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QUALIFICATION OF EQUIPMENT
ANNEX 5: QUALIFICATION OF AUTOMATIC TITRATORS

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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 cylinder used). The results should meet the specification provided by the manufacturer.

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.

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 (optional)	$r^2 \geq 0.9990$

*when a fresh commercial titrant is used

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. Recovery	97.5 % to 102.5 %
2.3. Linearity (optional)	$r^2 \geq 0.9990$

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
4.4 Precision	RSD ≤ 1.5 %
4.5 Recovery	95.0 % to 105.0 %.

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*	$d_{rel} \leq \pm 2.0$ %

*when a fresh commercial titrant is used

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 %

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

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 %

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. Recovery	95.0 % to 105.0 %.

ANNEX I

Level III. Periodic and motivated instrument checks

This Annex contains practical examples of parameters, methodologies and acceptance criteria 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 parameters, methodologies and acceptance criteria may slightly differ.

1. POTENTIOMETRIC TITRATORS

1.1. PRECISION

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 3 titrations with 3 independent additions of certified reference material 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 M to 1.0 M) to minimize the weighing error.

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

Limits: RSD $\leq$ 0.2 %

1.2. ACCURACY

Applicable only using commercial fresh titrant.

Materials:
Refer to 1.1. PRECISION.

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 titrant solution at 20°C is 1.000, with a decrease of 0.02 % per degree of temperature increase, according to the following formula:

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

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 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:

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

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 a fresh commercial titrant is used

1.3. LINEARITY

Materials:
Refer to 1.1. PRECISION.

Method: Linear regression volume/sample size

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.

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).

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 (M) /Titrant volume (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}

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

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 entails a consumption of reagent above 0.5 mL.
- For titrant standardisation and performance verification, suitable certified reference material or reference standard should be used (e.g. certified water standard solution e.g. HYDRANAL® water standard 1.0 or 10.0, certified solid standard e.g. HYDRANAL® standard sodium tartrate dihydrate) or amoxicillin trihydrate for performance verification CRS).
- 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 must be filled with fresh molecular sieve and moisture indicator.

2.1. PRECISION

See GENERAL RECOMMENDATIONS FOR KF TITRATIONS.

Method:
Perform a minimum of 3 titrations with 3 independent additions of water standard solution 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. RECOVERY

Materials:
See 2.1. Precision.

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:

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

Where:

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

Calculate the mean percentage recovery ($\bar{r}$).
Limits: $\bar{r}$ is between 97.5 per cent and 102.5 per cent.

In case of amoxicillin trihydrate for performance verification CRS is used, refer to the limits given in the accompanying Ph. Eur. leaflet.

2.3. LINEARITY (OPTIONAL)

Materials:
Refer to 2.1. PRECISION.

Method: Linear regression titrant volume/sample size (weight)
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
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).

Limits: $r^2 \geq 0.9990$.

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.

3.1. PRECISION

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 3 determinations with 3 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 recovery is calculated on the basis of the certified water content of the standard solution used.

Materials:
Refer to 3.1. PRECISION.

Method:
Perform a minimum of 3 determinations with an accurately weighed amount of water standard solution and perform the coulometric titration. Calculate the mean percentage recovery (r) of water from the water standard solution, 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 3.1. PRECISION.

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
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).

Limits: $r^2 \geq 0.990$

4. KARL FISCHER OVEN

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

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.

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.

Limits: RSD ≤ 1.5 %

4.5 RECOVERY

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

Materials:
Refer to 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:

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

Where:

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

Limits:
Recovery: 95.0 % to 105.0 %.

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:
See 1.1 Precision Level III

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

Applicable only using commercial titrant.

Materials:
See 1.1. Precision Level III

Method:
See 1.1 Precision. Calculate the mean of the titers obtained.

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

Limits:
The systematic deviation (d_{rel}) should be maximum ≤ ± 2.0 % of the theoretical titer.

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
Refer to Level III 2.1.

Limits: RSD ≤ 1.5 %

2.2. RECOVERY
Refer to Level III 2.2.

Recovery: 97.5 % to 102.5 %.

3. KARL FISCHER COULOMETRIC TITRATORS

3.1. RECOVERY
Refer to Level III 3.2.

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 %.

4. KARL FISCHER OVEN

4.1. RECOVERY
Refer to Level III 4.5

Recovery: 95.0 % to 105.0 %.

REFERENCES

(For all references, the latest version applies)

1) Ph. Eur. chapter 2.5.12 and 2.5.32.

ATTACHMENT 1

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:	
				Slope:	Limit:
Analytical balance: Inventory №:				pH (as): Difference in mV between pH…..and pH…..	
Determination of titer:				Mode: Determination of …	
No.	Sample size, g:	Volume, mL:	Titer:	Results:	
1				Mean =	a_{sys}, mL=
2				SD (s_{abs})=	$b_{T/Vol}$ =
3				RSD (s_{rel}),% =	
4				Titer $_{theoretical}$=	
5				D_{rel},% =	
				Limits: (Periodic check)□	**Limits: (Before analysis)** □
1. Precision:				RSD: ≤ 0.2 %	RSD: ≤ 0.2 %
2. Accuracy:				(d_{rel}): ≤ ± 0.5 %	(d_{rel}): ≤ ± 2.0 %
3. Linearity:				$r^2 \geq 0.9990$	
				a_{sys}<±10 µL (1 mL burettes) a_{sys}<± 50 µL (5, 10, 20 and 50 mL burettes)	
				$b_{T/Vol}$<± 0.0010 mL^{-1}	
				Conclusion: □ complies / □ does not comply	
Comments/Remark:					
Analyst:				Signature:	Date:
Supervisor:				Signature:	Date: