Ontwikkelingen in de Europese Farmacopee

Lab dag 4 December 2014

Oscar Smeets

KNMP - LNA

KNMP-organisatie te Den Haag

LNA producten en diensten voor laboratoria

KNMP-kennisbank

- FNA-voorschriften met kwaliteitseisen
- LNA-onderzoeksvoorschriften voor FNA-preparaten
- LNA-procedures en LNA-mededelingen

Farmaceutisch analytisch ringonderzoek

Deeltjestelonderzoek voor parenteralia en oogdruppels

Specifieke analyses op contractbasis

- Voorraadbereidingen en grondstoffen controles
- Individuele bereidingen validatie analyses
- Uiteenvaltijd capsules en zetpillen

Microbio: aseptische handelingen monitoren en spiegelen

Helpdesk: jaarlijks ruim 4000 vragen, 070-3737370 of lna@knmp.nl

Overzicht presentatie

- Keuringsbeleid
  - Monografie pharmaceutical preparations
  - Individuele bereidingen
  - VTGM producten
- Ontwikkelingen Ph. Eur.
  - Preparaat monografieën
  - Kwaliteitsdocumenten

Besluit Geneesmiddelenwet

Artikel 2
Geneesmiddelen die in een apotheek zijn bereid, niet zijnde geneesmiddelen voor onderzoek, worden slechts ter hand gesteld indien zij voldoen aan de voorschriften van de Europese Farmacopee of, bij ontstentenis daarvan, aan een in een lidstaat officieel in gebruik zijnde farmacopee, dan wel, bij ontstentenis daarvan, aan een in de Verenigde Staten of Japan officieel in gebruik zijnde farmacopee. Voor de samenstelling worden deugdelijke bestanddelen gebruikt.

IMPORTANT NOTICE

GENERAL MONOGRAPHS

The European Pharmacopoeia contains a number of general monographs covering classes of products. These general monographs give requirements that are applicable to all products in the given class or, in some cases, to any product in the given class for which there is a specific monograph in the Pharmacopoeia (see *1. General Notices*, General monographs). Where no restriction on scope of a general monograph is given in a preamble, it is applicable to all products in the class defined, irrespective of whether there is an individual monograph for the product in the Pharmacopoeia.

Whenever a monograph is used, it is essential to ascertain whether there is a general monograph applicable to the product in question. The general monographs listed below are published in the section General Monographs (unless otherwise stated). This list is updated where necessary and republished in each Supplement.

Dosage Forms monographs

Pharmaceutical preparations (2619)

Substances for pharmaceutical use (2034)

Europese Farmacopee

DOSAGE FORMS

04/2013:2619

PHARMACEUTICAL PREPARATIONS

INTRODUCTION

This monograph is intended to be a reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms, which are to be applied in the manufacture/preparation of pharmaceuticals, but not a guide on how to manufacture as there is specific guidance available covering methods of manufacture and associated controls.

It does not cover investigational medicinal products, but competent authorities may refer to pharmacopoeial standards when authorising clinical trials using investigational medicinal products.

04/2013:2619

PHARMACEUTICAL PREPARATIONS

DEFINITION

Pharmaceutical preparations may be licensed by the competent authority, or unlicensed and made to the specific needs of patients according to legislation. There are 2 categories of unlicensed pharmaceutical preparations:

- extemporaneous preparations, i.e. pharmaceutical preparations individually prepared for a specific patient or patient group, supplied after preparation;
- stock preparations, i.e. pharmaceutical preparations prepared in advance and stored until a request for a supply is received.

04/2013:2619

PHARMACEUTICAL PREPARATIONS

TESTS

Relevant tests to apply in order to ensure the appropriate quality of a particular dosage form are described in the specific dosage form monographs.

Where it is not practical, for unlicensed pharmaceutical preparations, to carry out the tests (e.g. batch size, time restraints), other suitable methods are implemented to ensure that the appropriate quality is achieved in accordance with the risk assessment carried out and any local guidance or legal requirements.

Stock preparations are normally tested to a greater extent than extemporaneous preparations.

Overzicht

- Voorraadbereidingen
- Individuele bereidingen
- VTGM producten

Algemeen: voor bereiden voor eigen patiënten is in de ziekenhuisapotheek de GMP-Z de “local guidance”

Beleid voor keuring van individuele bereidingen

- Proces versus productcontrole

- Productieprocessen identificeren en valideren
  - Bv. capsules maken uit tabletten
  - Bv. kleine charge capsules maken uit grondstoffen
  - Bv. kleine charge zetpillen maken uit grondstoffen
- Medewerkers kwalificeren is essentieel

- Op basis risico analyse: eventueel periodiek monsters met overmaat laten maken

Persoonsgebonden kwalificatie bij individuele bereidingen

Nummer

P03-7

Datum

Mei 2014

Versie

1.0

Principe

Deze procedure beschrijft de controle en het toezicht op de werkwijze van een medewerker die individuele bereidingen uitvoert. De persoonlijke kwalificatie is erop gericht dat een medewerker aantoont de specifieke bereidingshandelingen te beheersen die nodig zijn voor het bereiden van farmaceutische vormen die als individuele bereiding worden geproduceerd.

Gerelateerde documenten

- Beoordeling analyseresultaten
- Keuringsbeleid routinecontrole individuele bereidingen
- Keuringsbeleid validatie individuele bereidingen (niet-gestandaardiseerd)
- Kwaliteitseisen
- Persoonsgebonden kwalificatie bij aseptische handelingen
- Persoonsgebonden kwalificatie bij individuele bereidingen - Toelichting

Definities

- Laboratorium: Regionaal Apotheek Laboratorium (RAL) of ziekenhuislaboratorium.
- Gestandaardiseerde bereidingen: apotheekbereidingen die routinematig in de apotheek worden uitgevoerd als voorraadbereiding of als individuele bereiding, en waarvoor voldoende waarborgen aanwezig zijn om de kwaliteit te kunnen garanderen, zowel van de samenstelling als van het bereidingsvoorschrift.
- Niet-gestandaardiseerde bereidingen: apotheekbereidingen waarvoor geen goed onderzochte samenstelling en/of goed onderzocht (en gevalideerd) bereidingsvoorschrift beschikbaar zijn.

Zie ook de Toelichting.

Beleid voor keuring VTGM-producten

- VTGM is geen bereiden
- VTGM terrein is echter zeer breed
  - VTGM is oplossen gevriesdroogd materiaal conform instructies SPC
  - Maar ook VTGM spuiten op voorraad
- Uitkomst wel of niet keuren baseren op risico analyse
- Discussie loopt binnen vereniging en met IGZ

Farmacopee

Een farmacopee is een officieel, van staatswege uitgegeven handboek met voorschriften voor de bereiding van geneesmiddelen voor menselijk en dierlijk gebruik, en de vereisten waaraan zij moeten voldoen.

Geschiedenis

- 1636 Amsterdamse Farmacopee
- 1805 Bataafse Farmacopee
- 1851 Nederlandse Farmacopee I
- 1871 Nederlandse Farmacopee II
- 1958 Nederlandse Farmacopee VI
- 1964 Verdrag Europese Farmacopee
- 1978 Nederlandse Farmacopee VIII
- 1993 Nederlandse Farmacopee opgeheven
- 2014 50 jaar Europese Farmacopee

EDQM 50th Anniversary

50 years of leadership in the quality of medicines

For 50 years now, the EDQM has shown leadership in **protecting public health** by enabling the development, supporting the implementation and monitoring the application of **quality standards for safe medicines** and their safe use.

The EDQM celebrated the 50th anniversary of the Convention on the elaboration of a European Pharmacopeia on 6-8 October 2014.

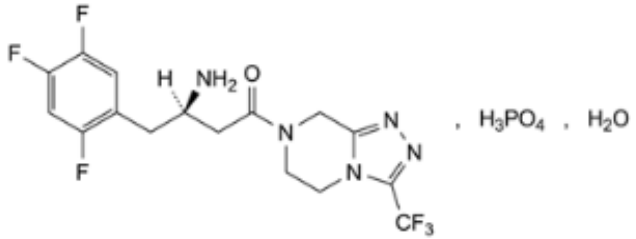
> Read the conference proceedings

Specifieke Product monografieen

- 1999 Discussie op agenda
- 2000 Geen groen licht door Commissie
- 2011 Reflection paper: toch niet doen?
- 2012 Groen licht voor pilot
- 2014 Resultaat twee concepten

SITAGLIPTIN PHOSPHATE MONOHYDRATE TABLETS

Sitagliptini phosphatis monohydrici compressi



$C_{16}H_{18}F_6N_5O_5P,H_2O$ M_r 523.3

DEFINITION

(3*R*)-3-Amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate monohydrate.

Sitagliptin phosphate monohydrate tablets contain *Sitagliptin phosphate monohydrate (2778)*.

The tablets comply with the monograph Tablets (0478) and with the following additional requirements.

Content: 95.0 per cent to 105.0 per cent of the content of sitagliptin ($C_{16}H_{15}F_6N_5O$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay with a diode array detector.

Spectral range: 200-350 nm.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

The following chromatogram is shown for information but will not be published in the European Pharmacopoeia.

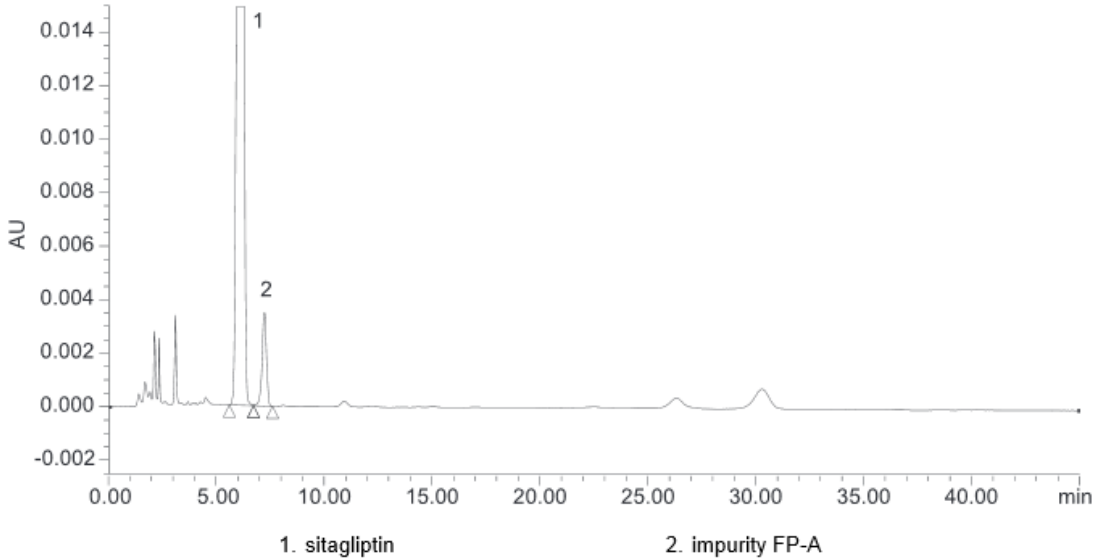


Figure 2927.-1. – *Chromatogram for the test for related substances of sitagliptin phosphate monohydrate tablets: reference solution (c)*

Solvent mixture: *acetonitrile R1*, 0.1 per cent *V/V* solution of *phosphoric acid R* (5:95 *V/V*).

Test solution. Place 10 tablets in an appropriate volumetric flask and add a suitable volume of the solvent mixture to obtain a concentration of 1 mg/mL of sitagliptin. Stir vigorously for 1 h. Dilute 2.0 mL of the solution to 25.0 mL with the solvent mixture. Centrifuge a portion of the solution until a clear supernatant is obtained. Use the supernatant.

Reference solution (a). Dissolve 25.0 mg of *sitagliptin phosphate monohydrate CRS* in the solvent mixture and dilute to 250.0 mL with the solvent mixture.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c). In order to prepare impurity A (fumarate adduct) *in situ*, place 10 mg of *sitagliptin phosphate monohydrate CRS* and 1 mg of *sodium stearyl fumarate R* in a scintillation vial, add 1 mL of *water R* and close the vial. Heat at 80 °C for 20-48 h. Transfer the contents of

Dissolution (*2.9.3, Apparatus 2*).

