

Guidelines for the Blood Transfusion Services

9.7: Recommended standards for environmental monitoring (EM) of processing facilities

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9.7: Recommended standards for environmental monitoring (EM) of processing facilities

EM programmes must be in place for both uncontrolled and controlled (GMP graded areas) processing facilities and must meet the requirements of appropriate regulatory bodies. Uncontrolled facilities include blood-processing laboratories and controlled facilities include cleanrooms used for the aseptic processing of tissues, stem cells and associated products.

The main aim of microbiological EM is to provide a means of monitoring trends over time thereby ensuring that processing facilities continue to operate within acceptable bioburden limits and comply with GMP recommended limits for microbial contamination and airborne particulate concentration for controlled (GMP graded) areas. The EM programme must form part of the quality risk management system (QRM) ensuring that products are processed to the highest possible standards and that microbial, particulate and pyrogen contamination associated with microbes is prevented in the final product.

The EM programme must be part of the contamination control strategy document. The locations, frequency, volume and duration of monitoring must be determined based on a risk assessment method (EU GMP i.e. Hazard Analysis Critical Control Points (HACCP)) and from the results obtained during room qualification.

9.7.1: Key elements of an EM programme

The monitoring programmes must define and document:

- The sites to be monitored and the rationale behind the selection of these sites.
- The formal risk assessment study for each process and GMP processing area listing the Critical Control Points, which must be monitored
- A location map of monitoring sites on local data sheets.
- Airflow visualisation studies (i.e. smoke tests) to define EM sites (N/A uncontrolled rooms).
- The types of samples to be taken and the techniques used.
- The monitoring frequency and the conditions under which the monitoring is to be performed, i.e. in the 'at rest' or 'in operation' states as defined by EU GMP Annex 1⁸. Routine monitoring for clean rooms, clean air devices and personnel must be performed 'in operation' during processing (N/A uncontrolled rooms).
- Which personnel are authorised to perform EM.
- The incubation regime for samples.
- The setting of limits (alert and action limits). Alert limits for controlled rooms must be established based on results of Performance Qualification (PQ) tests or trend data and must be subject to periodic review.
- The requirement for data and trend analysis.
- A procedure for the investigation of out-of-specification (OOS) results including the identification of colony growth and the possible causes of the contamination.

- A procedure for corrective and preventive action in the event of OOS results. A root-cause analysis (RCA) followed by a corrective and preventive action (CAPA) protocol.

9.7.2: Monitoring techniques

Monitoring must be performed using standardised techniques and the main areas of sampling should include:

- Surface sampling using contact and swab plates with the latter being used in areas inappropriate for contact plates.
- Passive air sampling using settle plates and in addition, in GMP graded areas, active air sampling and particle counting.
- Glove prints for assessing potential transfer of bacterial contamination to sterile product during aseptic processing in GMP grade A and B areas.

Viable and Non-viable EM techniques must comply with EU GMP Annex 1. Guidance and QRM principles⁸.

In controlled facilities, monitoring for fungal in addition to bacterial contamination must, as a minimum, be achieved by settle plates with media and incubation regimens specific for each type of contamination.

9.7.3: Culture media

Culture media used for EM must be appropriate for the type of environment in which it is to be used, i.e. irradiated and triple wrapped media for use in cleanrooms and for the range of organisms likely to be isolated. Media used for post-disinfection monitoring must contain agents, that will either individually or in combination, neutralise any residual surface disinfectant. Neutralising agents must be validated against the disinfectant(s) in use within the facility. Media storage must be in compliance with the manufacturer's recommendations and the monitored facility must be able to provide monitoring data to show that these storage requirements are being met.

9.7.4: Alert and action limits

9.7.4.1 Controlled Rooms (Cleanrooms)

In cleanroom facilities, alert and action limits must be set for the results of particulate and microbiological monitoring. Action limits are specified in Annex 1 of the EU Guidelines to GMP (Manufacture of Sterile Medicinal Products)⁸.

Action limits are initially set in alignment with EU GMP Annex 1 guidance values. However, if trend data for Grade B, C or D GMP areas indicates a consistently lower value, the action limits may be lowered to improve control. Alert limits must also be set to provide a warning of a possible deviation from normal operating conditions that may not require direct action but may need to be monitored more closely.

Alert limits must be established based on results of Performance Qualification (PQ) tests or trend data and must be subject to periodic review.

9.7.4.2 Uncontrolled facilities

Action limits must be established using historical data. The monitoring programmes must define how the action limits in uncontrolled rooms are to be determined.

9.7.5: Data and trend analysis

Trends may include:

- Increasing numbers of action or alert limit breaches
- Consecutive breaches of limits
- Regular but isolated breaches of limits that may have a common cause
- Changes in flora type and numbers

Monitoring results must be entered on a suitable database to allow data and trend analysis. The results must be reviewed by staff of the monitored facility on a regular basis with a formal documented review being held on a six-monthly basis. This formal review must involve senior cleanroom/processing staff and representatives from the quality and microbiology departments.

9.7.6: Cleanroom gowning

EM programmes for controlled rooms also need to include procedures for:

- The qualification of staff with respect to cleanroom gowning for grade A and B environments
- The assessment and confirmation of compliance with aseptic gowning procedures. This must be reassessed periodically, at least annually, and must involve both visual and microbiological assessment (using surface monitoring methods for locations such as hands (glove prints), arms, neck and chest)
- The monitoring of personnel after critical operations
- The monitoring of staff upon leaving an aseptic area as a means of assessing operator bioburden limits
- Exit suit monitoring must be performed for each cleanroom operator on a regular basis with the frequency, sampling method(s) used, and monitoring sites clearly defined in the procedures

9.7.7: Process simulations

Validation of aseptic processing must include a process simulation test using a nutrient medium. The process simulation test must imitate as closely as possible the routine process including all critical subsequent manufacturing steps. It must also take into account various interventions known to occur during the routine process as well as worst-case situations. Process simulation tests must be performed as initial validation with three consecutive satisfactory tests and repeated at defined intervals and after any significant modification to the heating, ventilation and air conditioning (HVAC) system, equipment or process.

Normally process simulation tests should be repeated twice a year (per shift and process). Acceptance criteria must be defined and documented, and any contamination investigated.

9.7.8: Cleaning and disinfection

Cleaning/disinfection validation must be performed to confirm the effectiveness of a cleaning/disinfection programme. As part of the validation, pre- and post-cleaning/disinfection EM must be used to verify the acceptability of the frequency and efficiency of the programme in terms of microbiological contamination. Pre- and post-EM limits must be established and documented within the cleaning/disinfection programme. The monitoring results must be reviewed and, where limits have been exceeded, the contamination investigated using RCA and CAPA implemented.

Typically, three consecutive applications of the cleaning/disinfection procedure must be performed and shown to be successful to prove that the method is validated.

The cleaning and disinfection of controlled rooms is particularly important and must be performed in accordance with a written programme. Where disinfectants are used, more than one type must be employed on a rotational basis. Disinfectants must be validated for their effectiveness and compatibility with the cleaning agents used. A sporicidal disinfectant must be included as one of the rotational disinfectants if practical. Detergents and disinfectants must be monitored for microbial contamination and when used in grade A and B areas, must be sterile prior to use and where possible single use.