General European OMCL Network (GEON)
QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (07) 108 R11

QUALIFICATION OF EQUIPMENT
ANNEX 5: QUALIFICATION OF AUTOMATIC TITRATORS

Full document title and reference	Qualification of Equipment Annex 5: Qualification of automatic titrators PA/PH/OMCL (07) 108 R11
Document type	Guideline
Legislative basis	Council Directive 2001/83/EC and 2001/82/EC, as amended
Date of first adoption	June 2008
Date of original entry into force	August 2008
Date of entry into force of revised document	March 2022
~~Previous titles/other references /~~ last valid version	PA/PH/OMCL (07) 108 R6
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
Concerned Network	GEON

**ANNEX 5 OF THE OMCL NETWORK GUIDELINE
"QUALIFICATION OF EQUIPMENT"**

Note: Mandatory requirements in this document 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.

CONTENTS

1. INTRODUCTION

The present document should be used in combination with the core document 'Qualification of Equipment' when planning, performing and documenting the qualification process of automatic titrators.

The core document contains the Introduction and general forms for Level I and II of qualification, which are common to all type of instruments.

It is recommended, at Level II of qualification of the automatic titrators (Installation and release for use), to perform a gravimetric test (by selecting 10 volumes in a random way from 20 to 100% of the total volume of the burette used). The results should meet the specification provided by the manufacturer.

Level III (Periodic and motivated instrument calibration/checks) and IV (In-use instrument checks) qualifications must be carried out as an ISO 17025 requirement.
The present annex contains instrument-related recommendations (parameters) to be verified at Level III and IV of qualification and the corresponding typical acceptance limits, as well as practical examples of the methodologies to be used.

Requirements and (if applicable) corresponding typical acceptance limits (given in bold) should be applied; however other appropriately justified approaches are acceptable. Exemplary procedures provided in this document have non-binding character. They can be helpful when carrying out the required qualification. Nevertheless, it is left to the professional judgement and background experience of each OMCL to decide on the most relevant procedures to be undertaken in order to provide evidence that their automatic titrators are working properly and are suitable for their intended use. If the qualification of equipment is done by the manufacturer or an external service provider, it is the responsibility of the OMCL to make sure that this is in line with the requirements set out in this guideline.

2. GLOSSARY / DEFINITIONS

Titrant — volumetric solution

Nominal concentration (C_{nom}) — the concentration of titrant determined by its preparation procedure

Actual concentration (C_{act}) — the concentration of the titrant known with high accuracy sufficient for the intended use

Titer (t) — the ratio of the actual concentation (C_{act}) of a titrant to the nominal concentration (C_{nom}).

$$t = \frac{C_{act}}{C_{nom}}$$

The determination follows a standardised procedure (standardisation) using a reference substance with a known concentration.

Effective concentration (C_{eff}) amount of analyte (m) equivalent to a volume of titrant ($V_{titrant}$)

$$C_{eff} = \frac{m}{V_{titrant}}$$

e.g. Karl-Fischer titration; the effective concentration corresponds to the amount of water (m_{water}) consuming 1 ml of KF-Reagent (V_{KFR}),

$$C_{eff} = \frac{m_{water}}{V_{KFR}}$$

The determination follows a standardised procedure (standardisation) using a reference substance with a known concentration of the analyte.

3. LEVEL III. PERIODIC AND MOTIVATED INSTRUMENT CHECKS
Recommendations for automatic titrators and related typical acceptance limits

3.1. POTENTIOMETRIC TITRATORS (Ph. Eur. 2.2.20)

Parameter to be checked	Typical tolerance limits
3.1.1. Precision	RSD ≤ 0.5%
3.1.2. Accuracy[*]	$d_{rel} \leq \pm\ 0.5\ \%$
3.1.3. Linearity	$r^2 \geq 0.999$

[*] when a fresh commercial titrant (according to the known stability data) is used the certified value will be used for the calculation of d_{rel}; when a self-prepared titrant is used, the theoretical titer must be calculated from the weight and the purity of the substance used in the preparation of the titrant; this theoretical titer will be used in the calculation of d_{rel}

3.2. KARL FISCHER VOLUMETRIC TITRATORS used for semi-micro determination of water (Karl Fischer Titration, Ph. Eur. 2.5.12)

Parameter to be checked	Typical tolerance limits
3.2.1. Precision	RSD ≤ 1.0 %
3.2.2. Recovery[*]	97.5 % to 102.5 %
3.2.3. Linearity	$r^2 \geq 0.999$

