European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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General European OMCL Network (GEON)
QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (10) 86 R8

QUALIFICATION OF MASS SPECTROMETERS

Full document title and reference	Qualification of Equipment Annex 7: Qualification of Mass Spectrometers *PA/PH/OMCL (10) 86 R8*
Document type	Guideline
Legislative basis	Council Directive 2001/83/EC and Regulation (EU) 2019/6, as amended
Date of first adoption	May 2011
Date of original entry into force	July 2011
Date of entry into force of revised document	April 2025
Previous titles/other references / last valid version	This document replaces document *PA/PH/OMCL (10) 86 R7*
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
Concerned Network	GEON

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ANNEX 7 OF THE OMCL NETWORK GUIDELINE "QUALIFICATION OF EQUIPMENT"

QUALIFICATION OF MASS SPECTROMETERS

Note: Mandatory requirements in this guideline and its annexes 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.

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1. Introduction

The present document is the 7th Annex of the core document "Qualification of Equipment" and it shall be used in combination with it when planning, performing and documenting the qualification process of Mass Spectrometers coupled with Chromatographic equipment.

The core document "Qualification of Equipment" contains the introduction and general forms for Level I and II of qualification, which are common to all types of instruments.

The present Annex 7 contains a general introduction and requirements for the mass spectrometry detectors which are a part of gas chromatography (GC-EI-MS) and liquid chromatography (LC-ESI-MS) systems. The qualification of the LC and GC systems shall be performed according to Annex 1: Qualification of Liquid Chromatography Equipment PA/PH/OMCL (11) 04 and Annex 2: Qualification of GC Equipment PA/PH/OMCL (16) 17 of the guideline Qualification of Equipment, respectively. Based on the documented justification, testing of the parameters which are not applicable for GC/MS and LC/MS may be skipped.

Level III and IV qualifications must be carried out being an ISO/IEC 17025 requirement.
Requirements and (if applicable) corresponding typical acceptance limits given in bold should be applied, however other appropriately justified deviations are acceptable provided they are traceable.

Exemplary procedures provided in this document have non-binding character. They can be helpful to carry out the required qualification. Nevertheless, other procedures can be applied depending on the model of the MS equipment.

2. Qualification of Gas Chromatography-Mass Spectrometers with Electron Impact ionization (GC-EI-MS)

2.1. LEVEL III. Periodic and motivated instrument checks - Recommendations and related typical acceptance limits

Parameter to be checked	Typical acceptance limits*
Mass accuracy (PFTBA ** (FC-43) or internal calibration gas)	m/z = 69.0 **± 0.5** m/z = 219.0 **± 0.5** m/z = 502.0 **± 0.5**
Linearity[***]	Limit to be set up based on OMCL experience/service provider instructions and type of regression mode chosen
System/instrument precision[***]	**RSD ≤ 10.0 %**

* Other figures given under column of “typical acceptance limits” are typical values obtained when applying the exemplary procedures provided in this document, therefore these values are not binding.

[**] PFTBA (FC-43): Perfluoro-tributyl-amine (CAS NO.: 311-89-7).

[***] To be checked when quantification is requested.

2.2. LEVEL IV. In-use instrument checks - Recommendations and related typical acceptance limits

Parameter to be checked / Typical acceptance limits
According to specific analysis method or Ph. Eur. monograph or MAH dossier (see examples in 2.4)

2.3. LEVEL III. Periodic and motivated instrument checks – Practical examples

Practical examples of procedures for several parameters related to the qualification of GC-EI-MS are described below.

These examples can be considered by the OMCLs as possible approaches to perform the Level III of the equipment qualification process: “Periodic and motivated instrument checks”.

However, alternative procedures can be applied.

GENERAL CONSIDERATION: GC-MS is mainly used for the identification of unknown substances or quantification of low concentrated substances where high specificity is needed.

Mass Accuracy

Materials:
PFTBA (FC-43) or internal calibration gas

Method:
Internal instrument check or spectrum of PFTBA (FC-43) in full scan mode

Linearity

Materials:
Stock solutions: 1-Octanol in methanol at concentrations of 0.2, 0.4, 0.6, 0.8, 1.0 µL/mL

Method:
Injection volume: 1.0 µL (2 injections of each level)

Limits:
Limit to be set up by OMCL based on experience and type of regression mode chosen

NOTE: Linearity is typically performed in SIM/MRM, since this mode is normally applied for quantification of analytes in low concentration.

System/Instrument Precision

Materials:
Stock solution: 1-Octanol in methanol at concentration of 1.0 µL/mL

Method:
Injection volume: 1.0 µL (6 injections)

2.4. LEVEL IV. In-use instrument checks – Practical examples

Identification (by mass spectral library)

Materials:
Papaverine 20.0 µg/mL in methanol, Caffeine 10.0 µg/mL in methanol or another compound chosen according to the specific method

Method:
Identification by mass spectral library

Limits:
Match reference spectra

System/Instrument Precision **

Materials:
See identification

Method:
Injection volume: 1.0 µL (6 injections)

Limits:
See 2.1.

** to be checked when performing quantification testing

3. Qualification of Liquid Chromatography-Mass Spectrometers by Electrospray Ionisation (LC-ESI-MS)

Ionisation sources of Mass Spectrometry include:

ESI: Electrospray Ionisation
APCI: Atmospheric Pressure Chemical Ionisation
APPI: Atmospheric Pressure Photo-Ionisation

3.1. LEVEL III. Periodic and motivated instrument checks - Recommendations and related typical acceptance limits

Identification - Positive mode:

Parameter to be checked	Typical acceptance limits (Low Resolution MS)*	Typical acceptance limits (High Resolution MS)*
Mass accuracy (Reserpine)	m/z = 609.3 **± 0.5**	**± 5.0 ppm**
Mass accuracy of fragments[*](Reserpine)	m/z = 448.2 **± 0.5** m/z = 195.1 **± 0.5**	**± 5.0 ppm** **± 5.0 ppm**
Resolution	See 3.3	See 3.3

[**] only for instruments with MS/MS capabilities.

Identification - Negative mode:

Parameter to be checked	Typical acceptance limits (Low Resolution MS)*	Typical acceptance limits (High Resolution MS)*
Mass accuracy (Chloramphenicol[**])	m/z = 321.0 **± 0.5**	**± 5.0 ppm**
Mass accuracy of fragments *** (Chloramphenicol)	m/z = 152.0 **± 0.5**	**± 5.0 ppm**
Resolution	See 3.3.	See 3.3

* Other figures given under column of “typical acceptance limits” are typical values obtained when applying the exemplary procedures provided in annexes, therefore these values are not binding.

[**] Chloramphenicol, CAS NO.: 56-75-7.

[***] only for instruments with MS/MS capabilities.

Quantification - Check following parameters both in positive and negative modes:

Parameter to be checked	Typical acceptance limits
Linearity	Limit to be set up based on OMCL experience/service provider instructions and type of regression mode chosen
System/instrument precision	**RSD ≤ 5.0 %**
Carry over:	**≤ 1.0 %**

3.2. LEVEL IV. In-use instrument checks - Recommendations

Parameter to be checked/ Typical acceptance limits
According to specific analysis method or Ph. Eur. monograph or MAH dossier

3.3. LEVEL III. Periodic and motivated instrument checks – Practical Examples

Practical examples of procedures for several parameters related to the performance of LC-ESI-MS are described below.

These examples can be considered by the OMCLs as possible approaches to perform the Level III of the equipment qualification process: “Periodic and motivated instrument checks”.

However, alternative procedures can be applied.

GENERAL CONSIDERATION: LC-MS is widely used for the identification of unknown substances or quantification of low concentrated substances where high specificity is needed.

Mass Accuracy

Materials:

ESI positive: Reserpine at concentration of 0.01 mg/mL in methanol/water (60/40 V/V)*

ESI negative: Chloramphenicol at concentration of 0.01 mg/mL in methanol containing 0.1% of formic acid*.

*Note: concentrations should be selected depending on the instrument and experimental conditions to be applied

Method:

Direct infusion or flow injection

Resolution

Procedure to be followed depends on the instrument. Instructions to check resolution can be provided by service supplier/ instrument manual.

Linearity

Materials:

Solutions as mixture of betamethasone-17,21-dipropionate and betamethasone-17-valerate in methanol at concentrations of 0.002, 0.004, 0.006, 0.008, 0.01 mg/mL.

Method:

Column: BEH-C18 1.7 µm 50 x 2.1 mm or equivalent
Suitable gradient of acetonitrile/water containing 0.1 % formic acid

Injection volume: 1.0 µL (2 injections at each concentration)

System/Instrument Precision

Materials:

Solution as mixture of betamethasone-17, 21-dipropionate and betamethasone-17-valerate in methanol at concentration of 0.006 mg/mL.

Method:

Injection volume: 1.0 µL (6 injections)

Carry Over

Materials:

- Solution as mixture of betamethasone 17, 21-dipropionate and betamethasone 17-valerate in methanol at concentration of 0.002 mg/mL.
- Methanol (blank)

Method:

Injection volume: 1.0 µL

The percentage of the peaks corresponding to betamethasone-17,21-dipropionate and betamethasone 17-valerate in the blank (injected after 0.002 mg/mL solution) does not exceed 1.0 % of the area of said peaks in the chromatogram obtained injecting 0.002 mg/mL solution of betamethasone-17,21-dipropionate and betamethasone 17-valerate.

4. References

(For all references, the latest version applies)

1) Ph. Eur. Chapter 2.2.43. MASS SPECTROMETRY.