OMCL Network of the Council of Europe QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (07) 108 4R

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 4R
Document type	Guideline
Legislative basis	The previous version of this document was also accepted by EA as recommendation document to be used in the context of Quality Management System audits of OMCLs
Date of first adoption	June 2008
Date of original entry into force	August 2008
Date of entry into force of revised document	1st May 2012
Previous titles/other references	This document replaces document PA/PH/OMCL (07) 108 3R
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"

QUALIFICATION OF AUTOMATIC TITRATORS

Introduction

The present document is the 5th Annex of the core document "Qualification of Equipment", and it should be used in combination with it 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 of the volumes (10 selected volumes in a random way from 20 to 100% of the cylinder volume).

The present annex contains instrument-related recommendations on parameters to be checked at Level III and IV of qualification and the corresponding typical acceptance limits, as well as practical examples on the methodology that can be used to carry out these checks.

TABLE III

Level III. Periodic and motivated instrument checks

Examples of requirements for automatic titrators

1. POTENTIOMETRIC TITRATORS (Ph. Eur. 2.2.20)

Parameter to be checked	Typical tolerance limits
1.1. Precision	RSD ≤ 0.2%
1.2. Accuracy	$d_{rel} \leq \pm 0.5$ %
1.3. Linearity	$r^2 \geq 0.9990$

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
2.1. Precision	RSD ≤ 1.0 %
2.2. Linearity (optional)	$r^2 \geq 0.9990$
2.3. Recovery (optional)	97.5 % to 102.5 %

TABLE III (cont.)

Level III. Periodic and motivated instrument checks

Examples of requirements for automatic titrators (cont.)

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
3.1. Precision	Standard 1000 µg/g H_2O: RSD ≤ 2.0 % Standard 100 µg/g H_2O: RSD ≤ 5.0 %
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. Linearity (optional)	$r^2 \geq 0.990$

4. KARL FISCHER OVEN used for micro determination of water using an evaporation technique (Coulometric Titration, Ph. Eur. 2.5.32)

Parameter to be checked	Typical tolerance limits
4.1. Temperature accuracy	± 5.0°C
4.2. Temperature stability	± 0.5°C
4.3. Carrier gas flow rate	± 10 ml/min

TABLE IV

Level IV. In-use instrument checks

Examples of requirements for automatic titrators

1. POTENTIOMETRIC TITRATORS

Parameter to be checked	Typical tolerance limits
1.1. Precision	RSD ≤ 0.2 %
1.2. Accuracy	$d_{rel} \leq \pm 2$ %

2. KARL FISCHER VOLUMETRIC TITRATORS

Parameter to be checked	Typical tolerance limits
2.1. Precision	RSD ≤ 1.5%
2.2. Recovery	97.5 % to 102.5 %

3. KARL FISCHER COULOMETRIC TITRATORS

Parameter to be checked	Typical tolerance limits
3.1. Recovery	Standard 1000 µg/g H_2O: 97.5 % to 102.5 % Standard 100 µg/g H_2O: 90.0 % to 110.0 %

ANNEX I

Level III. Periodic and motivated instrument checks

This Annex contains practical examples of tests and their associated tolerance limits for several parameters 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".

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.
- If several exchange units are used for different titrants, all units should be tested at Level III.
- The limits and specifications of this guideline have been set according to Metrohm documentation. For other manufacturers (e.g. Mettler-Toledo, Mitsubishi, etc) the specifications may slightly differ.

1. POTENTIOMETRIC TITRATORS

1.1. PRECISION

Materials:
Suitable certified standard RV (highly pure, dried), e.g. Benzoic acid RV or tris(hydroxymethyl)-aminomethane (TRIS).
Fresh titrant, appropriate to titrate the selected standard.

Method:
Perform a minimum of 3 titrations with 3 independent additions of certified standard (in random order if using different weights), which should result in a consumption of approx. 20 % to 90 % of the burette volume.