[*] in case Sodium Aminosalicylate dihydrate for equipment qualification CRS is used, refer to the limits given in the accompanying Ph. Eur. leaflet

3.3. KARL FISCHER COULOMETRIC TITRATORS used for micro determination of water (Coulometric Titration, Ph. Eur. 2.5.32)

Parameter to be checked	Typical tolerance limits
3.3.1. Precision	Standard 1000 µg/g H_2O: RSD ≤ 2.0 % Standard 100 µg/g H_2O: RSD ≤ 5.0 %
3.3.2. Recovery[*]	Standard 1000 µg/g H_2O: 97.5 % to 102.5 % Standard 100 µg/g H_2O: 90.0 % to 110.0 %
3.3.3. Linearity	$r^2 \geq 0.990$

[*] in case Sodium Aminosalicylate dihydrate for equipment qualification CRS is used refer to the limits given in the accompanying Ph. Eur. leaflet

3.4. KARL FISCHER OVEN connected to a coulometric titrator

Parameter to be checked	Typical tolerance limits
3.4.1. Temperature accuracy	± 5.0°C
3.4.2. Temperature stability	± 0.5°C
3.4.3. Carrier gas flow rate	± 10 mL/min
3.4.4. Precision	RSD ≤ 1.5 %
3.4.5. Recovery[*]	95.0 % to 105.0 %.

[*] in case amoxicillin trihydrate for performance verification CRS is used refer to the limits given in the accompanying Ph. Eur. leaflet.

4. LEVEL IV. IN-USE INSTRUMENT CHECKS
Recommendations for automatic titrators and related typical acceptance limits

4.1. POTENTIOMETRIC TITRATORS

Parameter to be checked	Typical tolerance limits
4.1.1. Precision	see Table 1

Table 1

type of reaction	titrant concentration [mol/L]	Maximum permitted relative standard deviation (RSD_{max}) ($n \geq 3$)
alkacimetry, argentometry, redoxometry	≥ 0.1	1.0%
alkacimetry, argentometry, redoxometry	< 0.1	2.0%
other than listed above	—	3.0%

4.2. KARL FISCHER VOLUMETRIC TITRATORS

Parameter to be checked	Typical tolerance limits
4.2.1. Precision	$RSD \leq 1.5\%$
4.2.2. Recovery[*] (in the presence of the test sample)	97.5 % to 102.5 %

[*]in case Sodium Aminosalicylate dihydrate for equipment qualification CRS is used refer to the limits given in the accompanying Ph. Eur. leaflet

4.3. KARL FISCHER COULOMETRIC TITRATORS

Parameter to be checked	Typical tolerance limits
4.3.1. Recovery[*] (in the presence of the test sample)	Standard 1000 μg/g H_2O: 97.5 % to 102.5 % Standard 100 μg/g H_2O: 90.0 % to 110.0 %

[*]in case Sodium Aminosalicylate dihydrate for equipment qualification CRS is used refer to the limits given in the accompanying Ph. Eur. leaflet

4.4. KARL FISCHER OVEN attached to a coulometric titrator

Parameter to be checked	Typical tolerance limits
4.4.1. Recovery*	95 % to 105 %.

*in case Amoxicillin trihydrate for performance verification CRS is used refer to the limits given in the accompanying Ph. Eur. leaflet

5. LEVEL III. PERIODIC AND MOTIVATED INSTRUMENT CHECKS

This section contains practical examples of parameters and methodologies related to the performance of automatic titrators.
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". The limits are referred to in the tables above and will not be repeated in the sections below.

GENERAL CONSIDERATIONS

- Due to the fact that a holistic approach has been taken, the verification of temperature probes and burettes is not included in this guideline, as the performance of these items is indirectly checked during the accuracy test.
- If available, the internal start-up test function may be used each time the instrument is switched on.
- The limits and specifications of this guideline have been set according to rele-vant chapters of Ph.Eur. considering also the manufacturers of automatic titrators currently on market.

5.1. POTENTIOMETRIC TITRATORS

5.1.1. PRECISION and LINEARITY

Materials:
Suitable certified material RV (highly pure, dried), e.g. Benzoic acid or Tris (hydroxymethyl)-aminomethane (TRIS) or other suitable for standardisation of the titrant to be used.
Use appropriate titrant for the selected material (for instance 0.1 M or 1.0 M hydrochloric acid or sodium hydroxide or other suitable certified titrant).

Method:
Perform a minimum of 5 titrations with 5 different weights of certified material, which should result in a consumption of approx. 20 % to 90 % of the burette volume.

Precision:
Calculate the titer for every titration. Determine the mean and the relative standard deviation of the titers obtained.

If available, this calculation can be performed directly with the built-in statistics function of the instrument.

Linear regression:
Calculate a linear regression of the titrant volume in mL (y-coordinate), versus the sample size (i.e. weight) of the certified material expressed in g (x-coordinate).

Note: In addition, using the same linearity data, systematic errors can be evaluated, as the y-axis intercept of the linear regression Titrant volume in mL/Sample size in g (a_{sys}),

Recommended values are:
$a_{sys} < \pm$ 10 µL for 1 mL-burettes; $a_{sys} < \pm$ 50 µL for all other volume-burettes

Report the results using a suitable report sheet, an example is provided in attachment 1.

5.1.2. ACCURACY

Use a fresh commercial titrant (according to the known stability data) and the certified value. Self-prepared titrants shall be used directly after preparation (This does not apply to thiosulphate nor permanganate solutions that need to be prepared 10-14 days ahead of use and the titer should be determined first, alkacimetric titrations are preferred) Calculate the titer from the weight and the purity of the used substance considering the total volume as precise as possible.

Materials:
Refer to 5.1.1. PRECISION and LINEARITY.

The accuracy of the results obtained depends on the content of the certified material guaranteed by its manufacturer.

Calculation of the theoretical titer value as a function of temperature:
The theoretical titer value of the aqueous titrant solution at 20°C is 1.000, with a decrease of 0.02 % per degree of temperature increase, according to the following formula:

$$\text{Titer}_{theoretical} \text{ (at X°C)} = \text{Titer}_{theoretical} \text{ (at 20°C)} \times (1.0000 + 0.0002 \times (20 - X))$$

Where:
X°C= mean of the initial and final temperature of the titrant solution (at the beginning and at the end of the measurement), in °C.

Note: The stated formula is only applicable for aqueous titrant solutions. As an example, the decrease of the titer of perchloric acid for non-aqueous titration is 0.1% per degree of temperature variation.

Method:
Perform a minimum of 3 titrations with 3 different weights of certified material, which should result in a consumption of approx. 20% to 90% of the burette volume
Note: Results from the precision test (see 1.1.) can be used.

Calculate the mean of the titers obtained.

Calculate the systematic deviation (d_{rel}) with the following formula:

$$d_{rel} \ [\%] = \frac{titer_{mean} - titer_{theoretical}}{titer_{theoretical}} \times 100$$

If available, this calculation can be performed directly with the built-in statistics function of the instrument.

5.2. KARL FISCHER (KF) VOLUMETRIC TITRATORS

GENERAL RECOMMENDATIONS FOR KF TITRATIONS

- To ensure accuracy and precision of the results, it is recommended to use an appropriate amount of sample i.e. containing at least 1 mg of water, to entail a consumption of reagent above 0.5 mL.
- The water equivalent is not less than 80 per cent of that indicated by the supplier. Standardise the titrant before the first use and at suitable intervals thereafter.
- For titrant standardisation and performance verification, a suitable amount of water in an appropriate form should be used (e.g. water R, certified water standard solution e.g. HYDRANAL® water standard 10.0, certified solid standard e.g. HYDRANAL® standard sodium tartrate dihydrate or sodium aminosalicylate dihydrate for equipment qualification CRS).
- If other solvent / titrant system is used instead of those prescribed by the validated method, the suitability test described in Ph. Eur. 2.5.12. shall be carried out.
- KF instruments should not be located in rooms that are subject to large variations of temperature, or close to refrigerators, radiators or sinks. The drying tube of the titration cell shall be filled with fresh molecular sieve and moisture indicator.

5.2.1. PRECISION and LINEARITY

See GENERAL RECOMMENDATIONS FOR KF TITRATIONS.

Materials:
Certified reference material, e.g. HYDRANAL® water standard 10.0, solid standard e.g. HYDRANAL® standard sodium tartrate dihydrate
Karl Fischer reagent for titration
suitable solvent, e.g. methanol dry

Method:
Perform a minimum of 5 titrations with 5 different weights of certified reference material, which should result in a consumption of approx. 20 % to 90 % of the burette volume

Precision:
Calculate the effective concentration for every titration. Determine the mean and the relative standard deviation of the effective concentrations obtained.
If available, this calculation can be performed directly with the built-in statistics function of the instrument.