Dissolution medium: *0.01 M hydrochloric acid*; use 1 L for the test.

Rotation speed: 50 r/min.

Time: 30 min.

Analysis

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Reference solution. Dissolve a suitable quantity of *sitagliptin phosphate monohydrate CRS* in a suitable quantity of the dissolution medium to obtain a concentration of sitagliptin corresponding to the theoretical concentration of sitagliptin in the test solution, based on the labelled content of the tablets.

Detection: spectrophotometer at 266 nm.

Injection: test solution from the dissolution test(62) and reference solution.

Run time: twice the retention time of sitagliptin.

Calculate the percentage dissolved of sitagliptin ($C_{16}H_{15}F_6N_5O$) taking into account the assigned content of *sitagliptin phosphate monohydrate CRS*.

Acceptance criteria:

– an evaluation is carried out according to Table 2.9.3.-1, with Q = 75 per cent.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection: test solution and reference solution (a).

Run time: twice the retention time of sitagliptin.

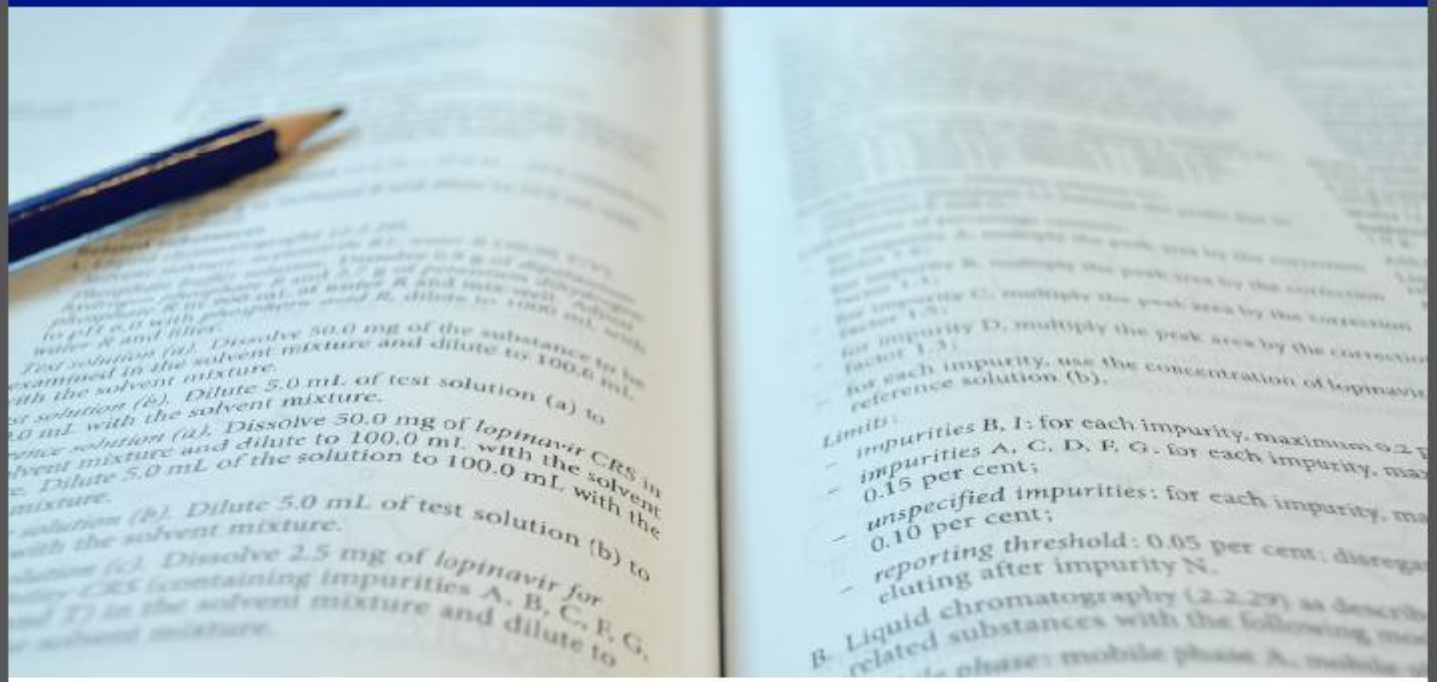
System suitability: reference solution (a):

– *repeatability*: maximum relative standard deviation of 1.5 per cent for the peak due to sitagliptin after 6 injections.

Calculate the percentage content of sitagliptin ($C_{16}H_{15}F_6N_5O$) taking into account the assigned content of *sitagliptin phosphate monohydrate CRS*.

Style Guide of the European Pharmacopoeia

Guide de rédaction de la Pharmacopée Européenne



European Pharmacopoeia

Pharmacopée Européenne

August 2014

Août 2014

Changes in titles for the 9th Edition

Following the implementation of the new policy for hydrates (see Style guide 2014, page 19), the word 'anhydrous' will be deleted from the titles of the monographs listed in the table below. These changes in title will be implemented for the 9th Edition and will therefore come into force on **1 January 2017**.

Old title	New title	Number
Ampicillin, anhydrous	**Ampicillin**	0167
Beclometasone dipropionate, anhydrous	**Beclometasone dipropionate**	0654
Calcipotriol, anhydrous	**Calcipotriol**	2011
Calcium acetate, anhydrous	**Calcium acetate**	2128
Calcium hydrogen phosphate, anhydrous	**Calcium hydrogen phosphate**	0981
Calcium lactate, anhydrous	**Calcium lactate**	2118
Chlorobutanol, anhydrous	**Chlorobutanol**	0382
Citric acid, anhydrous	**Citric acid**	0455
Copper sulfate, anhydrous	**Copper sulfate**	0893
Disodium phosphate, anhydrous	**Disodium phosphate**	1509
Docetaxel, anhydrous	**Docetaxel**	2593
Ephedrine, anhydrous	**Ephedrine**	0488
Glucose, anhydrous	**Glucose**	0177
Lactose, anhydrous	**Lactose**	1061
Lufenuron (anhydrous) for veterinary use	**Lufenuron for veterinary use**	2177
Magnesium citrate, anhydrous	**Magnesium citrate**	2339
Nevirapine, anhydrous	**Nevirapine**	2255
Niclosamide, anhydrous	**Niclosamide**	0679
Paroxetine hydrochloride, anhydrous	**Paroxetine hydrochloride**	2283
Phloroglucinol, anhydrous	**Phloroglucinol**	2301
Sodium carbonate, anhydrous	**Sodium carbonate**	0773

