Harald Flechl

GMP Series

A Pharma Guide to Planning and Constructing Cleanrooms

GMP VERLAG Peithes

Excerpt from the GMP Compliance Adviser

Harald Flechl

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Contents

1 Cleanroom construction components

Harald Flechl

Here you will find answers to the following questions:
- Which legal and regulatory requirements must be met when selecting construction components?
- How can different requirements and recommendations be met economically?
- What method can be used to achieve a GMP compliant and economical level of construction quality?
- Which systems are GMP compliant?
- What proven construction methods are there for the renovation and new construction of different cleanroom areas?
- What details should be kept in mind when selecting components depending on the purpose of use?
- How can one assess the risk of a component's surface?

1.1 Introduction

Depending on the cleanroom class and the manufacturing process, special requirements apply not only to the environmental conditions for the manufacture of pharmaceutical products, but also to the construction components of the production facilities.

The pharmaceutical industry is subject to strict regulation and is considered to be very averse to innovation. Indeed, authorities and auditors often misinterpret specifications from guidelines as binding, which are merely recommendations. Benchmarking with comparable projects and the sharing of experience with competitors and related industries are therefore very important and have made many innovations in the pharmaceutical industry possible.

This chapter is intended to provide support in the planning of new construction or remodelling projects in the pharmaceutical industry.

First, the basics and requirements for the planning of a construction project are presented. In the following chapters you will learn
- Which specifications need to be reflected when planning a construction project (chapter 1.2 *Requirements originating from laws, rules and guidelines*)
- How the process progresses from concept to completed room (chapter 1.3 *Selection and procurement*)
- How you can optimise the planning process by using new technology (chapter 1.4 *New technologies for project planning*)

In the subsequent chapters, the individual components are presented. What is the current state of the art? What design variants are there? What details have to be taken into account in order for the result to be GMP compliant? In these chapters you will also find selection checklists as well as numerous illustrations and schematic drawings.
- chapter 1.5 *Wall and ceiling systems*
- chapter 1.6 *Windows and doors*
- chapter 1.7 *Floor systems*

Given the large number of possible design variants and materials, the question arises as to which component and which design are suitable for which purpose. A tabular overview for the cleanroom classes A-F can be found in
- chapter 1.8 *Application areas of construction components for different cleanroom classes*

Since this classification is based on the interior room surfaces, a risk assessment of the surfaces can provide an important basis for decision-making. You will find an explanation of how this can be done in

- chapter 1.9 *Example of a risk assessment for surfaces*

1.2 Requirements originating from laws, rules and guidelines

1.2.1 Eurocode Standards

The requirements for the construction industry are regulated by the binding Eurocode standards. The Eurocodes are a set of European standards for the construction industry. There are currently 10 Eurocodes (EC 0 to EC 9 in standards EN 1990 to EN 1999, see figure 1). These are subdivided into 58 sub-norms with supplementary national annexes covering all main fields of construction.

The Eurocodes are used to implement directives of the European Commission. These guidelines must be transposed into national law by corresponding legislation. In Germany, the construction regulation for submitted building projects has been implemented since July 1, 2012 and the Eurocodes are therefore applicable law.

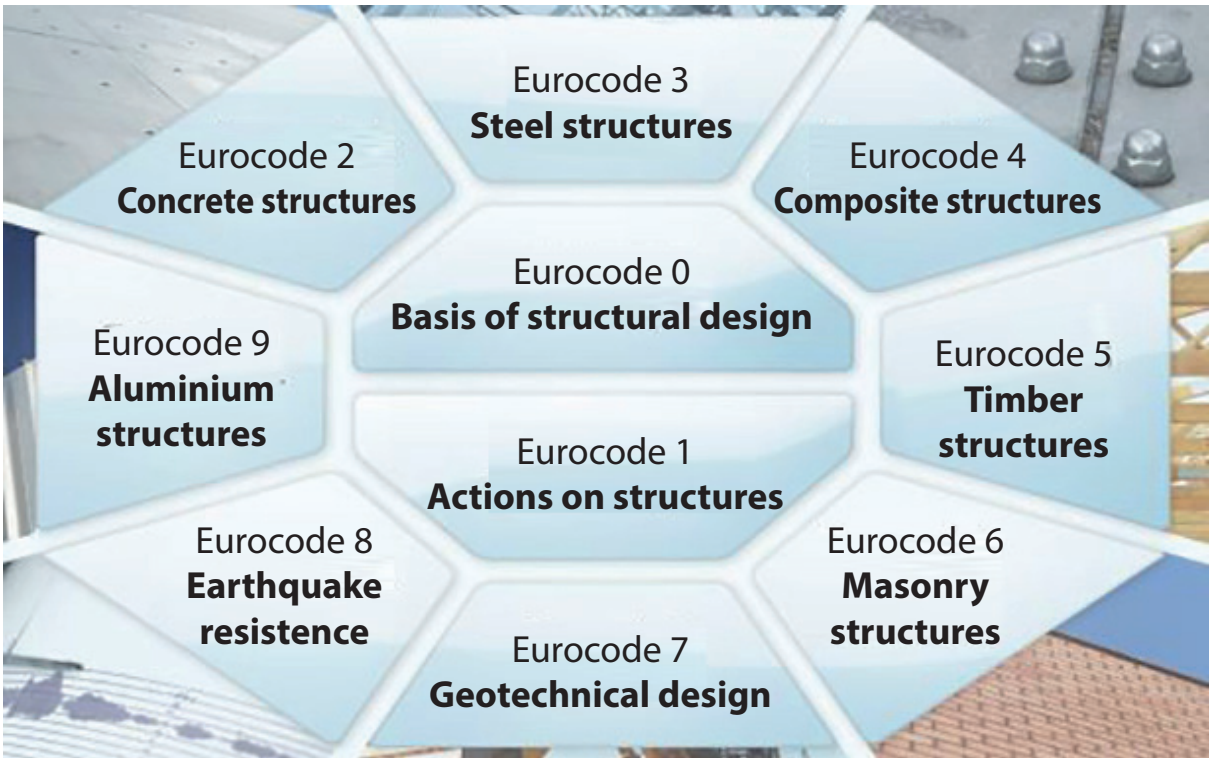

Figure 1 Eurocode groups (Beuth Verlag, 10787 Berlin, www.beuth.de)

1.2.2 Agency requirements

In addition to the GMP requirements, it is also mandatory to meet and comply with official specifications and requirements. These requirements can vary greatly from region to region and, in addition to the financial aspects (e.g. levies, taxes), constitute further decision-making criteria for a newly planned location or the renovation of an existing building. The requirements of change management must also be complied with.

Examples for mandatory agency requirements (laws and regulations) include:

- Federal and state construction code
- Construction laws, zoning of property
- Worker protection – provision of equal access for handicapped persons

- Fire protection
- Structural stability (earthquake zones)
- Commercial law
- Environmental protection – emissions and immisions
- Non-slip floor surfaces
- Noise emissions to surrounding residences
- Requirements placed by trade supervisory board (maximum noise level at workplaces, ability to view the outdoors from the workplace etc.)
- and further local authority requirements.

Sound absorption values for ceilings, walls and floors as well as footfall sound insulation are usually not specified by the authorities for industrial buildings.

1.2.3 Standards and guidelines

Recommendations for implementation are given in the various pharmaceutical guidelines and ISO as well as EU and country-specific standards (DIN, OENORM, etc.) to be able to comply with legal requirements.

While the standard ISO 14644-4 corresponding to VDI 2083 Part 4.1 defines only general structural and user-related requirements, the ISPE guideline (ISPE Baseline Guide Vol. 3 Sterile Manufacturing Facilities) makes specific recommendations for the selection of materials for surfaces and surface coverings.

In addition, there are a considerable number of technical rules for the construction and testing of floors, i.e. national, EN and EN-ISO standards. The construction of cleanroom floors can therefore be effected by considerably more technical regulations than the construction of cleanroom ceiling and wall systems.

A step-by-step and systematic procedure for GMP-compliant building expansion is described in VDI 2083 Part 4.1. The topics of risk assessment and quality assurance – basic elements in pharmaceutical plant construction – are also dealt with in detail in this guideline.

