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QUALIFICATION OF EQUIPMENT
ANNEX 2: QUALIFICATION OF GC EQUIPMENT

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ANNEX 2 OF THE OMCL NETWORK GUIDELINE
"QUALIFICATION OF EQUIPMENT"

QUALIFICATION OF GC EQUIPMENT

Introduction

The present document is the second Annex of the core document "Qualification of Equipment", and it should be used in combination with it when planning, performing and documenting the GC equipment qualification process.

The core document contains the general introduction and the Level I and II of qualification, common to all type of instruments, and the present annex contains GC instrument-related recommendations on parameters to be checked and the corresponding typical acceptance limits, as well as practical examples on the methodology that can be used to carry out these checks.

The tests proposed in the Level III and IV of qualification are based on an overall approach, in which several parameters are checked at the same time in a combined test procedure, to obtain information on the overall system performance (e.g. peak area precision, retention time precision, temperature programme reproducibility, etc).
Nevertheless, it should be noted that it is also acceptable to check these parameters individually by using other well-defined procedures.

TABLE III

Level III. Periodic and motivated instrument checks

Examples of requirements for GC instruments with FID

Instrument module	Parameter to be checked	Typical tolerance limits
1. Inlet system	1.1 Injector leak test	Pressure drop ≤ 15 kPa within 5 minutes
	1.2. Pressure/flow accuracy and stability	Covered by overall test 1
	1.3. Repeatability of GC injections (overall test 1)	
	Peak areas:	
	- In split mode	RSD ≤ 3.0%
	- In split less mode	RSD ≤ 3.0%
	Retention times:	RSD ≤ 2.0%
	1.4. Injector temperature accuracy and stability	Covered by overall test 2
	1.5. Carry-over (overall test 3)	≤ 0.2%
	Head space injector	
	1.6. Repeatability of Headspace injections	
	- Peak areas:	RSD ≤ 5.0 %
	- Retention times:	RSD ≤ 2.0%
	1.7 Vial heater temperature	± 4°C from set point
2. Oven	2.1. Repeatability of oven temperature characteristics	Covered by overall test 2
3. FID detector	3.1. Linearity (overall test 3)	$r^2 \geq 0.999$
	3.2. Constant detector response	Covered by overall test 1 or 2
	3.3. Noise	See Annex I
	3.3. Drift	See Annex I

TABLE IV

Level IV. In-use instrument checks

Examples of requirements for GC instruments with FID

Parameter to be checked	Typical tolerance limits
1. System suitability check for the method	According to Ph. Eur. or MAH dossier or validated in-house method
2. Peak area precision - GC injections - Headspace injections	 RSD ≤ 3.0% unless otherwise prescribed* RSD ≤ 5.0% unless otherwise prescribed*
3. Retention time repeatability	RSD ≤ 2.0%
4. Sensitivity (where relevant, e.g. for related substances tests)	According to Ph. Eur. or MAH dossier or validated in-house method

***** This is to be defined in conjunction with the target concentration of the analyte

All parameters given here should be checked when performing analyses **under the working conditions** for the actual sample determinations. Normally, the test and reference solutions to be prepared for this purpose are given as a part of the method.

ANNEX I

Level III. Periodic and motivated instrument checks

Practical examples of tests and their associated tolerance limits for several parameters related to the performance of the different modules of a GC are presented 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".

Several tests are proposed to check various parameters at the same time (overall tests). In order to run the tests in a more economical way, other suitable solutions can be used, as for example, the "Grob Test" mixture, available from different suppliers (e.g. Alltech, Sigma, Thames Restek). This commercial solution should be appropriate to the column material used.

It is recommended to run the overall tests by using always the same test column, exclusively dedicated to qualification purposes, to guarantee reproducible conditions.

1. INLET SYSTEM

The following tests are proposed for the periodic and motivated check of the GC Inlet System.

1.1. INJECTOR LEAK TEST

Method:
If not otherwise specified by the instrument manufacturer, the leak test is carried out according to the procedure laid down in the instrument manual or by the built in automatic leak check procedure of the instrument.

Otherwise use the test described below:
Disconnect the column from the injector and close the injector outlet with a sealed cap.
Close the septum purge and the bypass.
Adjust the flow and pressure controller to the maximal possible value of the pressure gauge.
Adjust the flow controller to zero.
Read the pressure after 1 minute and record the value.
Record the pressure after 5 minutes.

Limits:
Pressure drop $\leq$ 15 kPa within 5 minutes.

1.2. INLET PRESSURE/FLOW ACCURACY AND STABILITY

A direct measurement of these parameters was not deemed practical or necessary, but the optimal conditions of flow/pressure can be verified by the overall test 1.

Limits: refer to overall test 1.

1.3. REPEATABILITY OF GC INJECTION

The verification of this parameter is covered by the overall test 1.
This test is to be performed in both split **and** split less mode.

Limits: refer to overall test 1.

1.4. INJECTOR TEMPERATURE ACCURACY AND STABILITY

Due to the fact that the temperature cannot be reliably measured without opening and modifying the system and due to the difficulties of introducing a probe inside this module, the verification of this parameter is considered to be covered by the overall test 2.

Limits: refer to overall test 2.

1.5. INJECTOR CARRY OVER

After having injected the solutions for the linearity test of the FID detector, in increasing order, inject the blank and measure the peaks that correspond to the major peaks (= analytes) in the linearity solutions.
The verification of this parameter is covered by the overall test 3.

Limits: refer to overall test 3.

HEAD SPACE INJECTORS

1.6. REPEATABILITY OF HEADSPACE INJECTIONS

Method:
The GC-HS operating conditions below are provided as an example, adjustments may be needed depending on the equipment used.

Test solution: 0.5 % ethanol in water R (V/V)

GC-Settings:
Column: 95% Dimethyl / 5% diphenylpoly siloxane 30 m x 0.25 µm; 0.25 mm (HP-5 was found suitable)
Carrier gas: Helium
Column Flow: 1.2 ml/min
Injector temperature: 200 °C
Split ratio: 1:50
Oven temperature: 40°C isotherm
Detector temperature: 250 °C
Run time: 1.5 folds the retention time of the main peak
Retention time: about 2.2 min

Headspace-Settings:
Carrier pressure: 9.9 psi
Vial pressure: 14.2 psi
Shake: low

Oven Temperature: 80 °C
Loop Temperature: 90 °C
Transfer line Temperature: 100 °C
Vial size: 20 mL
Volume of sample solution/vial: 5 mL
Vial Equilibration Time: 15.0 min
Inject Time: 1.0 min
Loop Equilibration Time: 0.1 min
Loop Fill Time: 0.5 min
Vial Pressurization Time: 0.08 min

Carry out 6 consecutive injections of the test solution and calculate the RSD of the different peak areas and retention times.

Limits:
Peak areas: the RSD should be ≤ 5.0 %
Retention time: the RSD should be ≤ 2.0 %

1.7 VIAL HEATER TEMPERATURE
The heater temperatures are to be set up at values which depend on the operating conditions of the methods applied.

Suitable calibrated temperature devices are to be used.

Put the calibrated device in the oven of the head space compartment. Set the temperature at the required values. When equilibration is achieved, record the value displayed on the calibrated device.

Limits: ± 4°C from set point

2. OVEN

2.1. REPEATABILITY OF THE OVEN TEMPERATURE CHARACTERISTICS

Due to the fact that the temperature cannot be reliably measured without opening and modifying the system conditions and that even when introducing a probe inside the oven, its location would not reflect the real temperature conditions at all points, the verification of this parameter is covered by the overall tests 2A and 2B.

Limits: refer to overall test 2.

3. FID DETECTOR

The following tests are proposed for the periodic and motivated check of the GC FID detector.

3.1. FID DETECTOR LINEARITY

Increasing amounts of analyte are injected and a linear response should be obtained.
The verification of this parameter is covered by the overall test 3.

Limits: refer to overall test 3.

3.2. CONSTANT FID DETECTOR RESPONSE

The proper and reproducible functioning of the FID can be demonstrated by checking the peak areas obtained from a pre-defined standard solution.
The verification of this parameter is covered by the overall test 1 or 2.

Limits: refer to overall test 1 or 2.

3.3. FID DETECTOR NOISE AND DRIFT

If the instrument has a built-in automatic system for the verification of the noise and drift, follow the manufacturer's instructions and apply the defined acceptance criteria. Otherwise, use the test described below:

Settings:
Column installed
Suitable flow, depending on column length/diameter
No injection
Oven temperature: 40°C
Detector on and heated at working temperature (270-300°C)

Method:
After stabilisation of the system, record the signal for 15 minutes.
Noise: evaluate 10 periods of 1 minute and calculate the mean value.
Drift: evaluate the slope of the baseline over the 15 minutes.

Limits:
The acceptance criteria for these parameters have to be chosen in accordance with the instrument vendor's instructions and the intended use of the instrument. If no instructions are given, the user has to pre-define these acceptance criteria by taking into account the previous experience and the intended use of the instrument.
No fixed values can be pre-defined in this guideline due to the high variety of integration systems used and consequently the acceptance criteria may be expressed in different units (voltage, current, arbitrary units per time).

OVERALL TEST 1

The overall test 1 covers the following parameters:

- Pressure/flow accuracy and stability in the inlet system: Retention time repeatability
- Repeatability of injection: peak area precision
    - In split mode
    - In split less mode

The test may be combined with overall test 3.

Split mode:
Test solution:
1-octanol in n-hexane 1% (V/V).

Settings:
Column: 100% Dimethylpolysiloxane 30m x 0.32mm ID x 0.25µm film (SPB-1 was found suitable)
Carrier gas: Helium
Velocity: 25cm/sec
Split: 1:100
Injection: 1µl
Injector temperature: 220°C
Oven temperature: 100°C isotherm
Detector temperature: 300°C
Run time: 1.5 folds the retention time of the main peak
Retention time of 1-octanol: about 5 min

Split less mode:
Stock solution: 1-octanol in n-hexane 1% (V/V)

Test solution: Dilute 10 ml of the stock solution with n-hexane to 100 ml (corresponds to 1µl/ml of 1-octanol in n-hexane)

Settings:
Column: 100% Dimethylpolysiloxane 30m, 0.32mm ID, 0.25µm film (SPB-1 was found suitable)
Carrier: Helium
Velocity: 30cm/sec
Split less injection: purge valve closed during 2 min
Injection: 0.2µl of the test solution
Injector Temperature: 220°C
Oven Temperature: Initial 60°C for 4 min, 15°C/min. up to 135°C, final time 1min
Detector temperature: 300°C
Runtime: 1.5 folds the retention time of the main peak
Retention time of 1-octanol: about 8 min

Method:
Carry out 6 consecutive injections of the test solution and calculate the RSD of the different peak areas and retention times.

Limits:
Retention time repeatability: the RSD of the retention times should be ≤ 2.0%
Peak area precision (split **and** split-less mode): the RSD of the peak areas should be ≤ 3.0%

OVERALL TEST 2

The overall test 2 covers the following parameters:

- Injector, oven and detector temperature accuracy and stability: retention time repeatability

Two alternative tests are proposed:

Overall test 2A

Test solution:
0.035 ml 1-octanol
0.035 ml 2-octanone
0.035 ml 2,6-dimethylanilin
0.035 ml n-tridecane
0.035 ml n-tetradecane
35 mg n-eicosane
dissolved in 50 ml Dichloromethane

Settings:
Column: 100% Dimethylpolysiloxane 30m x 0.32mm ID x 0.25µm film (SPB-1 was found suitable)
Carrier gas: Helium
Velocity: 25 cm/s
Split: 1:100
Injection volume: 1 µl
Injector temperature: 220°C
Detector: FID
Detector temperature: 300°C
Gradient programme: 60°C (4 min), 5°C/min, 270°C (3 min)

Method:
Inject the solution twice and calculate the relative retention (RR) times in relation to n-eicosane (RR = 1)

The following table shows the approximately expected relative retention times.

