) to hand which regulates the exact procedure, the labelling and redistribution. Prior to awarding the contract, this PQP should be asked for and discussed.

## 12.7 Definitions/glossary

| | |
|---|---|
| ADI-free | (Raw materials) contain no animal-derived ingredients |
| BSE | Bovine spongiform encephalopathy |
| CIP | Cleaning in place (cleaning when installed) |
| DQ | Design qualification |
| FAT | Factory acceptance test |
| FDA | Food & Drug Administration |
| GEP | Good Engineering Practice |
| GMP | Good Manufacturing Practice |
| IQ | Installation qualification |
| OQ | Operational qualification |
| PCE | Process control engineering |
| PQP | Project quality plan |
| P&ID | Piping and instrumentation diagram |
| SAT | Site acceptance test |
| PLC | Programmable logic control |
| TSE | Transmissible spongiform encephalopathy |
| USP | US Pharmacopeia |

## 12.8 References

DIN EN 10204 – Metallic products – Types of inspection documents
DIN EN 62424 – Representation of process control engineering
DIN EN ISO 10628 – Diagrams for the chemical and petrochemical industry
DIN EN ISO 10993 – Biological evaluation of medical devices
ISPE Good Practice Guide – Good Engineering Practice

# 13. Requirements on quality assurance systems for equipment suppliers

- "Which aspects should the supplier's quality system offer to smoothly accomplish fulfilment of any ordered GMP-compliant equipment design?"

  **or**

- "Which supporting documents does a supplier have to present in order to be regarded as qualified supplier?"

The requirement for compliance with the GMP rules has reproduced itself in the supply chain for years, not only in the area of active substances where it is statutory (EU GMP Guide Part II) but in all areas of excipients, pharmaceutical services, systems and equipment. Since then, except in the field of the manufacture of finished medicinal products and active substances (as well as their distribution/storage), respectively, no official GxP certificates are awarded and so the requirement of "GMP-certified" cannot be officially fulfilled by an equipment supplier. This requirement is therefore not useful, whereas the requirement for a general quality management system (QMS) is. Obviously, a GMP-based QMS would be easier to explain to an equipment buyer coming from the pharmaceutical industry and he would approve it more easily. Therefore, producers of equipment primarily supplying the pharmaceutical industry have developed QM systems which are strongly geared towards GMP. The rise of single-use equipment and corresponding consumables that replace parts of the actual unit operations (single-use equipment: storage bags made of plastic, transfer tubing and assemblies, disposable filters) has certainly strengthened the specialisation of pharmaceutical suppliers with GMP QM systems, but has also increased complexity due to the required compliance with further aspects of quality management and regulation (e.g. requirements for plastics according to USP <87> & <88>). Hardware producers in particular, meaning producers of classical pharmaceutical equipment, traditionally work according to ISO 9001 and other sector-specific ISO standards that at first glance do not seem to be completely compatible with GMP, whereas the compliance with further (ISO) standards is essential for safe operation. In practice, such apparent discrepancies can be overcome eventually and the creation of functioning hybrid systems - or of systems accepted by the pharmaceutical customers, respectively - is achievable. It is not by accident that one of the core aspects of the very flexible ISO 9001:2015 is to identify customer requirements.

## 13.1 Quality management systems: DIN ISO 9001 as a basis

The prerequisite for successful cooperation with a pharmaceutical customer and for the supply of accordingly GMP-compliant equipment is certainly to understand the pharmaceutical requirement for quality management systems and the pharmaceutical sector's point of view. The equipment producer should also keep in mind that, in relation to the critical assessment of the equipment producer's systems, his counterpart might not be an engineer with experience in the production of hardware/equipment or discrete production in general. It is equally important to understand that GMP is prescribed by law – unlike the voluntary application of an ISO QMS. The competent authority will not issue a manufacturing authorisation to the pharmaceutical entrepreneur if GMP is missing, resulting in an inability to put medicinal products on the market.