Linear regression:
Calculate a linear regression of the titrant volume in mL (y-coordinate), versus the sample size (i.e. weight) of the certified material expressed in g (x-coordinate).

5.2.2. RECOVERY

Materials:
Certified reference material, e.g. HYDRANAL® water standard 10.0, solid standard e.g. HYDRANAL® standard sodium tartrate dehydrate, sodium aminosalicylate dihydrate for equipment qualification CRS
standardized Karl Fischer reagent for titration
suitable solvent, e.g. methanol dry

Method:
Perform a minimum of 3 additions with an accurately weighed amount of water standard, perform the titration and determine the water content after each addition. Calculate the percentage recovery (r) of water after each addition of water, using the following expression:

$$r \, [\%] = \frac{W_2}{W_1} \cdot 100$$

    Where:

        r: percentage recovery.
        W_1: amount of water added, in mg.
        W_2: amount of water found, in mg.

Calculate the mean percentage recovery ($\bar{r}$).

5.3. KARL FISCHER COULOMETRIC TITRATORS

GENERAL RECOMMENDATIONS FOR KF COULOMETRIC TITRATIONS

- To ensure accuracy and precision of the results, it is recommended to use an appropriate weight of sample i.e. containing at least 100 to 1000 µg of water.
- In addition, perform the determination of water in the solvent used for dissolving the substance ('blank') and subtract it. It is desirable to obtain a value below 100 µg, if not achievable consider to use a fresh open bottle.
- Instrument performance qualification is carried out according to established quality system procedures, for example using a suitable certified reference material. Sodium aminosalicylate dihydrate for equipment qualification CRS may be used when proceeding by direct or liquid sample introduction. In such case, refer to the limits given in the accompanying Ph. Eur. leaflet.

5.3.1. PRECISION and LINEARITY

Materials:
Certified reference material e.g. HYDRANAL® water standard solution 1.0 or 0.1 with exactly known water content respectively of 1000 µg/g and 100 µg/g.
Karl Fischer reagents for coulometry.

Method:
Perform a minimum of 5 determinations with 5 independent additions of water standard solution (in random order if using different weights), between 0.2 and 2.0 g for a water standard solution 1000 µg/g, and between 0.5 and 5.0 g for a water standard solution 100 µg/g.

Precision:
Calculate the water content (in µg/g) for every titration. Determine the mean and the relative standard deviation of the water contents obtained.

If available, this calculation can be performed directly with the built-in statistics function of the instrument.

Linearity:
Calculate the linear regression of the found water in µg (y-coordinate), versus the sample size (i.e. weight) of the certified material expressed in g (x-coordinate).

5.3.2. RECOVERY

Materials:
Certified reference material e.g. HYDRANAL® water standard solution 1.0 or 0.1 with exactly known water content respectively of 1000 µg/g and 100 µg/g or sodium aminosalicylate dihydrate for equipment qualification CRS
Karl Fischer reagents for coulometry.

Method:
Perform a minimum of 3 determinations with an accurately weighed amount of water standard solution. Calculate the mean percentage recovery (r) of water from the water standard solution, using the following formula:

$$r \, [\%] = \frac{W_2}{W_1} \cdot 100$$

   Where:
   r: percentage recovery.
   W_1: amount of water added, in mg.
   W_2: amount of water found, in mg.

5.4. KARL FISCHER OVEN

The following tests may be performed in case the Karl Fischer coulometric titrator is coupled to an oven where the sample, under the effect of heating, releases its water which is driven out by a stream of carrier gas and transferred to the titration vessel.

5.4.1. TEMPERATURE ACCURACY

Materials:
Calibrated temperature probe.

Method:
Set the oven temperature at 150°C. Wait until the system is equilibrated.
By means of the calibrated probe, measure the actual temperature in the oven (always in the same position) and compare it to the temperature displayed by the oven.

5.4.2. TEMPERATURE STABILITY

Materials:
Calibrated temperature probe.

Method:
Set the oven temperature at 150°C. Wait until the system is equilibrated.
Insert the calibrated temperature probe into the oven block (always in the same position). Read the initial temperature and repeat the reading after 20 minutes.

5.4.3. CARRIER GAS FLOW RATE

Materials:
Calibrated flowmeter or flow meter used in connection with a calibrated watch.