1.2.4 GMP requirements

With respect to the requirements for pharmaceutical production premises, the GMP regulations contain only general statements such as:

- Appropriate for the intended use
- Adequate space for production including materials, equipment and personnel
- Design according to the current state-of-the-art
- Properly sealed components (walls, floors, suspended ceiling)
- No uncontrolled dead spaces or links to the surrounding environment.

Premises for sterile production should be smooth, leak-proof and free of cracks according to the pharmaceutical guidelines (e.g. Annex 1 of the EU GMP Guidelines and other GMP regulations). The release or accumulation of particles and microorganisms or emissions of molecular gases should be avoided.

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

- Smooth, sealed, leak-free surfaces without cracks or non-accessible seals
- No emission or collection of particles possible
- No breeding ground for microorganisms
- Ease of cleaning and avoidance of hard-to-reach surfaces
- Proven compatibility for intended cleaning agents and disinfectant as well as the frequency of use
- Access for maintenance from outside the cleanroom if possible

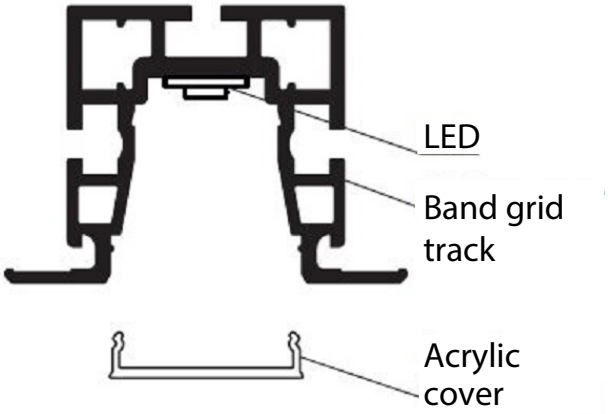

Figure 23 *Grid track for installation of LEDs (source: OCTANORM-Vertriebs GmbH, D-70794 Filderstadt, www.octanorm-reinraum.de)*

Figure 24 *View from below of monoblock ceiling with installed fixtures*

1.6 Windows and doors

The same surface requirements apply to windows and doors as to wall and ceiling systems. They should be designed and installed in such a way as to avoid inaccessible areas for cleaning. Concerning the cleanly grouted surfaces of windows, cloths used for wiping should not lose fibres from abrasion or adhesion, neither should it occur that residues of cleaning agents remain in the surface recesses.

1.6.1 Cleanroom windows

Windows are usually integrated as double-pane safety glass into the double-faced wall elements and exhibit no protrusions where deposits may accumulate (see figure 25). Ready-made and sealed double pane elements can be integrated into the wall (commonly used in monoblock systems) or each pane can be inserted into each wall side and sealed with installation profiles and gaskets as shown in figure 25.

Windows constructed with frames are hardly in use any more and rather unusual in class C/ISO8 or higher cleanrooms. Single-pane glazing with corresponding profiles (no horizontal surfaces, figure 26) is definitely a feasible and more cost-effective option.

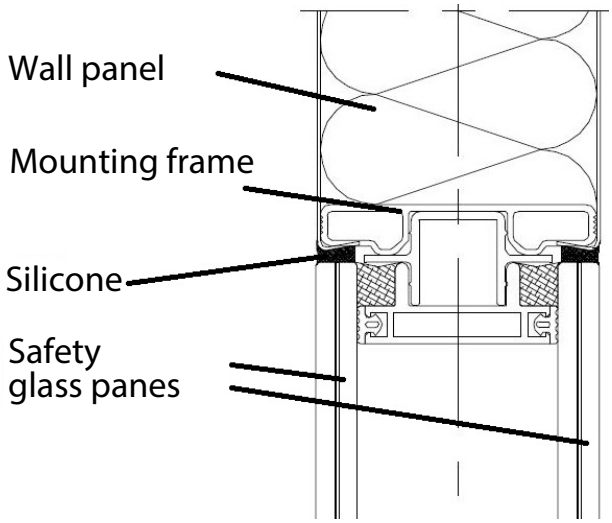

Figure 25 Design principle: double glazed safety glass in a wall element

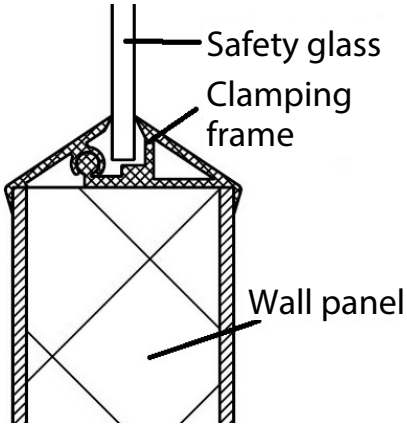

Figure 26 Design principle: single pane safety glass in a wall element

Drutex is currently offering a concept version of a technical innovation that follows the trend of the "IoT" (Internet of Things). An interactive window, which allows multimedia content to be displayed directly in the window glass and can be operated like a tablet, will be available for regular sale in the near future. This means that SOPs, drawings (see figure 27), process steps, messages and much more can be made accessible directly in the clean room for the production area and may even replace the computers in the clean room in the future.

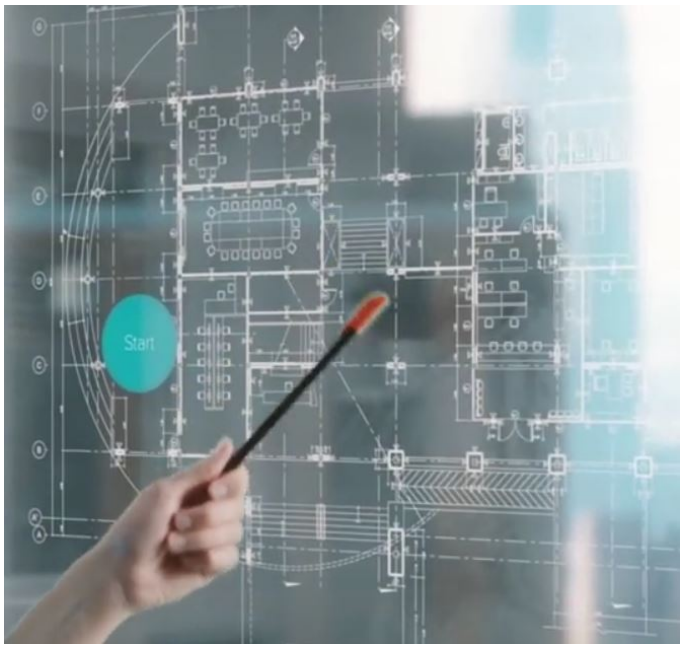

Figure 27 Interactive window pane (Drutex S.A., www.drutex.de)

1.6.2 Cleanroom doors

Hinged doors, single or double-leaf with inactive and active leaves, striking plate, hinges and handle sets are the most frequently used doors in cleanrooms (for designations, see figure 28). The frames are usually designed as block frames (flush with the wall element, usually in monoblock systems) or as clasping closed frames (wrap-around frame profile encloses the wall element, figure 29).

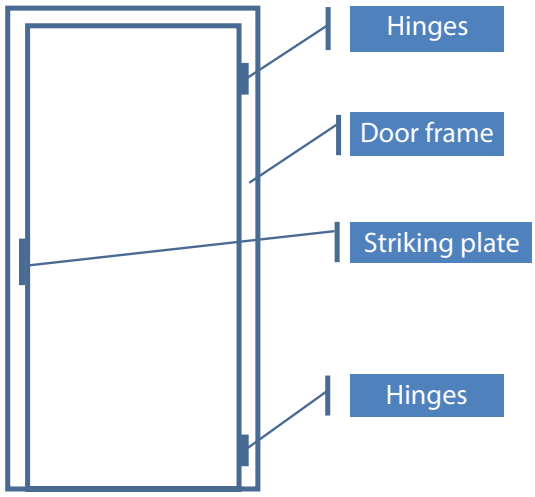

Figure 28 Designations of door components

The integration of components in the striking plates or frames for so-called asynchronous interlocking, which prevents the simultaneous opening of multiple doors, is already regarded as a technical standard today.