Although many quality management systems within the industry are very similar and also are based on ISO 9001, GMP is a somewhat more special QMS[12] that is quite unique to the pharmaceutical

[12] In the meantime, and with the application of ICH Q10, GMP is even regarded as being only a part of the pharmaceutical QMS that needs to be complemented by further aspects such as risk management and quality monitoring.

industry. It puts a strong focus on the documentation of requirements and evidence and on the executing persons acting accordingly, including their training. Any deviation is seen critically at first and a variation which also includes an (apparent) improvement is not authorised without systematic change control. As a result, everything must always be the same and compliant with the specifications [in ISO 9001: conforming criteria]. This is proven by means of qualification and validation. In this respect it has to be kept in mind that the pharmaceutical manufacturing process and product specifications are part of the marketing authorisation, which in turn guarantees patient safety based on positive clinical studies. This means that any change would potentially not be proven by studies as being safe for patients. And finally, in practice the quality unit approves everything in the GMP environment.

This means that a pharmaceutical customer will often expect these systematics, including an independent quality assurance unit (QA), from the supplier's QMS too. Fortunately, the GMP requirements can be fulfilled to a large extent by the ISO 9001 requirements which are applied in many companies anyway. Some aspects of the ISO 9001 standard are not entirely relevant to the pharmaceutical customer (e.g. customer focus [5.1.2.]/customer satisfaction [9.1.2.] and realisation of opportunities [6.1.]) or even associated with a certain risk (continuous improvement [10.1.a][13] – *cf. corresponding paragraph*), and the process-orientated classification of ISO 9001:2015 is unfavourable for a direct comparison of the two standards. On the other hand, however, aspects such as management review [in ISO 9001 chapter 9.3.1.] have been adopted from the ISO world to the GMP rules.

## 13.2 Quality management systems: overlap with GMP

What does the QMS of an equipment producer have to offer despite all the general similarities of quality management systems in order to guarantee GMP-compliant equipment? The general answer is: control over the manufacturing process and the final product. This is also the intention of the frequently used ISO 9001 [*cf. respective paragraph* 0.1.a)]. It is worth looking in detail at the individual steps of the value chain. From the pharmaceutical point of view the ordered and supplied equipment must in the end formally comply with the requirements defined at the beginning. In practice, however, especially complex and large equipment is *designed* in steps and improved during the development process. As this phase is often accompanied by the design qualification (DQ), which is required from the GMP point of view and which represents the matching of the functional design specification with the user requirement specification, and since it is not permissible to carry out (uncontrolled) changes on the equipment after such a DQ, the equipment producer's QMS has to contain detailed specifications concerning design freezes and version controls of the design documents/drawings. This automatically results in the demand for document control, even for development documents, including awareness raising (training) among the staff involved. From the time of delivery of the functional design specification, a change control process must be effective with reference to the version of the design documents applicable at that time. The change control process assesses the influence of any changes on the specifications and enables potentially required communication with the customer. Document control [7.5] and change control [8.3.6; 6.3; 7.5.3.2.c); 8.1] are also required by the ISO standard and the applicability to development should be assured specifically [8.3.6].

With regard to equipment which appears to be standard "off-the-shelf" equipment, change control concerning design also has to be observed since apparently structurally identical equipment is often not exactly the same over its lifecycle and improvement cycles, respectively. This can result in problems during qualification at the pharmaceutical manufacturer, especially if he carries out a simplified qualification based on an erroneously presumed alikeness. The apparent improvement -

[13] The respective (GMP-analogous) ISO 9001:2015 references are given in square brackets.

desirable according to ISO - becomes a possible dangerous disadvantage (for patients) within the GMP environment! From the point of view of the equipment constructor, the criticality regarding the subsequent use for manufacture might be impossible to assess completely, despite the requirements in the user requirement specification.

Before being used for manufacture, each piece of equipment is subject to qualification at the pharmaceutical manufacturer during which the equipment is revised with regard to the requirements previously set down in writing (the user requirement specification/functional design specification). As a consequence, the equipment producer's QMS should support the customer's predefined or typically expectable requirements. Ideally, the equipment producer's QMS fits with the subsequent qualification carried out at the customer's or pharmaceutical manufacturer's premises. This, again, includes control and continuity/unchangeability of the components, but also the supply of reliable documents and certificates that can be traced back to the components. Examples include material certificates (steels, plastics etc.), surface characteristics, welding certificates, calibrations etc., as well as information on electronic components and - with the heavily increased use of computerised systems and components - configuration certificates and so on. For such documents, a good systematic control system is required, for instance using unique numbering. Due to the required unique assignability, all components - even the small parts - must be clearly identifiable and traceable [8.5.2.].

In the event that control software is installed that goes beyond simple hard-to-configure PLCs, it must also comply with the requirements expected from the pharmaceutical companies such as user and access management or audit trail records, respectively. In most cases, compliance with the GAMP[14] standard is expected or specified.

## 13.3 Qualification and validation at the equipment supplier

But what about the qualification and validation of the supplier's equipment and processes used for production? The machines and instruments used for the actual manufacture of equipment have only a few analogies to the production machines and processes used in pharmaceutical manufacturing. There is also no unambiguous record on qualification in the ISO 9001 standard. The terms "qualification" and "validation" on the subject of computer validation can be used interchangeably, however. Validation as aspect of the "revision/review - verification - validation" control sequence is a requirement in ISO [8.5.1 f)], "*where the resulting output cannot be verified by subsequent monitoring or measurement*". Hence, the testing of process capabilities by means of validation should be taken into consideration for critical processes such as welding or electropolishing, for example. Equally, compliance with requirements by means of design - the "functionality" so to speak - should be verified or validated during development [8.3.2 c); 8.3.4 d)], since the manufacturing process finally leads to a "functioning" developed product, at least as regards the capability of the manufacturing processes to produce the (new) product/equipment. Essentially, all processes should be evaluated with regard to the need for validation by means of a risk analysis.

In any event, measurement instruments should be qualified [ISO 7.1.5.1], and this qualification should encompass calibration [7.1.5.2] and maintenance [7.1.3]. Further qualification requirements can be deduced from the requirement for "controlled conditions" [8.5.1 d)]. Just as when assessing the validation requirement for processes, a streamlined procedure by means of risk analyses can be used here for the identification of critical equipment and instruments with a corresponding test definition.

One aspect gaining in importance is computer system validation (CSV), which constitutes a critical question in the GMP environment and which is not mentioned explicitly in the ISO standard. According

[14] Good Automated Manufacturing Practice Supplier Guide for Validation of Automated Systems in Pharmaceutical Manufacture.

to the ISO standard [7.1.3], software is part of the infrastructure, however, so that the requirements for qualification and validation take effect as described above. An approach according to GAMP known from the pharmaceutical sector might be too complex as regards the depths of the potential tests, however the principles of this approach can be used - again risk-based and abstracted from patient risk to process stability - to guarantee the safe operation of the (control) software used. Particularly with regard to modern systems and due to the technical possibilities already in existence, this should include the individual assignment of accounts with rights management, configuration and parameter definition including (uncontrolled) un-alterability as well as an, at least selective, audit trail review (for instance in the context of maintenance). In the case of legacy systems, logbooks help with the appropriate control and assignability of potential necessary changes of parameters *(cf. below, data integrity)*. Critical system calculations, including by means of Excel sheets, should be verified and the relevant data should be subject to checks. This means that, apart from the initial review of the correctness of the calculations, it must also be guaranteed that integrated formulas and parameters cannot be changed in an uncontrolled or undocumented manner.

Consequently, with such procedures for qualification and validation, it should be possible to fulfil the GMP requirement of the pharmaceutical customer in this area.

## 13.4 Further supplier quality systems

The requirements on the equipment producer's quality management system concerning the control of actual routine production can easily be fulfilled by applying ISO 9001.