Method:
Set the carrier gas (air or N_2) flow rate at 50 mL/min. By means of the calibrated flowmeter, measure the actual flow rate and compare it to the set value.

5.4.4. PRECISION

Materials:
Certified reference material e.g. water standard oven 1 % 10 mg/g (solid water standard for KF oven method) or chemical reference standard (e.g. amoxicillin trihydrate for performance qualification CRS).

Method:
Perform a minimum of 3 determinations with 3 independent additions of standard (in random order if using different weights).
Calculate the relative standard deviation. If available, this calculation can be performed directly with the built-in statistics function of the instrument.

5.4.5 RECOVERY

The recovery is calculated on the basis of the certified water content of the standard used.

Materials:
Refer to 5.4.4. PRECISION.

Method:
Perform a minimum of 3 determinations (e.g. 50 mg) with an accurately weighed amount of water standard solution and perform the titration. Calculate the mean percentage recovery (r) of water from the water standard solution, using the following formula:

$$r\,[\%] = \frac{W_2}{W_1} \cdot 100$$

Where:

  r [%]: percentage recovery.
  W1: amount of water added, in mg.
  W2: amount of water found, in mg.

6. LEVEL IV. IN-USE INSTRUMENT CHECKS

This section contains practical examples of tests for several parameters related to the performance of an automatic titrator.

These examples can be considered by the OMCLs as possible approaches to perform the Level IV of the equipment qualification process: "In-use instrument checks". The limits are referred to in the tables above and will not be repeated in the sections below.

6.1. POTENTIOMETRIC TITRATORS

6.1.1. PRECISION

Materials:
Sample or reference material

Method:
Perform a minimum of 3 titrations with 3 independent sample weights
Calculate the mean sample content and the relative standard deviation.
If available, this calculation can be performed directly with the built-in statistics function of the instrument.

6.2. KARL FISCHER VOLUMETRIC TITRATORS

6.2.1. PRECISION

Materials:
Certified reference material, e.g. HYDRANAL® water standard 10.0, solid standard e.g. HYDRANAL® standard sodium tartrate dihydrate
Karl Fischer reagent for titration
suitable solvent, e.g. methanol dry

Method:
Perform a minimum of 3 titrations with 3 independent weights of certified reference material, which should result in a consumption of approx. 20 % to 90 % of the burette volume
Precision:
Calculate the effective concentration for every titration. Determine the mean and the relative standard deviation of the effective concentrations obtained.
If available, this calculation can be performed directly with the built-in statistics function of the instrument.

6.2.2. RECOVERY

Refer to Level III 5.2.2.

6.3. KARL FISCHER COULOMETRIC TITRATORS

6.3.1. RECOVERY

Refer to Level III 5.3.2.

6.4. KARL FISCHER OVEN

6.4.1. RECOVERY

Refer to Level III 5.4.5.

7. REFERENCES

(For all references, the latest version applies)

1) Ph. Eur. 2.2.20, Potentiometric titration
2) Ph. Eur. 2.5.12, Water: semi-micro determination
3) Ph. Eur. 2.5.32, Water: micro determination

ATTACHMENT

REPORT SHEET_POTENTIOMETRIC TITRATORS

The check performed according to: …………………………………….............................

Temperature (ºC):				Instrument: Inventory №	
Titrant: Concentration[mol/L]: Lot/date of manufacturing: Date of preparation (if diluted):				Certified standard: Purity of standard [%]: Manufacturer: Lot: Molar mass [g/mol]:	
Burette size [mL]: Inventory №				Electrode:	
Analytical balance: Inventory №:					
Determination of titer:				Mode: Determination of …	
No.	Sample size, g:	Volume, mL:	Titer:	Results:	
1				Mean =	asys, mL=
2				SD (s_{abs})=	
3				RSD (srel),% =	
4				Titer theoretical=	
5				D_{rel},% =	
				Limits: **(Periodic check)**☐	
1. Precision:				**RSD: ≤ 0.5 %**	
2. Accuracy:				**(d_{rel}): ≤ ± 0.5 %**	
3. Linearity:				$r^2 \geq 0.999$	
				$a_{sys}<\pm10$ μL (1 mL burettes) $a_{sys}<\pm 50$ μL (5, 10, 20 and 50 mL burettes)	
				Conclusion: ☐ complies / ☐ does not comply	
Comments/Remark:					
Analyst:				Signature:	Date:
Supervisor:				Signature:	Date: