Comparison of the EU GMP Guide Annex 1 Sterile Manufacturing

An excerpt from the new Download [Comparison of the EU GMP Guide Annex 1 Sterile Manufacturing]

5 min reading time

by Fritz Röder

The new draft of Annex 1 of the EU GMP Guidelines keeps numerous responsible persons in the pharmaceutical industry busy. Are you already prepared for the possible changes?

Based on a **comparison with the currently valid version** this download demonstrates where action is needed.

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e) Processes associated with the finishing and transport of sterile products should not compromise the finished sterile product in terms of container integrity or pose a risk of contamination and ensure that medicinal products are stored and maintained in accordance with registered storage conditions.		*Finishing and transport shall not pose a risk to the product (e.g. container closure integrity, storage conditions)*	2
f) Persons responsible the quality release of sterile medicines should have appropriate access to manufacturing and quality information and possess adequate knowledge and experience in the manufacture of sterile dosage forms and their critical quality attributes in order to be able to ascertain that the medicines have been manufactured in accordance with the registered specification and are of the required safety, quality and efficacy.		*Cross reference to know-how and experience of responsible personnel*	2
3.2 Investigations should be performed into non-conformities, such as sterility test failures or environmental monitoring excursions or deviations from established procedures, with a specific focus regarding the potential impact to sterility, to not only the specific batch concerned but also any other potentially impacted batch. The reasons for including or excluding product from the scope of the investigation should be clearly recorded and justified within the investigation.		*- Deviations shall also include sterility of the product.* *- Further batches shall also be included in the analysis. If batches are excluded from an analysis, a rationale must be provided.*	2
4. Personnel	**Personnel**		
4.1 The manufacturer should ensure that there are sufficient appropriate personnel, suitably qualified and experienced in the manufacture and testing of sterile medicines and any of the specific manufacturing technologies used in the site's manufacturing operations, to ensure compliance with Good Manufacturing Practice applicable to the manufacture of sterile medicinal products.		*New note on "sufficient and sufficiently qualified" personnel. As this requirement is also mentioned in the EU GMP Guidelines, Part I, section 2.1, it is already common practice.*	1
4.2 Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in critical areas should be determined based on QRM principles, documented in the contamination control strategy, and validated during activities such as initial qualification and aseptic process simulations, so as not to compromise sterility assurance. This is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.	36. Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible. 71. Care should be taken that any validation does not compromise the processes.	*A maximum number of personnel shall be defined based on risk and confirmed during media fill execution (new nomenclature: "aseptic process simulation")*	2

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4.3 All personnel (including those performing cleaning and maintenance) employed in such areas should receive regular training, qualification (including sampling of the operators bioburden, using methods such as contact plates, at key locations e.g. hands arms and chest) and assessment in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene, cleanroom practices, contamination control, aseptic techniques, and potential safety implications to the patient of a loss of product sterility and in the basic elements of microbiology.	37. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.	*Qualification of personnel has been newly added including bioburden test with contact plates; in addition, the training scope has been extended.*	2
4.4 The personnel working in a grade A/B cleanroom should be trained for aseptic gowning and aseptic practices. Compliance with aseptic gowning procedures should be assessed and confirmed and this should be periodically reassessed at least annually and should involve both visual and microbiological assessment (using additional locations such as arms and chest). Only trained personnel who have passed the gowning assessment and have participated in a successful aseptic process simulation (APS) test, during which they performed their normal duties, should be authorized to enter any grade A/B area, in which aseptic operations will be conducted, or are being conducted, whilst unsupervised. The microbial monitoring of personnel in the grade A/B area should be performed to assess their aseptic behaviour. This monitoring should take place immediately after completion of a critical intervention and upon each exit from the cleanroom. It should be noted that there should also be an ongoing continuous monitoring program for personnel including some consideration of periodic monitoring under the supervision of the quality unit.		*Microbial monitoring of personnel as described in this section is a new requirement but has already been common practice so far.* *Personnel present in cleanrooms A/B during manufacturing shall be trained during the aseptic process simulation (APS) execution.*	3
4.5 There should be systems in place for disqualification of personnel from entry into cleanrooms, based on aspects including ongoing assessment and/or the identification of an adverse trend from the personnel monitoring program. Once disqualified, retraining and requalification is required before permitting the operator to have any further involvement in aseptic practices. This should include consideration of participation in a successful Aseptic Process Simulation (APS).		*New:* *A procedure for disqualification of personnel for entry of clean rooms A/B is required.*	3
4.6 Manufacturers should establish written procedures outlining the process by which outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought into grade A/B areas. Access by these persons should only be given in exceptional circumstances, evaluated and recorded in accordance with the PQS.		*New:* *A procedure for behaviour of externals entering clean room class B (e.g. for maintenance purposes) must be developed.*	2

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4.7 High standards of personal hygiene and cleanliness are essential. Personnel involved inthe manufacture of sterile preparations should be instructed to report any specific health conditions or ailments which may cause the shedding of abnormal numbers or types of contaminants and therefore preclude clean room access; periodic health checks for such conditions should be performed. Actions to be taken with regard to personnel who could be introducing an undue microbiological hazard should be described in procedures decided by a designated competent person.	39. High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.	*New:* *The mentioned standards must also be described in a SOP.*	1
4.8 Staff who have been engaged in the processing of human or animal tissue materials or of cultures of micro-organisms, other than those used in the current manufacturing process, or any activities that may have a negative impact to quality, e.g. microbial contamination, should not enter sterile product areas unless rigorous, clearly defined and effective entry procedures have been followed.	38. Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.	*New:* *Human tissue materials and other "materials with potential negative impact" are listed as well.*	2
4.9 Wristwatches, make-up and jewellery and other personal items such as mobile phones should not be allowed in clean areas.	40. Wristwatches, make-up and jewellery should not be worn in clean areas.	*New:* *Prohibition of personal materials (e.g. mobile phones) in cleanrooms*	2
4.10 Changing and hand washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas. Garments should be visually checked for cleanliness and integrity prior to entry to the clean room. For sterilized garments, particular attention should be taken to ensure that garments and eye coverings have been sterilized and that their packaging is integral before use. Reusable garments should be replaced based at a set frequency determined by qualification or if damage is identified.	41. Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.	*New:* *There should be a visual check of the garments. This is already considered as common practice. Reusable garments must be periodically checked.*	2
4.11 The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.	42. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.	*No delta in the intent.*	1
4.12 The description of clothing required for each grade is given below:	43. The description of clothing required for each grade is given below:	*No delta in the intent.*	1
a) Grade D: Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.	• Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.	*New:* *Shoes shall be disinfected.*	1

This text is an excerpt from the new Download Comparison of the EU GMP Guide Annex 1 Sterile Manufacturing

The draft of Annex 1 of the EU GMP Guidelines keeps many responsible persons in the pharmaceutical industry busy.

- Which aspects are going to change?
- Am I already prepared for this?
- What do I have to do now?

This download will help you answer these questions. The author Fritz Röder has compared the currently valid Annex 1 with the draft, thereby providing an excellent overview and pointing out where action is needed. A criticality index of 1-3 evaluates the various changes.

Even if the draft is not valid yet, it shows in which direction the authorities are thinking. You should be prepared for this, as a final version will soon be available.

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