For a better presentation (to the outside) but also or rather primarily to give the own staff a better understanding, it is advisable to use the quality manual, which had been removed from the ISO 9001 version of 2015, as the uniting reference and overview document. It can give a logical structure to the company's own requirements (SOPs). Moreover, the GMP world is about to become familiar with the quality manual. Further overarching QMS aspects such as risk management, management responsibility & review, as well as internal audits [9.2], stem from ISO anyway and should also comply with GMP requirements if carried out correctly and in a properly documented manner. As far as the implementation of risk management is concerned, it should be kept in mind that the use of FMEAs is established in the pharmaceutical environment. In this context, however, it should be realised that this is only one risk analysis tool out of many, and risk analysis is only one aspect of risk management. Other sound and well documented, science- and technology-based approaches should surely be accepted by the pharmaceutical customers if thoroughly explained.

Let's now proceed further along the value and material stream. Quality starts with clearly defined and specified starting materials and corresponding supplier qualification, which does not necessarily mean auditing. This requirement can only be found in rudimentary form in chapter 8.4 of the ISO standard, but it is a typical expectation in the pharmaceutical environment. As always, the efforts of such processes have to be defined on a criticality or risk-based platform. Examples are the services of external welders associated with many requirements and the procurement of steels where the alloy and the corresponding certificates are strictly observed (in addition to internal tests such as the ferrite content etc. - see below). Once starting materials are supplied, the QMS should require clear procedures for testing/analysis and storage [ISO 8.4.2.(b)&(d)]. The definitive identification and consequently assignment of material to particular test procedures should not pose a problem when using current ERP systems. The test instructions have to be clearly set out and the results have to be documented; this requirement results from the ISO standard too [e. g. 8.1.(e); 8.5.1.(a)]. The QMS should predefine specifications - with wording that cannot be found like the ISO standard but which is required nevertheless [8.1. (b)2)] - because only clear specifications allow for unequivocal acceptance and rejection decisions. Supplier certificates can be used in general, but an identity verification as well

as the verification of critical attributes should at least be carried out. Moreover, the equipment producer should be able to answer the question why he trusts the supplier's certificates.

## 13.5 Documentation

At the latest from this point onwards, the requirement for document control [7.5] applies, which recurs throughout the entire QMS and manufacturing process, respectively. There should actually not be a big difference between GMP and ISO. Documents have to be clearly named and be identifiable. Only the current version is to be used - old versions have to be withdrawn. Production records which are also required in the ISO quality management system according to 8.1.(e)1)&2) should be issued in a controlled way and based on an authorised master; reprints of records or parts of them should not be possible/allowed in general; retrospective changes may not take place or only if they are traceable and if they are carried out in a controlled manner; results [8.1.(e)2)] or raw data that feeds into recordings and protocols ("evidence") [7.5.3.2.] must be added in its original/recorded form. In the pharmaceutical environment, this is called data integrity which must also be guaranteed when using electronic systems for instance by means of individual accounts and audit trail reviews. Each change of documents must clearly be carried out in a controlled way. Data that is not specific for a batch, product or equipment must be recorded in alternative forms of documents such as (machine) logbooks or test journals or in the corresponding electronic systems. Each use of such tools for production/testing, but also calibration and maintenance as well as defects/problems, should rather be recorded in logbooks/journals. A regular review of such logbooks by supervisors/ QA is then an "add-on".

When equipment is being produced, this should be done according to precise specifications which are specified and controlled by means of SOP and a production record. This encompasses a clear batch assignability regarding starting materials, as well as in particular the assignment of a traceable batch or identification number of the equipment produced and sub-parts. Evidence such as printouts of the welding machine parameters or any tests for the control of the intermediate and final results should also be documented in an assignable manner, including primary data such as photos of the checks of welds or manual isometry checks (*cf. above*). Such intermediate results can and should indeed be reviewed and released if they are critical for further processing [8.6]. The final result, in any case, requires acceptance against clear specifications, with review of the production process and test records regarding completeness and correctness, as well as the final release by an independent instance, usually the QA [8.6.]. It should in no way be possible, for example, for the production department management to overrule the person responsible for QA and the idea that "it's almost ok" should not be accepted. Regarding errors in the broadest sense, i.e. deviations from the requirements and specifications, non-complying (measurement) results and the like, systematic and documented deviation management must take effect [8.7; 10.2.1] and measures have to be defined as to if and how the result can be corrected and consequently whether the product/equipment can be released and used. The final decision concerning the measures and use of results/products lies again with QA [8.7.2 d)] (the QA is not directly mentioned in the ISO 9001 (even if required indirectly), but from the pharmaceutical point of view only an independent instance as such is accepted). For the implementation of such corrective measures and of corrective and preventive measures concerning any form of improvement of the quality system, including the reaction to complaints (which are only a deviation that was not discovered in-house) the establishment of a CAPA (or deviation) system is recommended [10.2]. Each reasonable measure is preceded by a sound analysis of causes□an approach expected or required from both systems (GMP, ISO). This quality aspect again offers the possibility to collect "GMP-add-on-points" by additionally applying a system for reviewing the effectiveness of CAPAs [10.2.1 d)].

