

# General European OMCL Network (GEON) QUALITY MANAGEMENT DOCUMENT

## PA/PH/OMCL (16) 86 R6

### MANAGEMENT OF ENVIRONMENTAL CONDITIONS

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<b>Concerned Network</b>	GEON

N.B. This OMCL Quality Management System document is applicable to members of the European OMCL Network only. Other laboratories might use the document on a voluntary basis. However, please note that the EDQM cannot treat any questions related to the application of the documents submitted by laboratories other than the OMCLs of the Network.

## MANAGEMENT OF ENVIRONMENTAL CONDITIONS

**Note: Mandatory requirements in this guideline are defined using the terms «shall» or «must». The use of «should» indicates a recommendation. For these parts of the text, other appropriately justified approaches are acceptable. The term «can» indicates a possibility or an example with non-binding character.**

### 1. Introduction

This document provides requirements and recommendations on how to monitor, check, control and manage the environmental conditions in an OMCL. Usually, environmental monitoring and controlling refers to facilities and operations performed in them. The laboratory shall identify all environmental conditions that influence the results. The impact on receipt, handling, testing and storage of the sample, reagents, standards, reference materials and media used shall be considered as well. The identified conditions shall be monitored and controlled by the laboratory. For some testing conditions, special requirements and controlling measurements might exist (clean room facilities, cell culture facilities, animal housing) and these should be described in separate QMS documents, taking into consideration the national regulations.

Environmental conditions can be roughly divided into physical (e.g. temperature, humidity, particle count) and microbiological conditions, and are controlled accordingly. By monitoring, controlling and managing the testing environment in the laboratory, the OMCL can secure the overall quality of its functions.

Conditions in parts of apparatus used by the OMCL (e.g. oven, LC sampler, incubators) are not included in this document.

The requirements for environmental conditions monitoring are based on the ISO/IEC 17025:2017 requirements. In Chapter 6.3 "Facilities and environmental conditions" the impact of environmental conditions on results and the need to monitor, control and record information about the environmental conditions in accordance with relevant specifications are mentioned and in chapter 7.4.1 "Handling of test or calibration items" includes information about the need to have a procedure for the transportation, receipt, handling, protection and storage of test items with regards to their storage instructions.

The OMCL should define the starting point of its responsibility to monitor environmental conditions. Normally this begins with the receipt of material (e.g. reference material, reagents and samples...) in the OMCL facilities. An exception has to be made if the sampling is carried out by the OMCL. If the OMCL does its own sampling, conditions during the sampling and transportation of the sample(s) must be described and controlled (e.g. temperature data loggers etc.). Registration of temperature during the transportation maybe not necessary when no specific temperature of storage is mentioned in Marketing Authorization or if the transportation is described and followed in such a way that it does not impact the quality of samples.

### 2. Definitions

**Monitor** - Surveillance of the environmental conditions

**Check** - Verification of the records collected during surveillance

**Control** - Surveillance and ability to influence the environmental conditions

**Storage conditions** - Required conditions for the items/substances

**Environmental conditions** - Conditions of the ambient environment where the items/substances are kept

**Cross-contamination** - contamination indirectly or directly through people, pests, equipment, organisms, procedures or products.

### 3. Requirements for an OMCL's activities

The main task of an OMCL is to perform analyses on medical products. The environmental conditions may have an impact on the products tested and on the results of the testing performed in the laboratory.

The OMCL shall evaluate possible risks posed by environmental conditions on the quality of results using a risk based approach and should strive to minimise risks caused by inappropriate conditions.

Examples of controllable parameters:

1. Critical parameters with impact on substances and samples:

- Humidity
- Temperature
- Light
- Cross-contamination
- Particle counts (viable, non-viable)

May affect:

- Stability of sample (degradation of samples and variations of volume in case of liquid samples and sample solutions)
- Stability of standard and reference material (integrity in terms of degradation and variations of volume in case of solutions)
- Stability of test kits used
- Detection of additional microorganisms

These could be minimised by e.g. controlling temperature and humidity levels (air conditioning), having separate working areas and ensuring proper working conditions.

2. Critical parameters with impact on equipment:

- Vibrations
- Wind or airflow (ventilation)
- Energy or other essential goods (e.g. analytical gases)
- Temperature or humidity
- Light and radiation

These could be minimised by for example constructional measures, positioning the equipment properly, stable work surfaces, automatic temperature and humidity control and regular cleaning of equipment.

3. Other critical parameters:

- Contamination
- Dust

These can be minimised by performing regular cleaning of the facilities. Clear requirements and description for the cleaning should be given in a SOP or in other QMS documentation and/or in a contract with the service provider. It is recommended to monitor the effect of cleaning at regular intervals and to perform a risk evaluation if considered necessary (e.g. in special cases like clean room facilities).

#### 4. Areas within the OMCL's activities

The OMCL shall define the requirements for environmental conditions management on the basis of the activities, areas, equipment, rooms or defined places applicable to the OMCL. For critical activities, deviations from the stated conditions shall be documented and commented on if the reliability of the results is questioned.