The opening sides classified as DIN left or DIN right are shown in figure 30.

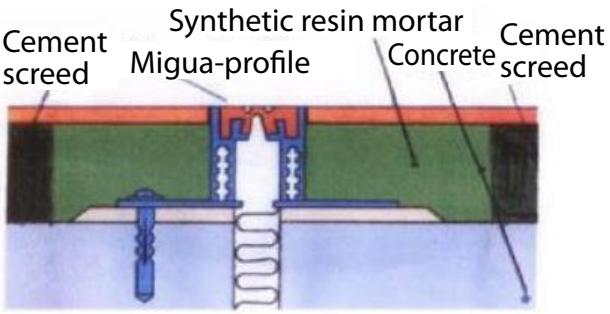

Figure 55 *Floor expansion joint cover (e.g. type Migua, https://www.migua.com/en/products/migutec/)*

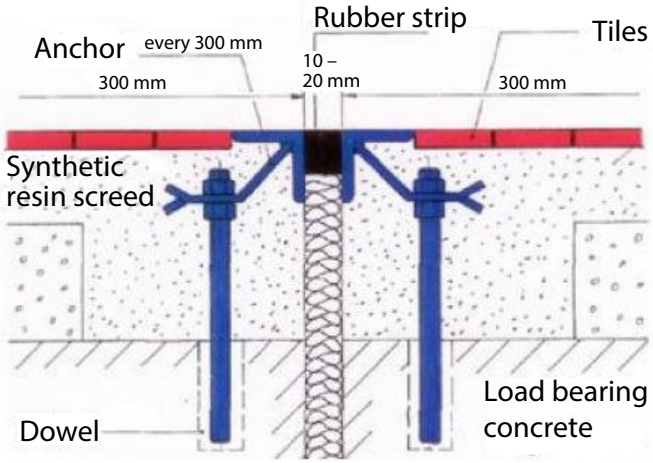

Figure 56 *Expansion joint for tile flooring*

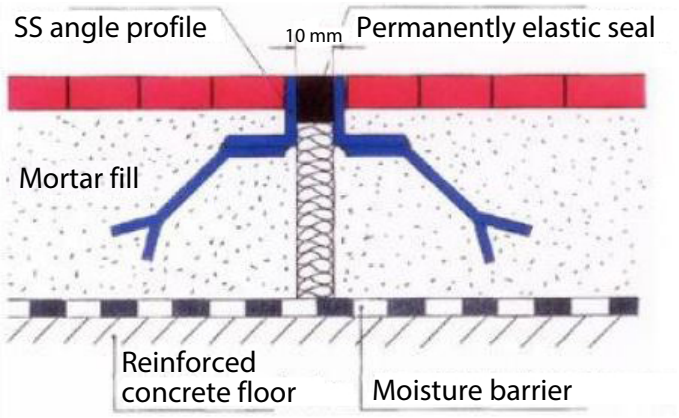

Figure 57 *Expansion joint in traffic areas with tile flooring*

Constructions such as ramming protection and bollards are mounted directly on the concrete of the unfinished floor to ensure the necessary stability.

Floor openings are constructed as double pipes (sleeve pipe, slip-on pipe, figure 58).