Analyte	1-octanol	2-octanone	2,6-dimethylaniline	n-tridecane	n-tetradecane
RRT	0.30	0.22	0.37	0.52	0.60

Limits:
The RSD of each RR from two consecutive injections should be ≤ 1.0%

Overall test 2B

Test Solution:
1.0% (m/m) n-Nonane and Hexadecane in Tetradecane.

Settings:
Column: 100% Dimethylpolysiloxane 25m x 0.32mm ID x 0.52µm film (Ultra-1 was found suitable)
Injection volume: 1 µl
Solvent: Tetradecane
Oven temperature: 110°C
Gradient programme: 110°C, 20°C/min, 180°C (final time: 3.5 min)
Detector temperature: 250°C
Injector temperature: 200°C

Detector: FID
Flow rates: as defined by the instrument manufacturer
Split ratio: 1:15
Split vent: 30 ± 3.0 ml/min
Septum purge: 3-5 ml/min

Method:
Allow the system to equilibrate.
Injection sequence:
1) blank (Tetradecane)
2) 6 replicates of the test solution. Calculate the mean of the retention times and peak areas and the relative standard deviation of n-Nonane and n-Hexadecane.

Limits:
Retention time repeatability: RSD of the peak retention times of the 6 replicates ≤ 2.0%
Retention time (Rt) accuracy: for this example, the retention time ranges shown in the table below are proposed. Nevertheless, individual ranges should be predefined by the laboratory depending on the column used (e.g. Rt ± 0.2 min).

Compound	Rt (min)
n-Nonane (C_9)	1.3 – 1.7
Tetradecane (C_{14})	4.0 – 4.7
Hexadecane (C_{16})	5.1 – 6.0

OVERALL TEST 3

This test is a modified version of the overall test 1 to be used for the verification of:
- Detector linearity: linearity of the areas recorded
- Injector carry-over: area recorded in the blank run

It is described for both split and split less mode and may be combined with overall test 1.

Split mode:
Test solution: 1-octanol in n-hexane 1% (V/V)
Prepare further *reference solutions* by diluting the *test solution* as described below.

Settings: see overall test 1

Injection sequence:
5.0 ml of the test solution diluted to 25.0 ml with n-hexane (2 µl/ml): 2 injections
10.0 ml of the test solution diluted to 25.0 ml with n-hexane (4 µl/ml): 2 injections
15.0 ml of the test solution diluted to 25.0 ml with n-hexane (6 µl/ml): 2 injections
20.0 ml of the test solution diluted to 25.0 ml with n-hexane (8 µl/ml): 2 injections
if combined with overall test 1 for repeatability: test solution (10 µl/ml): 6 injections
n-hexane as blank (carry over)

Split-less mode:
Stock solution: 1-octanol in n-hexane 1% (V/V)

Test solution: Dilute 10 ml of the stock solution with n-hexane to 100 ml (corresponds to 1µl/ml of 1-octanol in n-hexane).
Prepare further *reference solutions* by diluting the *test solution* with n-hexane.

Settings: see overall test 1

Injection sequence:
5.0 ml of the test solution diluted to 25.0 ml with n-hexane (0.2 µl/ml): 2 injections
10.0 ml of the test solution diluted to 25.0 ml with n-hexane (0.4 µl/ml): 2 injections
15.0 ml of the test solution diluted to 25.0 ml with n-hexane (0.6 µl/ml): 2 injections
20.0 ml of the test solution diluted to 25.0 ml with n-hexane (0.8 µl/ml): 2 injections
if combined with overall test 1 for repeatability: test solution (1 µl/ml): 6 injections
n-hexane as blank (carry over)

Limits:
Linearity: coefficient of correlation of the calibration line obtained with the reference solutions and the test solution: $r^2 \geq 0.999$.

Carry-over: the percentage of the peak area corresponding to the analyte in the blank solution should be $\leq 0.2\%$ of the peak area of this analyte in the chromatogram obtained with the solution with the highest concentration within the sequence.