Simple systems based on paper forms [10.2.2] or an ERP Q module or other electronic QM software can be used for deviations and CAPAs. The same applies to change management and most of the

other QM-relevant processes (for the control of individual quality events). In this group of usually retrospective quality elements, the change management process, being a prospective tool, has a sort of special status, the advantages of which should be used: changes especially of processes, measurement instruments, test and review procedures, specifications/requirements and of the quality management system itself - should be planned and described prospectively and in a stepwise manner, be evaluated by several relevant experts regarding their impacts on the product quality or customer expectations and finally be released by the QA. It is very important to check whether changes at the equipment producers` have to be discussed with the customer or even approved by him.

The best QMS is ineffective if the persons acting according to it do not know it. Therefore, the (relevant) staff has to be trained – with regular refreshes - on the fundamentals, on aspects and processes/SOPs of the QMS. Further necessary trainings on special procedures as well as required skills [7.2] have to be identified. Such processes should - as always - be well planned and documented by means of individual training files, training plans/matrices and documented evidence (attendance sheets, tests, certificates). On the basis of general business requirements, such processes should be in place anyway, at least in limited form, within human resources and/or occupational safety/HSE.

A functioning QMS is not only about a lot of paper, however, even if this chapter may have created this impression so far. The means of production must also be controlled. Such means of production - infrastructure, machines, tools, measuring instruments – have to be clearly identifiable and subject to preventive maintenance [7.1.3] and where necessary a calibration regime [7.1.5.2] at specified intervals with provisions concerning the implementation and specifications. Measuring instruments in particular have to be neatly managed and kept. For this, a systematic, documented management of measuring instruments (including initial qualification [7.1.5.1]) and, among other things, close calibration and traceability (calibration of the calibrator) is necessary, for business risk aspects alone. Corresponding documentation and status labelling must be established. The next "add-on" from an ISO point of view is the fulfilment of the requirement for a retrospective assessment of so-called out-of-calibration events regarding measurements that have already been carried out (and were wrong). In this case, the impacts on production have to be assessed until the time of the last successful calibration. As always, this has to be documented, too.

## 13.6 Production conditions

The topics of cleanliness and hygiene play an important role and this not just in the pharmaceutical environment. Pharmaceutical equipment should be easy to clean, but this is primarily a design characteristic. The environment, however, where the equipment is produced should also "make a good impression" - as every one of us can confirm when visiting a restaurant or even a car repair shop. This starts outside of the production hall and continues on the inside with adequate pest control. There should be a system for defined order keeping and cleaning. Cleaning should refer to machines and tools and include the controlled use of cleaning agents, lubricants and other production aids which are not supposed to end up in the subsequently processed medicinal product via the equipment. Food-grade lubricants can be used for risk reduction, for example. Correspondingly, there should also be provisions to hand over the finished equipment in a clean state. The concept of cleaning validation known from the pharmaceutical operation is rather unnecessary in the production of equipment. But any type of cleaning should be effective and generally prevent contamination [8.5.4].