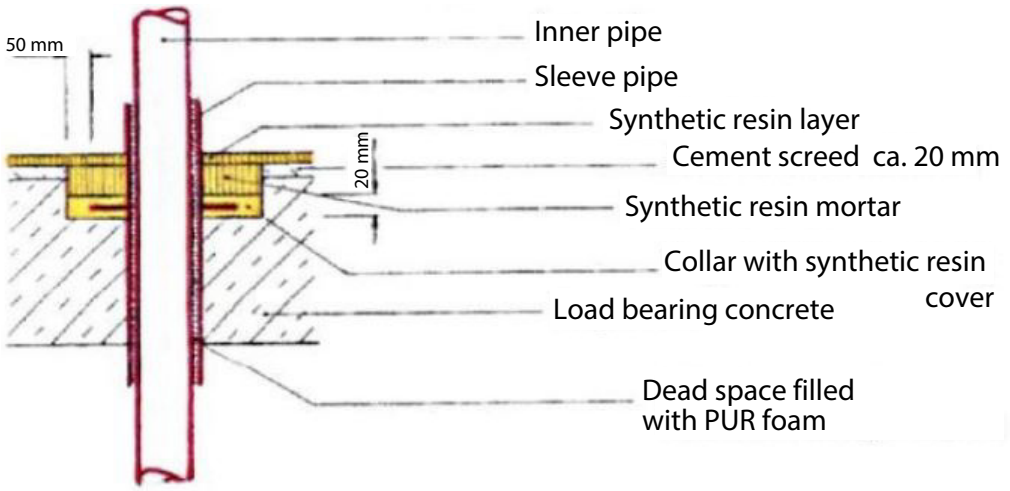

Figure 58 Floor pass through opening with sealed double pipe

Flat floor troughs (figure 59), deep box troughs and floor inlets (figure 60) are enclosed in plastic with their metal collars. The connection of the floor covering shall also be tight. When selecting the covers for the floor inlets, the load class must be taken into account – it must meet the operating requirements.

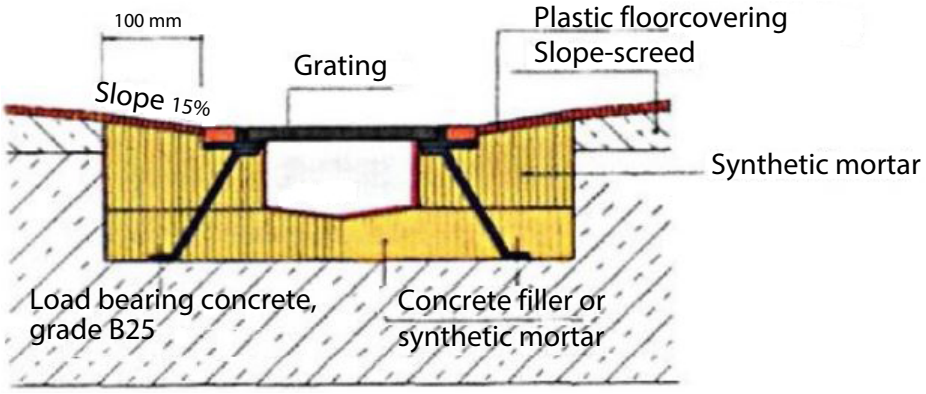

Figure 59 Installation of flat floor troughs

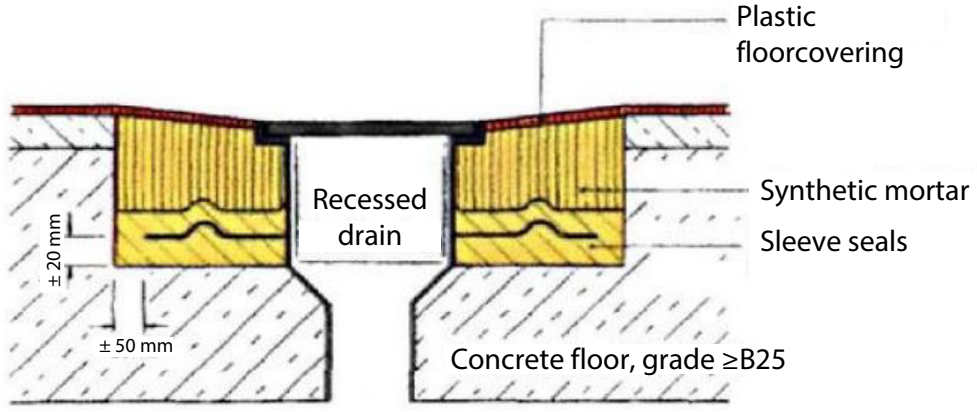

Figure 60 Installation of floor inlet

The GMP compliant installation of a **floor drain** is impacted by the following special design requirements:

- Material made of CrNi steel (1.4301)
- Odour trap and dirt trap can be pulled out fully
  - optional: Closing plug for the downpipe
- The downpipe is accessible for disinfection (steam or chemical)
- Hermetically sealed lid with rubber ring seal

1.7.4 Acceptance testing of floors

The user or his planner determines what is inspected during acceptance testing and with what specifications. The definition of the specifications, such as the electrical/electrostatic properties, is usually performed by experts.