Note: If necessary, for lower volume burettes, increase the molarity of the titrant (for example, from 0.1 to 1.0M) to minimize the weighing error of the standard.

Calculate 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.

Limits: RSD ≤ 0.2 %

1.2. ACCURACY

Materials:
Refer to chapter 1.1. Precision.

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

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

$$\text{Titer}_{\text{theoretical}} \text{ (at X°C)} = 1.000 + 0.0002\ (20 - x)$$

Where:

x = 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 (see Application Bulletin No. 252, Metrohm). For example, the given reduction in the titer of Perchloric acid is 0.1% per degree of temperature rise.

Method:
Perform a minimum of 3 titrations with 3 different weights of certified standard.
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:

$$d_{rel} = \frac{\text{titer}_{\text{mean}} - \text{titer}_{\text{theoretical}}}{\text{titer}_{\text{theoretical}}} \text{ x } 100$$

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

Limits:
The systematic deviation (d_{rel}) should be maximum ± 0.5 % (when using a freshly opened titrant container).

1.3. LINEARITY

Materials:
Refer to chapter 1.1. Precision.

Method: Linear regression volume/sample size
Calculate a linear regression of the titrant volume in ml (y-coordinate), versus the weight of the certified standard in g (x-coordinate) on a minimum of 5 weights.

Limits: $r^2 \geq 0.9990$.

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}), and the slope of the linear regression Titer in M/Titrant volume in ml ($b_{T/Vol}$).

Limits:
$a_{sys} < \pm$ 10 µl for 1 ml-burettes; $a_{sys} < \pm$ 50 µl for 5, 10, 20 and 50 ml-burettes
$b_{T/Vol} < \pm$ 0.0010 ml^{-1}

2. KARL FISCHER (KF) VOLUMETRIC TITRATORS

GENERAL RECOMMENDATIONS FOR KF TITRATIONS

- It is recommended to work with certified water standard solutions for water determination, with exactly known water contents, e.g. HYDRANAL®. Solid substances, such as disodium tartrate dihydrate, can also be used.
- KF instruments should not be located in rooms that are subject to large variations of temperature, or close to refrigerators or radiators. A protection should be installed if they are located close to water baths or sinks, or in direct sunlight.

2.1. PRECISION

Materials:
Certified water standard solution with a defined guaranteed water contents of 10 mg/g.
Karl Fischer reagents for volumetric water determination.
Note: The drying tube of the titration cell must be filled with fresh molecular sieve.

Method:
Perform a minimum of 6 titrations with 6 independent additions of water standard solution (in random order if using different weights), which should result in a consumption of approx. 20 % to 90 % of the burette volume.
Calculate 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.

Limits: RSD ≤ 1.0 %.

2.2. LINEARITY (optional)

Materials:
Refer to chapter 2.1. Precision.

Method: Linear regression volume/sample size
Calculate a linear regression of the titrant volume in ml (y-coordinate), versus the weight of the certified standard in g (x-coordinate) on a minimum of 5 weights.

Limits: $r^2 \geq 0.9990$.

2.3. RECOVERY

Materials:
Refer to chapter 2.1. Precision.

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

$$r = 100\frac{W_2}{W_1}$$

Where:

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

Limits: 97.5 % to 102.5 %.

3. KARL FISCHER COULOMETRIC TITRATORS

3.1. PRECISION

Materials:
Certified standard solution (highly pure, stable) with exactly known water content: 1000 µg/g or 100 µg/g.
Karl Fischer reagents for coulometry.

Method:
Perform a minimum of 6 determinations with 6 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.
Calculate the relative standard deviation of the water contents found (in µg/g).
If available, this calculation can be performed directly with the built-in statistics function of the instrument.

Limits:
Water standard solution 1000 µg/g: RSD ≤ 2.0 %.
Water standard solution 100 µg/g: RSD ≤ 5.0 %.