In order to prevent such impurities, contamination or cross contamination, the 5S workplace optimisation method can be used – although this is rarely used in the pharmaceutical environment, is not required and possibly complex/expensive on the one hand, but very effective and powerful on the other. In the end, however, the devil is in the detail and it is necessary to raise awareness among staff and to establish equipment or system-specific provisions. Here, the strict separation of stainless

steel and black steel including bolts and nuts should be mentioned. It might even be safer to avoid the use of black steel in the corresponding factories/areas in order to prevent errors. This should be given serious consideration, bearing in mind for example that the exchange of the wrong bolts in a larger piece of pharmaceutical equipment may quickly entail costs in the lower five-digit range. Also, the ends of tubes have to always be kept closed in order to prevent the entry of dirt or insects. Such measures must also be observed and controlled when installing the equipment on the customer's site. The author also has heard tales of dead mice in tubes but also about sandwich paper in tubes which surely did not get there by accident. No matter what is written in the QMS, high quality is achieved by paying attention to such important "small details".

## 13.7 Differences between suppliers and pharmaceutical manufacturers

What are the differences or rather "simplifications", therefore, for suppliers of equipment as compared to GMP? The differences or lower requirements are indeed small taking ISO 9001 as a basis. ISO 9001 surely is an appropriate, if not even the minimum, standard for more complex organisations, especially as regards supplying the pharmaceutical industry. Only very small companies that have only a few employees and which rely on the experience of the employees and on interactions of the staff may possibly defend a less formalised QM with limited intensity of documentation (in fact, the US FDA has accepted such QMS approaches in the area of medical devices[15]).

It is doubtlessly possible to reduce the width, depth and level of detail of requirements and proofs, putting the focus selectively on critical aspects. The reason for this is in particular that the significant aspects of "patient safety" and regulatory approval are missing. Furthermore, the production of equipment is a discrete manufacturing process with higher controllability of the results compared to the process technology in the pharmaceutical industry. Nonetheless, the equipment delivered must directly manufacture a product with relevance for patient safety. The QA's involvement can be reduced, leaving the definition of requirements, documents, procedures and specifications to the experts (the selective control by QA is then carried out "automatically", for instance during self-inspection). The stringency regarding requirements for the equipment control such as qualification, maintenance and calibration can be reduced - as long as failures are detectable for sure and potential reworking can be accepted from a business point of view. Complex, multi-stage QM processes such as qualification/validation or change management can be simplified. Document control in the area of forms, which is a problematic topic (data integrity) for many pharmaceutical companies anyway, can be handled less stringently with simplified issuance. The frequencies of review can be prolonged and some controls can be carried out only selectively, statistically or on a risk-based basis. And finally, many assessments regarding the criticality of errors/deviations will be less impactful without entailing exuberant measures since there is no direct patient hazard.

Consequently, it will always be possible to adapt a well-established ISO 9001 system to GMP expectations. It will ideally not only be reliable and efficient also from a business point of view, but will also generate satisfaction among the staff because of the clear processes involved and satisfy the expectations of pharmaceutical customers.

## 13.8 Definitions

| | |
|---|---|
| Audit trail | (automatic and electronic) recording of all events of an (electronic) system |
| CAPA | Corrective and preventive action (system for corrective and preventive action) |
| ERP System | Enterprise resource planning |

[15] MEDICAL DEVICE QUALITY SYSTEMS MANUAL: A SMALL ENTITY COMPLIANCE GUIDE. 1996

| | |
|---|---|
| FMEA | Failure modes and effects analysis – tabular risk analysis tool for the systematic assessment of possible (causes for) failures and their impacts |
| GMP | Good Manufacturing Practice |
| USP | United States Pharmacopoeia |
| Validation | Documented evidence for meeting the requirements by means of tests (repeated several times) – typically for processes |

## 13.9 References

ISO 9001:2015
EU GMP Guide part 1 & 2
EU GMP Guide Annex 15
EU GMP Guide Annex 11
ISPE GAMP5 Guide
ICH Q10
US Pharmacopeia
Medical Device Quality Systems Manual: A Small Entity Compliance Guide. FDA, 1996

## 14 Change history

| | |
|---|---|
| 1.1 | Clarification in chapter 5.2 Surfaces<br>Correction in chapter 6.4 Explanation of terms. Changed ‘process contact’ to ‘product contact’ in one place’ |
| 1.2 | Addition of excursus ‘Delta ferrite’ in chapter 6 |

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