The acceptance testing for cleanroom floors regarding its functionality can be performed as follows, for example:

1. Acceptance testing according to contractually agreed test norms and guidelines versus the following properties:
   - electrical/electrostatic properties
   - flatness
   - screed quality
   - tensile bond strength
   - slip resistance
   - residual impression depth, if applicable
2. Document reviews (certificates, test reports), for cases where testing on site is not sensible or possible. Examples include:
   - Fire prevention or noise protection characteristics
   - Grinding losses/wear resistance
   - Thermoshock resistance
   - Chemical resistance etc.
3. Visual inspections, such as:
   - Levelling and edge offset on fixtures according to agreement
   - Floor transitions and wall connections as shown in sample/as drawn
   - Cleanliness after basic cleaning as agreed, cleaning result after fine cleaning (and disinfection if necessary) as agreed/if necessary according to USP
   - Freedom from cracks according to agreement, and others.

In the case of quantifiable properties, the permissible deviation from the target value shall be indicated in each case, and information on statistics, e.g. number of samples, shall also be provided. Examples include values for the adhesive tensile strength in the case of synthetic floor screeds or sheet flooring.

Figure 61 shows an example of the acceptance parameters for a GMP-compliant (jointless) ESD rubber sheet covering.

Technical Specifications

- Electrostatic charge affinity/voltage of the system footwear + person + floor:
  - According to IEC 61340-4-5 and ESD-STM 97.1: <10 V (semiconductor industry)
  - Electrostatic properties according to EN 1815: <1 kV (example from micro-electronics)
- Ground discharge resistance according to EN 1081: 10^6 to 9 x 10^7
- Insulator resistance according to VDE 0100/part 610: >5 x 10^4
- Fire behaviour characteristics according to EN 13501-1: C_{fl} s1
- Adhesion of surface covering to fill screed: as agreed (or QS from producer as applicable)
- Residual impression according to EN 433: < 0.05 mm
- Abrasion according to EN ISO 4649/5 N load: < 180 mm^3

GMP characteristics for cleanrooms

- Inspect for "smooth surfaces free from cracks": visual, with optical devices if applicable
- Test for impenetrability: visual, but mostly by reviewing expert certification
- Durability with regard to defined impact of specified detergents and disinfectants

Figure 61 Acceptance testing parameters and specifications for seamless laid ESD sheet floor covering for critical areas

Contributors

Harald Flechl, Senior Engineer
flechlh@gmx.at harald.flechl@chello.at

Air conditioning technician – clean room technology

Harald Flechl is a senior engineer with more than 30 years of professional experience in planning, implementing and maintaining ventilation systems in the pharmaceuticals, electronics and health care industries. From 2008 to 2017, he was responsible for the design of building technology systems and clean room and support systems at Shire plc.
Mr Flechl retired in 2018. However, he continues to write and speak at conferences. As an ISPE member, he prepares expert reports and provides consultancy services.

Mr Flechl graduated from the Vienna School for Higher Technical Education (HTL) with an Engineering degree. In 1974, he started working in the area of industrial plant engineering. He moved to Luwa in 1980 where he was primarily involved in the further development of a patented sterile air distributor for low-turbulence displacement flow. In the following years, he worked in a number of different companies in the areas of customer services, facility construction and maintenance. In 2006, he took up a position at Shire (formerly Baxter AG/Baxalta) in the media supply department. Since 2012, he has been working as a "Global Engineering" expert with responsibility for technical design, energy optimisation and the life cycle aspects of the heating, ventilation and air conditioning systems, and compressed air systems.

Mr Flechl has completed a large number of training courses in the areas of contract law, air conditioning and quality assurance. He has worked at the Austrian Standards institute and as a court-certified expert for air conditioning and clean room technology. In addition, he provides presentations on air conditioning technology for staff training courses, compliance, technical implementation and life cycle considerations.