3.2. RECOVERY

The determination of the recovery is based upon the water content of the standard guaranteed by the manufacturer.

Materials:
Refer to chapter 3.1. Precision.

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

$$r = 100\frac{W_2}{W_1}$$

Where:

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

Limits:
Water standard solution 1000 µg/g - Recovery: 97.5 % to 102.5 %.
Water standard solution 100 µg/g - Recovery: 90.0 % to 110.0 %.

3.3. LINEARITY (optional)

Materials:
Refer to chapter 3.1. Precision.

Method:
Calculate the regression line of the amount of water found in µg (y-coordinate), versus the sample size in g (x-coordinate).

Limits: $r^2 = 0.990$

4. KARL FISCHER OVEN

The following tests may be performed in case the Karl Fischer titrator (volumetric or coulometric) is coupled to an oven.

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.

Limits:
The actual temperature may not differ more than ± 5.0°C with respect to the set temperature.

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.

Limits:
The temperature after 20 minutes may not differ more than ± 0.5°C with respect to the initial temperature.

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.

Limits:
The actual flow rate may not differ more than ± 10 ml/min. with respect to the set flow rate.

ANNEX II

Level IV. In-use instrument checks

This Annex contains practical examples of tests and their associated tolerance limits 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".

1. POTENTIOMETRIC TITRATORS

1.1. PRECISION

Materials:
Suitable certified standard RV (highly pure, dried), e.g. Benzoic acid RV or tris(hydroxymethyl)-aminomethane (TRIS).
Fresh titrant, appropriate to titrate the selected standard.

Method:
Perform a minimum of 3 titrations with 3 independent additions of certified standard (in random order if using different weights), which should result in a consumption of approx. 20 % to 90 % of the burette volume.
Calculate 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.

Limits: RSD ≤ 0.2 %

1.2. ACCURACY

Materials:
Refer to chapter 1.1. Precision.

Method:
Calculate the mean of the titers obtained in chapter 1.1. Precision.

For the calculation of the theoretical titer value of the titrant solution and the systematic deviation (d_{rel}), refer to Level III, chapter POTENTIOMETRIC TITRATORS; 1.2. ACCURACY.

Limits:
The systematic deviation (d_{rel}) should be maximum ≤ ± 2% of the theoretical titer (determined on a freshly opened titrant container).
Note: The implementation of the suggested limit depends on the quality of the used volumetric solution. The use of a new solution and/or the check of the titer are recommended.

2. KARL FISCHER VOLUMETRIC TITRATORS

2.1. PRECISION

Materials:
Certified water standard solution with a defined guaranteed water contents of 10 mg/g.
Karl Fischer reagents for volumetric water determination.

Method:
Perform a minimum of 3 titrations with 3 independent additions of water standard solution (in random order if using different weights), which should result in a consumption of approx. 20 % to 90 % of the burette volume.
Calculate 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.

Limits: RSD ≤ 1.5 %.

2.2. RECOVERY

Materials and Method:
Refer to Recovery test in Level III.

Limits: 97.5 % to 102.5 %.

3. KARL FISCHER COULOMETRIC TITRATORS

3.1. RECOVERY

Materials and Method:
Refer to Recovery test in Level III.

Limits:
Water standard solution 1000 µg/g - Recovery: 97.5 % to 102.5 %.
Water standard solution 100 µg/g - Recovery: 90.0 % to 110.0 %.

REFERENCES

(For all references, the latest version applies)

1) Ph. Eur. (2.5.12, 2.5.32).
2) Application Bulletin No. 255 - Validation of Metrohm KF Titrators according to GLP/ISO 9001. Metrohm.
3) Application Bulletin No. 252 - Validation of Metrohm titrators (potentiometric) according to GLP/ISO 9001. Metrohm.
4) Application Bulletin No. 273 - Validation of Metrohm KF coulometers using Standard Operating Procedures. Metrohm.
5) Application Bulletin No. 283 – Validation of Metrohm burets. Metrohm.