13 July 2026

EMA/INS/GMP/161750/2026

Human Medicines Division

What are technical and organisational measures that should be taken into consideration to prevent microbial contamination of non-sterile medicinal products

Background

The likelihood of non-sterile medicinal products being contaminated by microbes is closely linked to the manufacturer's processes, particularly in terms of how well cleaning and gowning protocols are followed. To minimise the risk of product quality defects the following Q&A´s highlights technical and organisational measures that should be taken into consideration to prevent microbial contamination of non-sterile medicinal products.

The importance of proper controls of microbiological contamination in non-sterile products is also supported by individual cases of multi-resistant microorganism present in non-sterile antibiotics

Chapter 5, section 5.10 of the GMP guidance stresses the significance of protecting products and materials from microbial and other types of contamination at every processing step, albeit without delving into specifics. Further guidance can be found in the scope of Annex 1 and Annex 15.

Even for a non-sterile product, a microbial contamination might pose a hazard for the product or the patient, such as opportunistic microbes in the final formulation or multi antibiotic resistant microbes. Consideration should be taken for such risks, applying QRM principles similar to chapter 5.17 - 5.22 EU GMP guide part 1.

Special focus is expected for cleaning of equipment in accordance with cleaning validation principles. In general, critical cleaning procedures should be thoroughly explained in SOPs, verified and properly documented during execution.

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Q1

What other measures should be taken into consideration to prevent microbial contamination of non-sterile medicinal products?

A1

Facility/equipment design and use, material flow, microbiological controls process characteristics, and cleaning processes may be considered in relation to established limits. The results of the Quality Risk Management process should drive decisions on implementing various technical measures.

Manufacturing plants may consider using principles from Contamination Control Strategy (CCS) in accordance with Annex 1 guidance.

Based on the outcome of the Risk Management process the following technical measures may be included:

- Inclusion of suppliers of detergents/ cleaning agents in the supplier evaluation program.

- In the event of a deviation, it is important to consider implementing a phenotypical identification strategy for growths for further assessment.

- The expiry date of solutions of cleaning agents and detergents should be considered. When preparing these solutions, care should be taken to ensure that the preparation does not constitute a source of contamination.

Measures described in EU GMP Part 1 should be included if relevant:

Cleaning validation study should include microbiological samples of surfaces that get into direct contact with the drug product in order to determine the cleaning success with appropriate documentation of sampling locations and techniques explained. The cleaning validation study should also incorporate other parameters of the cleaning process, such as the drying step, in order to prevent microbial contamination from residual humidity in the equipment.

- Validated methods should be used for microbial contamination testing of the APIs, excipients, water, primary packaging materials, equipment, the environment and finished products.

- Water used in the manufacture should be demonstrated to be suitable for its intended use.

- In case of microbial contamination, it is expected to use validated cleaning methods and/or disinfection methods. When area disinfection is performed either scheduled or when needed, (e.g. microbial contamination) it should be demonstrated that the detergents/cleaning agents are suitable for their intended use.

Q2

What organizational measures should be taken into consideration to prevent microbial contamination of non-sterile medicinal products?

A2

Based on the outcome of the Risk Management process the following organisational measures may be included among others:

- Proper gowning should be in place including gloves and facemasks at critical operations.
- Glove disinfection should be considered before entering critical areas.

Organizational measures described in EU GMP Part 1 should be included if relevant:

- Personnel performing gowning and cleaning should receive regular practical training and assessment in disciplines.
- Training of production personnel should include correct behaviour during production activities and other critical activities
- Personnel hygiene and health status should be closely monitored and reviewed.
- Environmental monitoring should be in place to ensure that the facility is suitable for manufacture and there is no risk of contamination

References

- EU GMP Chapter 5, 5.21, Technical Measures: vii (e.g. polishing brushes), viii, ix, x, xi, xii, xiii
- EU GMP Chapter 5, 5.21, Organisational Measures: iii, v, vi, vii, viii, ix, x
- EU GMP Annex 1 (with proper modifications): 4.5, 4.7, 4.8, 4.34, 4.35, 6.18, 7.7, 7.8, 7.9, 7.13 (iii&iv), 9.4 (i&ii), 9.5, 9.6, 9.8, 9.11, 9.12, 9.13, 9.30 (Grade D), 9.31 (Grade D), 10.2, 10.9, 10.10
- EU GMP Annex 15: 10
- EU Guideline 2015/C 95/02
- EU Guideline CHMP/CVMP/QWP/496873/2018 Guideline on the quality of water for pharmaceutical use
- ICH Q9 Quality Risk Management