Temperature excursions should be documented and their potential impact assessed. The use of Mean Kinetic Temperature (MKT - a simplified way of expressing the overall effect of temperature fluctuations during storage or transit of sensitive goods) can be useful for this evaluation.

Humidity only needs to be checked in rooms where, for the analyses and/or operations performed, there is a potential effect on the quality of the results or when the laboratory rooms have issues with air conditioning/ventilation system.

Examples (not exhaustive):

Activity	Critical parameter	Requirement
Storage room (room temperature)	Temperature	15 °C – 25 °C (Ph.Eur. General Notices)
Storage room (cold or cool)	Temperature	8 °C to 15 °C (Ph.Eur. General Notices)
Storage room (refrigerator)	Temperature	2 °C – 8 °C (Ph.Eur. General Notices)
Storage room (deep-freeze)	Temperature	Below -15 °C (Ph.Eur. General Notices)
Room for sample preparation	Temperature, humidity (if applicable)	15 °C – 25 °C, 20 - 80% RH (usually)
Balance room	Temperature, humidity, vibration	15 °C-25 °C, for humidity see OMCL GL "Qualification of balances" (for information only: typically 40-60% of relative humidity), no vibrations
Qualification of automatic pipettes (and Volumetric Glassware)	Temperature, humidity	15°C-30°C, for humidity see OMCL GL "Qualification of piston pipettes"
Equipment room (no sample preparation, equipment with closed system e.g. HPLC auto sampler cooling function)	Temperature, humidity (if applicable)	Manufacturer requirements
Sterility testing	Particle and microbial Counts	GMP Eudralex Vol 4 Annex 1
Particulate contamination	Particle counts	Ph. Eur. 2.9.19

#### 5. Environmental conditions in the chemical testing laboratory

In the chemical testing laboratory the most critical parameters are temperature and humidity. For monitoring both parameters, manual devices or automatic systems can be used. The frequency of monitoring, calibration intervals of the measuring devices and action in case of excursions must be defined.

Sources to define minimum requirements for the temperature are for example:

- Ph. Eur. chapter 1 "*General notices*" 1.2 "*Other Provisions applying to General Chapters and Monographs*" in which temperatures for analytical procedures are given
- Ph. Eur. Substance monographs
- Pharmaceutical file of finished products, as well as the labelling on the package
- CoAs of substances which contain storage requirements
- Information given by the manufacturer of test kits
- Information given by the manufacturer of equipment
- Definition of acceptable temperature limits from other sources (e.g. pH-measurement).

Humidity is critical if hygroscopic material is processed during analyses. Therefore special measures, such as use of special cabinets, should be taken.

## **6. Environmental conditions in the microbiological testing laboratory**

The environmental condition requirements for a microbiological laboratory are more specific than those for a chemical laboratory due to the nature of microbiological testing. The most important environmental requirements include microbial counts, non-viable particle counts (clean rooms), temperature, humidity (if applicable) and cross-contamination. There may also be special facilities in the microbiological laboratory which have specified requirements like clean room, isolators and cell culture facilities. For the proper environmental control, a risk analysis for the critical phases of work should be carried out to define environmental sampling and measurement points. The risk analysis should be updated regularly.

Temperature and humidity control can be done either manually or automatically, and special attention must be paid to monitoring room temperature and humidity level. Appropriate limits for both temperature and humidity must be set. Frequency of monitoring must be described and fluctuation of temperature and humidity with seasonal changes must be considered, if necessary.

Regarding sterility testing environmental control must be done according the facility and area where it is performed. If the laboratory has a clean room facility for sterility testing, the facility must be controlled appropriately. In clean room facilities the environmental conditions measured are both physical and microbiological. Physical measurement includes, in addition to temperature and humidity, differential pressure monitoring and total particle counting which is also used for defining the cleanliness class of the facility (A, B, C, D or ISO 1 to ISO9). Microbiological measurements are also used for class definition and monitoring the effectiveness of aseptic working conditions inside the facility. Detailed definitions and descriptions for clean room facilities can be found in:

- EN ISO 14644 series for cleanrooms (1-4)
- GMP Eudralex Vol 4 Annex 1
- Ph. Eur. 2.6.1

If an isolator is used for sterility testing, environmental control must also be performed taking into consideration the inside of the isolator and the surroundings according to the background environment classification. Access to the isolator area must be limited to essential staff to avoid cross-contamination. Monitoring should be carried out according the result of the risk analysis. Detailed definitions and descriptions for isolators can be found in:

- PIC/S Isolators used for Aseptic Processing and Sterility Testing (PI 014-3) Sept 2007

## **7. Systems, equipment and devices for monitoring of environmental conditions**

The OMCL shall establish one or more systems, depending on the parameter(s), for monitoring the environmental conditions. Systems can be either manual or automated computerised controlling systems. The environmental monitoring system should be described in QMS documents.

The measurement devices used have to be calibrated and/or qualified with respect to EDQM equipment guidelines or general requirements and should be embedded on the OMCLs' QMS. The devices also must have a useful reading precision depending on the requirements and the working range.

In the case of use of an external service, the supplier has to prove compliance with the requirements of the OMCL and should be included in the list of OMCLs' external suppliers.

In cases of both external or internal calibration of the measuring devices used for environmental monitoring, the OMCL shall evaluate the calibration certificate and approve it, after checking if the measuring ability of the device still meets the requirements of the laboratory and it is within the predefined specifications. In the event of deviation the laboratory, where appropriate, shall implement actions, such as for example applying corrective factors in respect of the acceptance limits of the measurement.

The OMCL should evaluate the overall effectiveness of its environmental controlling policy, e.g. with the help of risk analysis. All critical phases regarding handling of the sample should be taken into consideration as well as equipment, materials, reagents, chemicals etc. In the environmental controlling system the places where these devices are put must be defined in the area or room, considering specific conditions (e.g. not next to GC-oven, 30 cm above working table, in front of balances...).

Mapping of areas and definition of locations of control devices are recommended when a parameter is especially critical or when inhomogeneity of a room is well known and important. The mapping of areas can be done by placing one or several probes in different locations during a specified time, to obtain results and to evaluate which are the most critical places and the number of probes needed for continuous monitoring. Normally for rooms, winter and summer mapping is performed to evaluate the conditions in the most extreme environmental conditions, according to your risk evaluation.

The location of these devices must not be changed without separate evaluation and justification. Depending on the type of activity performed in the facility, mapping the possible points of higher risks and thus sampling of the area might be useful (e.g. settle plates in clean room facilities).

The OMCL should define the measurement interval and the type of measurement in QMS documentation based on risk assessment.

Examples of typical measurement devices:

- Thermo hygrometer
- Thermometer
- Min-max thermometers
- Electronic probes such as local data loggers
- Data loggers with connection to server
- Agar plates/contact plates for monitoring microbiological contamination
- Air samplers (microbiological contamination)
- Particle counter

## **8. Examples of frequency for monitoring of environmental conditions**

The frequency for environmental monitoring should be defined. The frequency decided must be based on risk analysis and existing trends in the laboratory environment. When defining frequencies for different monitoring points, the importance of the measuring condition for the function to be monitored must be considered. Some examples of monitoring frequencies are given below, but it is a responsibility of the laboratory to define these according to needs:

- Temperature monitoring: one point every 30 minutes using a computerised surveillance system
- Evaluating the minimum and maximum temperature once a week using a min/max thermometer
- Microbiological contamination: evaluation of the microbial counts / bioburden in the air/on the surfaces by an appropriate method (e.g. air sampler, settle or contact plates). Frequency of sampling should take into account the type of activities being conducted based on a risk analysis, with a special focus on the "at work"

The results obtained by the monitoring systems shall be checked periodically and records of the checks shall be available. This check is even more critical when the measurement devices do not have an alarm system.

## **9. General managing of environmental conditions**

Environmental control and monitoring management in the OMCL should be based on evaluated conditions and risk factors, existing and known, in the laboratory (using e.g. trend analyses as one tool for evaluation). There should be appropriate SOP's in place to describe required actions to maintain suitable conditions for different laboratory functions including predefined points and measures of intervention if the compliance of the detected environmental conditions is endangered.

There should also be a contingency plan in place, which includes at least, but is not limited to, these:

- Responsible persons to be informed about events (including during the night and at weekends)
- Contact data of the supplier (such as telephone number, e-mail...)
- Deputies of responsible persons
- Backup systems
- Reaction times
- Actions to be taken in case of emergency
- Actions in case of deviation

Any deviation of the required environmental conditions and the impact on the results shall be evaluated, documented and shall be included in the Quality Management System for implementation of actions.

For the evaluation of the impact of the deviation on the results the following sources can be useful:

- MAH files, stability part
- Contacting the MAH
- Contacting the supplier
- Supplier catalogues
- Former deviations

The conclusions and actions implemented have to be justified on a scientific basis and documented.

## 10. Documentation & Archiving

All data generated from environmental controls must be documented. All records (e.g. control charts, protocols, forms...) shall be included in the QMS.

Special care should be taken in the case of storage of electronic files on a server. The minimum storage time, including the possibility of reading these files, must be equal to the retention time of raw data linked to the analyses. If an external service provider is responsible for environmental control, the server location, functions, back up and the restore of data must be confirmed and validated.

Archiving facilities must be appropriate to ensure storage and integrity of different kinds of documentation. If needed, environmental conditions (temperature, humidity) of archiving rooms can be also controlled.

## 11. References

- ISO/IEC 17025:2017
  - Chapter 6.3 "Facilities and environmental conditions"
  - Chapter 7.4. "Handling of test and calibration items"
- Ph.Eur. chapter 1 "General notices"
  - 1.2 Other Provisions applying to General Chapters and Monographs
- Ph. Eur. 2.6.1 "Sterility"
- Ph. Eur. 2.9.19 "Particulate contamination: sub-visible particles"
- PI 014-3: Isolators used for Aseptic Processing and Sterility Testing (PIC/S 25 September 2007)
- ISO 14644-1 Cleanrooms and associated controlled environments - Part 1: Classification of air cleanliness by particle concentration
- ISO 13408-6 Aseptic processing of healthcare products - Part 6: Isolator Systems
- GMP Eudralex Vol 4 Annex 1