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Regulatory and Industrial Standards for the Qualification of Premises and Air Handling Technology

Excerpt from the GMP Compliance Adviser, Chapter 3.J.1

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Note by the author

This chapter is already based on the requirements of the revised Annex 1 *Manufacture of Sterile Medicinal Products* to the EU GMP Guide.

Annex 1 was published on 08/25/2022 with a transition period until 08/25/2023 (Item 8.123 until 08/25/2024).

The transition period is intended to give companies the time they need to implement an adaptation according to Annex 1 until the effective date of entry into force.

For this purpose, it is necessary to provide these new contents as information already now and to give hints for the implementation.

In the essentials – as a "philosophy for sterile manufacturing" – the 2008 and 2022 versions differ only insignificantly, but the 2022 version goes into more detail on some points (CCS, isolator-RABS, distinction between qualification and monitoring, etc.).

As with the previous version, the supervising authorities expect that the new 2022 version will already be complied with and that the changes will have been implemented, or at least begun to be implemented, within the period before it comes into force.

In the pharmaceutical industry, qualification and validation are the prerequisites for GMP compliant production of medicinal products. *Qualification* relates to the equipment (rooms and premises, plants and equipment and IT systems), while *validation* relates to the processes (production and packaging, cleaning, IT processes). Qualification and validation verify the suitability of the equipment and processes for the intended purpose.

The legal basis for this is provided by EU regulations, in particular **Commission Directive (EU) 2017/1572** which was transposed into national law together with other European directives. For Germany, this is the Ordinance on the Manufacture of Medicinal Products and Active Ingredients,for Austria the Pharmaceutical Works Ordinance.

For premises and equipment, it is defined in Article 8 of the EU Directive as follows (shortened excerpt):

1. ...the premises must be *suitable for the intended operations*...
2. ...any adverse effect on *the quality of the product* is to be minimised...
3. ... they are to be subjected to appropriate *qualification and validation*.

Paragraph 3 guides us to prove the suitability of the rooms and air handling units (AHUs), that is their qualification. A documented proof of suitability is therefore mandatory under the GMP regulations.

Annex 15 to the **EU GMP Guide** and the identical Annex 15 to the PIC/S Guide to Good Manufacturing Practice of Medicinal Products provides assistance or guidance on how this proof of suitability for the qualification of premises and AHUs in the pharmaceuticals industry can be carried out. EU Annex 1 applies specifically to the manufacture of sterile medicinal products, which, however, again refers to Annex 15 for equipment qualification.

What is new in Annex 1 (2022)?

Here you will find a brief summary of the most important changes and innovations with references to the corresponding subchapters.

- Physical measurands for the qualification of cleanrooms and clean air systems (chapter 3.J.5.3 Qualification test protocols)
- Performance qualification (chapter 3.J.9 Performance Qualification (PQ))
    - Limits for microbial contamination in the context of qualification
    - Measurement "at rest" and "in operation
    - Recovery time and clean up period
- Requalification (Chapter 3.J.10 Requalification)
    - Specifications for time periods and scope of testing

For details of the implementation of the air purity classification, reference is made in Annex 1 to **EN ISO 14644-1**. For other metrological requirements of rooms classified as cleanrooms, **EN ISO 14644-3** is particularly suitable. Among other things, it contains detailed instructions for the acquisition of further physical measured quantities, which must be specified in the user requirements specification (URS) with regard to the process/product requirements prior to qualification. In addition, it specifies minimum requirements to be met by the measuring instruments. Alternatively, the guideline **VDI 2083 Sheet 3** *Cleanroom technology Metrology* can be used. However, it is not yet harmonised with EN ISO 14644-3.

The **EN ISO 16170** procedure *In situ test methods for high efficiency filter systems in industrial facilities* is also frequently used for filter tests in exhaust systems. Here, procedures are described for testing filters that are not accessible from the room as so-called "terminal" filters but are integrated into air ducts as exhaust or supply air filters. It applies where these filter units are installed in facilities that process or handle toxic/radioactive/biological material. They are used to largely clean the air leaving the room from airborne particles before releasing it to the environment. This international standard excludes those applications already covered by EN ISO 14644-3, but can be applied mutatis mutandis to high performance filters in pharmaceutical exhaust air systems.

For microbiological assessments, **EN 17141** *Biocontamination control* is often used as the basis (the previously applicable EN ISO 14698 was withdrawn in 2021). This sets out the requirements, recommendations and methodologies for microbiological contamination control in areas controlled for cleanliness. However, this document is limited to viable microbiological contamination and excludes all considerations of endotoxin, proteinaceous-infectious and viral contamination.

Additional important guidance regarding Planning, initial commissioning and technical approval can be found in the informative **Annex D to ISO 14644-4**. Documents from the initial commissioning can partly also be used for the qualification.

The most important regulations and standards are summarised in Figure 1.

Important regulations and standards on the qualification of premises and air handling units
EU Directive 2017/1572
EU GMP Guide, Annex 1 and PIC/S Annex 1 *Manufacture of sterile medicinal products*
EU GMP Guide, Annex 15 and PIC/S Annex 15 *Qualification and validation*
EN ISO 14644 *Cleanrooms and associated controlled environments* Part 1: *Classification of air cleanliness* Part 2: *Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration* Part 3: *Metrology and test methods* Part 4: *Design, construction and start-up, Annex D*
EN ISO 16170 *In-situ test methods for high efficiency air filter systems in industrial facilities*
EN 17141 *Biocontamination control*
VDI 2083 Sheet 3 *Cleanroom technology - Metrology and test methods*
VDI 2083 Sheet 4.1 *Cleanroom technology - Planning, construction and start-up of cleanrooms*

Figure 1 Important regulations and standards for the qualification of premises and AHU systems

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