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Organ Tranplantation
Pharmaceutical Care
The Medicrime Convention
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The Certification of Suitability (CEP) in Brief

- Established in 1994.
- Over 3500 certificates covering 850 substances have been granted in more than 50 countries.
- Assessment is jointly performed by assessors from the national competent authorities and EDQM assessors
- Organises an inspection programme to check compliance with both GMP and the CEP with a network of national inspectors.

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Latest News

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08 October 2014

Certification Monthly Report of Activities

The last monthly activity report for the Certification of Substances Division (DCEP)...

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06 October 2014

WHO 4th International Meeting of World Pharmacopoeias

8-10 October 2014: The EDQM will host the World Health Organization's...

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Focus

European Pharmacopoeia

Member & Observers

During its 148th Session, the PhEur Commission unanimously decided to grant **Azerbaijan** observer status. This brings to 27 the number of observers, from 6 continents. As an observer, Azerbaijan can participate in the scientific work of the Commission and its expert meetings, attend Commission sessions and become involved in the other EDQM activities. Observer status also facilitates development of a mutually-beneficial relationship and sharing of expertise on issues pertinent to the

European Pharmacopoeia: 8th edition and its Supplements Publication schedule

Commission Sessions		8th Edition Supplements	Publication Schedule	Implementation Date
Session N°	Date			
–	–	**8th Edition**	**15 July 2013**	**1 Jan. 2014**
145	Mar. 2013	8.1	1 Oct. 2013	1 Apr. 2014
146	June 2013	8.2	1 Jan. 2014	1 July 2014
147	Nov. 2013	8.3	1 July 2014	1 Jan. 2015
148	Mar. 2014	8.4	1 Oct. 2014	1 Apr. 2015
149	June 2014	8.5	1 Jan. 2015	1 July 2015
150	Nov. 2014	8.6	1 July 2015	1 Jan. 2016
151	Mar. 2015	8.7	1 Oct. 2015	1 Apr. 2016
152	June 2015	8.8	1 Jan. 2016	1 July 2016
153	**Nov. 2015**	**9th Edition**	**15 July 2016**	**1 Jan. 2017**

QUALITY MANAGEMENT (QM) GUIDELINES

Publications, Products and Services

Publications
- European Pharmacopoeia 7th Edition
- Pharmeuropa, Pharmeuropa Bio & Scientific Notes
- Standard Terms
- Blood Transfusion & Organ Transplantation Guides
- Cosmetics Guides
- Pharmaceutical Care
- Proceedings of International Conferences
- Technical Guides
- Product Specific Guidelines / Model Protocol Templates (OCABR/OBPR)
- Quality Management (QM) Guidelines

Reference Standards

CombiStats

Proficiency Testing Scheme (PTS)

Certificates of Suitability

Most viewed pages

FAQ - Helpdesk List

Quality Management Guidelines

Quality Management (QM) guidelines have been developed for application within the General European OMCL Network. They are available to download below.

Those marked with an asterisk* have been approved by the European co-operation for Accreditation (EA).

- Scope of Accreditation of Official Medicines Control Laboratories*
- Validation of Analytical Procedures*
- Uncertainty of Measurement-Part 1: General OMCL Policy for implementation of Measurement of Uncertainty in Compliance Testing*
- Uncertainty of Measurement-Part 2: OMCL Policy on the Estimation and Application of Uncertainty in Analytical Measurement
- Standard 'Aide-Mémoire' for the Mutual Joint Audit of Official Medicines Control Laboratories*
- 'Aide-Mémoire' for Environmental Conditions & Treatment of Biological Models*
- Evaluation & Reporting of Results

Important Information

For information about the Quality Management (QM) Programme, visit the Control of Medicines section.

Catalogue

Products & Services Catalogue 2012

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

OMCL Network of the Council of Europe
QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (11) 157 5R

MANAGEMENT OF REAGENTS

Full document title and reference	Management of reagents PA/PH/OMCL (11) 157 5R
Document type	Guideline
Legislative basis	
Date of first adoption	4th April 2012
Date of original entry into force	
Date of entry into force of revised document	1st May 2012
Previous titles/other references	
Custodian Organisation	The present document was elaborated by the OMCL Network/ EDQM of the Council of Europe
Concerned Network	GEON

Management of Reagents

Introduction:

The aim of this guideline is to describe the management of reagents and volumetric solutions in the OMCLs.

The term "reagent" in this guideline covers solvents, media for microbiological use, solid, liquid and gaseous substances and preparations of substances that are not reference standards or reference materials, nor preparations of reference standards.

These reagents can be divided into five categories:

1. Purchased reagents in their original container
2. Purchased reagents which have been transferred into another container
3. In-house reagents
4. Water manufactured by the OMCL
5. Volumetric solutions

Management of the reagents covers the entire life-cycle of the reagents from purchasing/manufacturing (in the case of preparations) to use and disposal.

The major points to consider in the life-cycle of reagents are:

- Types of reagent and the quality, depending on their use.
  - This should be part of an SOP or an individual testing plan.
- Selection of the supplier based on the suppliers' qualification.
  - This qualification should be documented in a list of suppliers that is linked to the quality management system.
- Verification of reagents upon receipt.
  - This could be divided into an administrative part (documented checking of the invoice, delivery note and the integrity of the container, including storage temperature) and a scientific part (documented checking of the actual quality of the reagent given by the label or certificate against the requested quality). Specific in-house testing may be required for particular reagents.
- Ensuring that the reagent is not compromised in any way before being used.
  This is to be ensured by proper storage conditions, as suggested by the manufacturer or the OMCL.
- Checking the expiry dates of reagents before use (it is not necessary to document this verification)
- Avoiding misuse by misidentification of a reagent.
  - This is ensured by proper labelling and/or storage in dedicated areas.
- The reagents used in the analysis of a specific sample must be documented.

OMCL Network of the Council of Europe
QUALITY ASSURANCE DOCUMENT

PA/PH/OMCL (13) 113 2R

Evaluation and Reporting of Results
Core document

Full document title and reference	Evaluation and Reporting of Results – Core Document PA/PH/OMCL (13) 113 2R
Document type	Guideline
Legislative basis	/
Date of first adoption	October 1999
Date of original entry into force	February 2000
Date of entry into force of revised document	October 2014
Previous titles / other references / last valid version	This document replaces document PA/PH/OMCL (07) 28 DEF CORR Former titles / references: Evaluation and Reporting of Results from Assays, PA/PH/OMCL (02) 52 DEF Evaluation and Reporting of Results, PA/PH/OMCL (99) 38 DEF
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
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OMCL Network of the Council of Europe
QUALITY ASSURANCE DOCUMENT

PA/PH/OMCL (14) 87

Evaluation and Reporting of Results
Annex 1A

Full document title and reference	Evaluation and Reporting of Results – Annex 1A Model Template for Failure Investigation of OOS Results PA/PH/OMCL (14) 87
Document type	Guideline
Legislative basis	/
Date of first adoption	August 2014
Date of original entry into force	October 2014
Date of entry into force of revised document	/
Previous titles / other references / last valid version	/
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
Concerned Network	GEON

MODEL TEMPLATE FOR FAILURE INVESTIGATION OF OOS RESULTS

Sample information (name and laboratory code)	
Analytical procedure / Test / Parameter (suspect OOS result)	

Y	N/NA		Y	N/NA	
General					
☐	☐	weighing error	☐	☐	inadequate ambient conditions (temperature, moisture, etc.)
☐	☐	contamination from surfaces or glassware	☐	☐	presence of interfering substances
☐	☐	other possible reasons for OOS result:			
Samples, Reagents, Solvents & Solutions					
☐	☐	use of wrong reagents/chemical form	☐	☐	error during filtration
☐	☐	wrong quality or purity of reagents and solvents	☐	☐	inappropriate storage of samples
☐	☐	inappropriate storage of reagents, solvents and solutions	☐	☐	carry–over
☐	☐	solutions or reagents expired	☐	☐	abnormal appearance of samples, reagents solvents or solutions
☐	☐	reagents not dissolved completely	☐	☐	water of sub-standard quality
Reference Standards					
☐	☐	wrong reference standard or inadequate quality used	☐	☐	error in weighing, dissolution and dilution
☐	☐	reference standard expired	☐	☐	inappropriate storage of reference standard
Dilutions & Pipetting					
☐	☐	glassware or pipetting device with wrong volume	☐	☐	uncalibrated/leaking piston pipettes
☐	☐	uncalibrated/sub-standard glassware	☐	☐	dilution error
☐	☐	pipettes with broken tip	☐	☐	wrong dilution technique
Method Verification					
☐	☐	deviations from the specified (authorised) method	☐	☐	values below limit of detection/quantitation
☐	☐	imprecision of observations/results of sample higher than acceptable (RSD, 95%CI)	☐	☐	blank value ignored
☐	☐	imprecision of observations/results of reference standard higher than acceptable	☐	☐	system suitability test or assay validity criteria (controls, statistics) missing/failed
☐	☐	measurement outside linear/validated range	☐	☐	trend of routine method (control chart, comparison with manufacturer in OCABR)
Equipment Verification					
☐	☐	wrong instrument used	☐	☐	wrong instrument parameters
☐	☐	instrument calibration missing or criteria not met	☐	☐	computerised system (including software) inappropriate
Calculations					
☐	☐	calculation error	☐	☐	data transfer error
☐	☐	formula or factor wrong	☐	☐	inappropriate validation of calculating software

☐	**The reason(s) indicated above invalidate the results**
☐	**During this failure investigation, no reason to invalidate the OOS result could be found**

Decision on the re-test programme:	(e.g. number of replicates, operator, reference material, equipment, methods / parameters)

Technician(s) (Signature, Date)		**Supervisor** (Signature, Date)	

OMCL Network of the Council of Europe
QUALITY ASSURANCE DOCUMENT

PA/PH/OMCL (14) 88

Evaluation and Reporting of Results
Annex 1B

Full document title and reference	Evaluation and Reporting of Results – Annex 1B Responsibilities of the Laboratory Supervisor PA/PH/OMCL (14) 88
Document type	Guideline
Legislative basis	/
Date of first adoption	August 2014
Date of original entry into force	October 2014
Date of entry into force of revised document	/
Previous titles / other references / last valid version	/
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
Concerned Network	GEON

ANNEX I B OF THE OMCL NETWORK GUIDELINE

"EVALUATION AND REPORTING OF RESULTS"

RESPONSIBILITIES OF THE LABORATORY SUPERVISOR

Extract from the FDA Guidance for Industry "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production", chapter III B: Responsibilities of the Laboratory Supervisor

Once an OOS result has been identified, the supervisor's assessment should be objective and timely. There should be no preconceived assumptions as to the cause of the OOS results. Data should be assessed promptly to ascertain if the results may be attributed to laboratory error, or whether the results could indicate problems in the manufacturing process. An immediate assessment could include re-examination of the actual solutions, test units, and glassware used in the original measurements and preparations, which might provide more credibility for laboratory error hypotheses.

The following steps should be taken as part of the supervisor's assessment:

1. Discuss the test method with the analyst; confirm analyst knowledge of and performance of the correct procedure.
2. Examine the raw data obtained in the analysis, including chromatograms and spectra, and identify anomalous or suspect information.
3. Verify that the calculations used to convert raw data values into a final result are scientifically sound, appropriate, and correct; also determine if unauthorized or unvalidated changes have been made to automated calculation methods.
4. Confirm the performance of the instruments.
5. Determine that appropriate reference standards, solvents, reagents, and other solutions were used and that they meet quality control specifications.
6. Evaluate the performance of the testing method to ensure that it is performing according to the standard expected based on method validation data and historical data.
7. Fully document and preserve records of this laboratory assessment.

The assignment of a cause for OOS results will be greatly facilitated if the retained sample preparations are examined promptly. Hypotheses regarding what might have happened (e.g. dilution error, instrument malfunction) should be tested. Examination of the retained solutions should be performed as part of the laboratory investigation.

OMCL Network of the Council of Europe
QUALITY ASSURANCE DOCUMENT

PA/PH/OMCL (14) 89

Evaluation and Reporting of Results
Annex 2A

Full document title and reference	Evaluation and Reporting of Results – Annex 2A Examples of Re-test Programmes for Quantitative Tests PA/PH/OMCL (14) 89
Document type	Guideline
Legislative basis	/
Date of first adoption	August 2014
Date of original entry into force	October 2014
Date of entry into force of revised document	/
Previous titles / other references / last valid version	/
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
Concerned Network	GEON

ANNEX II A OF THE OMCL NETWORK GUIDELINE

"EVALUATION AND REPORTING OF RESULTS"

EXAMPLES OF RE-TEST PROGRAMMES FOR QUANTITATIVE TESTS

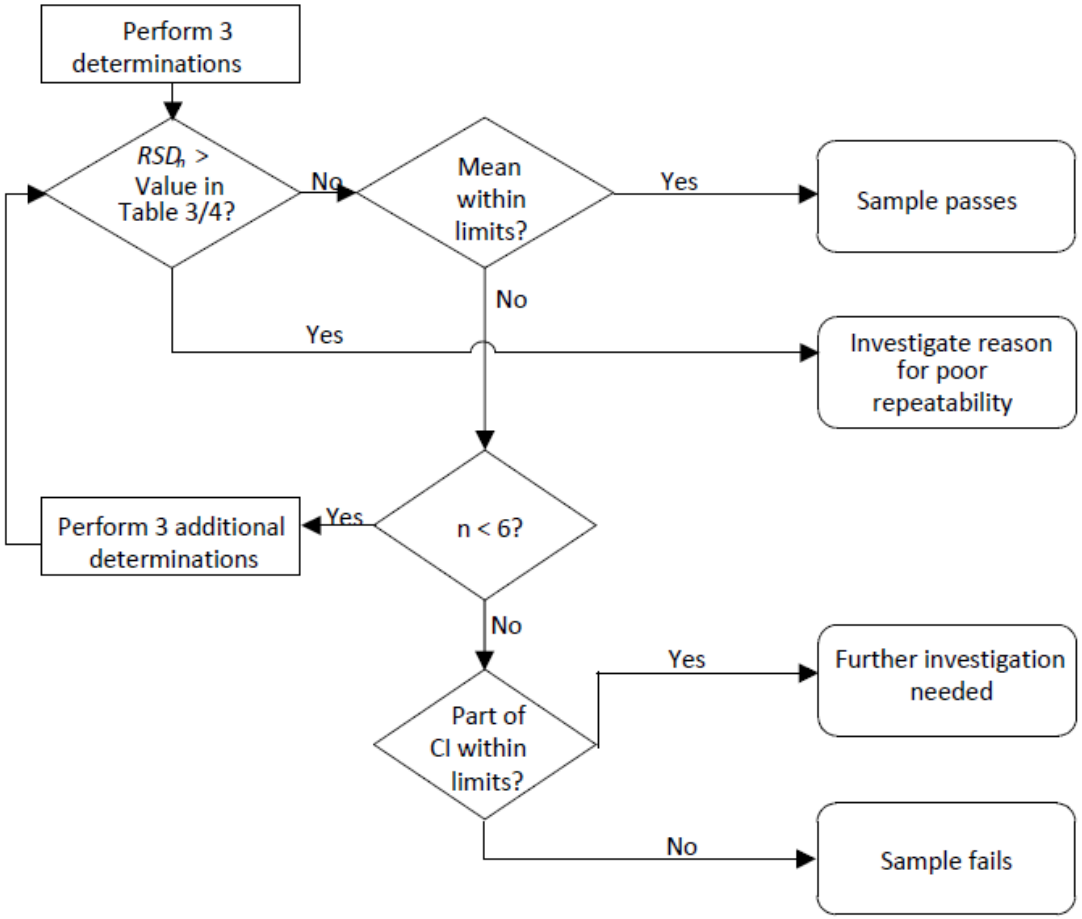
TABLE OF CONTENT

INTRODUCTION

This document is an Annex to the core document "Evaluation and reporting of results", *PA/PH/OMCL (13) 113* (in its current version), and it should be used in combination with it when planning, performing and documenting the evaluation process and reporting of results of quantitative tests with the expected Gaussian distribution.

The core document contains the Introduction, Scope and General requirements for the evaluation of results (in routine cases or otherwise) and the reporting of results.

Figure 4 - Decision tree for Approach 4



If the OMCL decides to use internal quality control criteria to evaluate the repeatability of the results of the test, Tables 3 and 4 are not applicable. The steps 1 to 8, as well as the decision tree (Figure 4), can be applied as long as the comparison of the obtained RSD is performed with the internal quality control criteria (step 3).

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QUALITY ASSURANCE DOCUMENT

PA/PH/OMCL (14) 91

Evaluation and Reporting of Results
Annex 2C

Full document title and reference	Evaluation and Reporting of Results – Annex 2C Re-test Programme for Qualitative Tests PA/PH/OMCL (14) 91
Document type	Guideline
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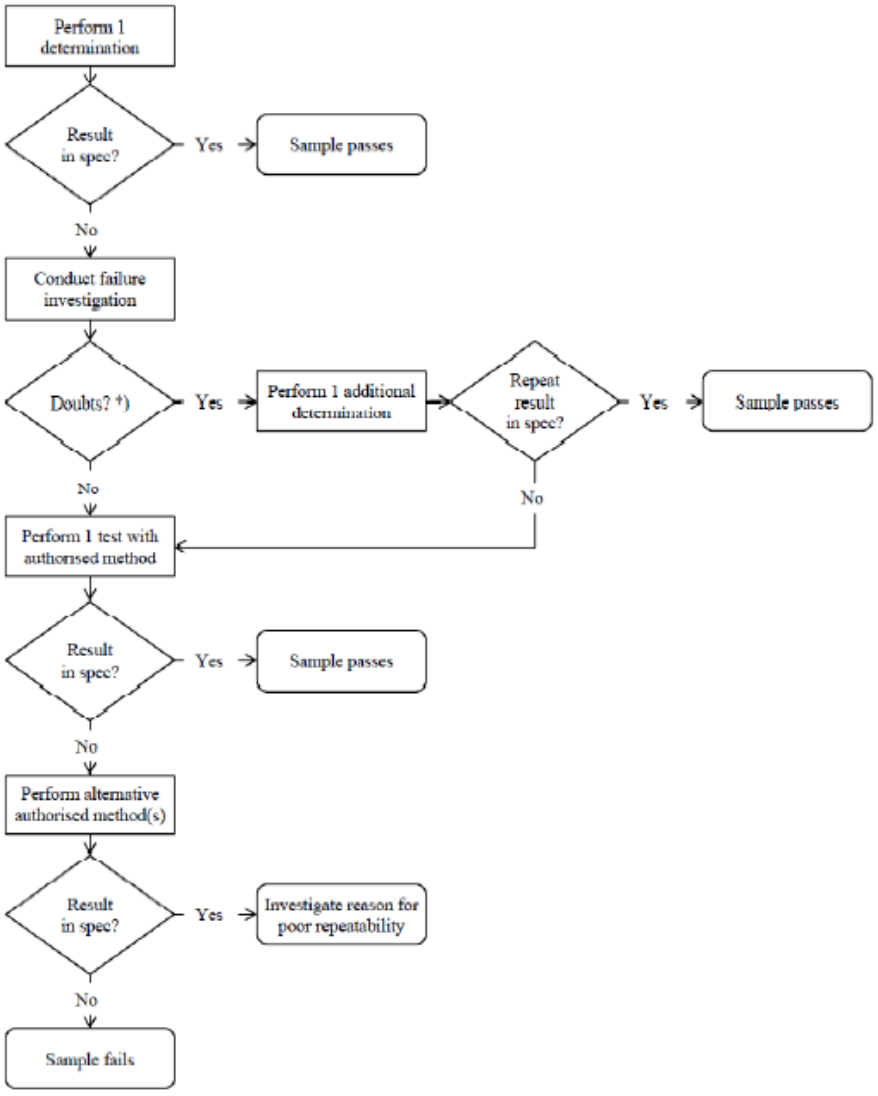
Previous titles / other references / last valid version	/
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
Concerned Network	GEON

Figure 1 - Decision tree for qualitative methods



*) Any doubts regarding sample presence / cross contamination?

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QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (08) 73 2R

QUALIFICATION OF EQUIPMENT
CORE DOCUMENT

Full document title and reference	Qualification of Equipment – Core document PA/PH/OMCL (08) 73 2R
Document type	Guideline
Legislative basis	The present 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	1st October 1999
Date of original entry into force	1st February 2000
Date of entry into force of revised document	1st July 2011
Previous titles/other references	This document replaces document PA/PH/OMCL (08) 73 R
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Concerned Network	GEON

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OMCL Network of the Council of Europe
QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (11) 04

QUALIFICATION OF EQUIPMENT
ANNEX 1: QUALIFICATION OF HPLC EQUIPMENT

Full document title and reference	Qualification of Equipment Annex 1: Qualification of HPLC equipment PA/PH/OMCL (11) 04
Document type	Guideline
Legislative basis	The present 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	May 2005
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Date of entry into force of revised document	1st July 2011
Previous titles/other references	This document replaces document PA/PH/OMCL (07) 17 DEF
Custodian Organisation	The present document was elaborated by the OMCL Network/ EDQM of the Council of Europe
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PA/PH/OMCL (06) 86 DEF

QUALIFICATION OF EQUIPMENT
ANNEX 2: QUALIFICATION OF GC EQUIPMENT

Full document title and reference	Qualification of Equipment Annex 2: Qualification of GC Equipment PA/PH/OMCL (06) 86 DEF
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Legislative basis	The present document was also accepted by EA as recommendation document to be used in the context of Quality Management System audits of OMCLs
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Previous titles/other references	This document replaces part of document PA/PH/OMCL (06) 46 DEF
Custodian Organisation	The present document was elaborated by the OMCL Network/EDQM of the Council of Europe
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PA/PH/OMCL (07) 11 DEF CORR

QUALIFICATION OF EQUIPMENT

ANNEX 3: QUALIFICATION OF UV-VISIBLE SPECTROPHOTOMETERS

Full document title and reference	Qualification of Equipment Annex 3: Qualification of UV-Visible spectrophotometers PA/PH/OMCL (07) 11 DEF CORR
Document type	Guideline
Legislative basis	The present document was also accepted by EA as recommendation document to be used in the context of Quality Management System audits of OMCLs
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Previous titles/other references	This document replaces document PA/PH/OMCL (07) 11 DEF
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PA/PH/OMCL (07) 12 DEF CORR

QUALIFICATION OF EQUIPMENT

ANNEX 4: QUALIFICATION OF IR SPECTROPHOTOMETERS

Full document title and reference	Qualification of Equipment Annex 4: Qualification of IR spectrophotometers PA/PH/OMCL (07) 12 DEF CORR
Document type	Guideline
Legislative basis	The present document was also accepted by EA as recommendation document to be used in the context of Quality Management System audits of OMCLs
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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
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Custodian Organisation	The present document was elaborated by the OMCL Network/ EDQM of the Council of Europe
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PA/PH/OMCL (10) 86 2R

QUALIFICATION OF EQUIPMENT
ANNEX 7: QUALIFICATION OF MASS SPECTROMETERS

Full document title and reference	Qualification of Equipment Annex 7: Qualification of mass spectrometers PA/PH/OMCL (10) 86 2R
Document type	Guideline
Legislative basis	-
Date of first adoption	25th May 2011
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Previous titles/other references	-
Custodian Organisation	The present document was elaborated by the OMCL Network/EDQM of the Council of Europe
Concerned Network	GEON

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OMCL Network of the Council of Europe
QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (12) 77 7R

QUALIFICATION OF EQUIPMENT
ANNEX 8: QUALIFICATION OF BALANCES

Full document title and reference	Qualification of Balances Annex 8 to the OMCL Network Guideline "Qualification of Equipment" PA/PH/OMCL (12) 77 7R
Document type	Guideline
Legislative basis	
Date of first adoption	August 2013
Date of original entry into force	December 2013
Date of entry into force of revised document	n/a
Previous titles/other references / last valid version	n/a
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
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ANNEX 8 OF THE OMCL NETWORK GUIDELINE
"QUALIFICATION OF EQUIPMENT"

QUALIFICATION OF BALANCES

1. INTRODUCTION

This document is the 8th Annex to the core document "Qualification of Equipment", which together should be used when planning, performing and documenting the qualification process of balances.
The core document contains the introduction and general forms for Level I and II of qualification, which are common to all types of instruments.
Annex 8 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.

2. AIM AND SCOPE OF THE GUIDELINE

This guideline describes the requirements for balances (electronic - digital) used in chemical and biological tests in OMCLs.

The following types of balances are considered in this guideline (Table 1):

Table 1

Type	Ordinary name	Number of digits after decimal position (g)	Accuracy Class
1.	Ultra Micro Balances	7	I
2.	Micro Balances	6	I
3.	Semi-micro Balances	5	I
4.	Analytical Balances	4	I
5.	Precision Balances	1 to 3	II
6.	Technical Balances	0 to 1	III

The classifications are based on the OIML R 76-1 International Recommendation document (see Table 2).

Table 3

Parameter to be checked	Frequency	Typical tolerance limit
Levelling	every day before weighing begins	Acceptance limits of the balance
Internal calibration (adjustment) (automatic or manual)	every day before weighing begins	Automatic acceptance limits of the balance
Verification (in use control)	At least once a week	OMCLs shall define their own acceptance criteria
Accuracy	Frequency to be defined by OMCL, typically once a year	OMCLs shall define their own acceptance criteria
Linearity	Frequency to be defined by OMCL, typically once a year	OMCLs shall define their own acceptance criteria ($k = 1 \pm 0.0001$)
Precision	Frequency to be defined by OMCL, typically once a year	OMCLs shall define their own acceptance criteria (SD = maximum $5*d$)
Eccentricity	Frequency to be defined by OMCL, typically once a year	OMCLs shall define their own acceptance criteria (RSD = 0.05%)

k = correlation coefficient
SD = standard deviation
RSD = relative standard deviation

The following qualification tests may also be performed in addition to those described in Table 3 (recommended, not obligatory):

Parameter to be checked	Frequency (recommended)	Typical tolerance limit
Linearity error	once every six months	OMCLs shall define their own acceptance criteria ($\leq$ accuracy of the balances)
Drift test	once every six months	OMCLs shall define their own acceptance criteria (RSD = 0.05%)
Minimum weight	once a year	OMCLs shall define their own acceptance criteria depending on the type of the balance
Measurement uncertainty	once a year	OMCLs shall define their own acceptance criteria depending on the type of the balance

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QUALITY ASSURANCE DOCUMENT

PA/PH/OMCL (08) 69 3R

VALIDATION OF COMPUTERISED SYSTEMS

CORE DOCUMENT

Full document title and reference	Validation of Computerised Systems - Core Document PA/PH/OMCL (08) 69 3R
Document type	Guideline
Legislative basis	-
Date of first adoption	May 2009
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Custodian Organisation	The present document was elaborated by the OMCL Network/EDQM of the Council of Europe
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PA/PH/OMCL (08) 87 2R

VALIDATION OF COMPUTERISED SYSTEMS

ANNEX 1: VALIDATION OF COMPUTERISED CALCULATION SYSTEMS: EXAMPLE OF VALIDATION OF IN-HOUSE SOFTWARE

Full document title and reference	Validation of Computerised Systems Annex 1: Validation of computerised calculation systems: example of validation of in-house software PA/PH/OMCL (08) 87 2R
Document type	Guideline
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PA/PH/OMCL (08) 88 R

VALIDATION OF COMPUTERISED SYSTEMS

ANNEX 2: VALIDATION OF DATABASES (DB), LABORATORY INFORMATION MANAGEMENT SYSTEMS (LIMS) AND ELECTRONIC LABORATORY NOTEBOOKS (ELN)

Full document title and reference	Validation of Computerised Systems Annex 2: Validation of Databases (DB), Laboratory Information Management Systems (LIMS) and Electronic Laboratory Notebooks (ELN) PA/PH/OMCL (08) 88 R
Document type	Guideline
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Custodian Organisation	The present document was elaborated by the OMCL Network/EDQM of the Council of Europe
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PA/PH/OMCL (08) 89 R

VALIDATION OF COMPUTERISED SYSTEMS

ANNEX 3: VALIDATION OF COMPUTERS AS PART OF TEST EQUIPMENT

Full document title and reference	Validation of Computerised Systems Annex 3: Validation of computers as part of test equipment PA/PH/OMCL (08) 89 R
Document type	Guideline
Legislative basis	-
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Custodian Organisation	The present document was elaborated by the OMCL Network/EDQM of the Council of Europe
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QUALITY ASSURANCE DOCUMENT

PA/PH/OMCL (09) 64 2R

QUALIFICATION OF EQUIPMENT
ANNEX 6: QUALIFICATION OF PISTON PIPETTES

Full document title and reference	Qualification of Equipment Annex 6: Qualification of piston pipettes PA/PH/OMCL (09) 64 2R
Document type	Guideline
Legislative basis	-
Date of first adoption	19th May 2010
Date of original entry into force	1st July 2010
Date of entry into force of revised document	-
Previous titles/other references	-
Custodian Organisation	The present document was elaborated by the OMCL Network/EDQM of the Council of Europe
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CONSIDERATIONS FOR LEVEL I AND II OF EQUIPMENT QUALIFICATION

It is recommended, at Level I of the qualification of pipettes (Selection of instruments and suppliers) to select a manufacturer of pipettes that can certify its compliance with the requirements of EN ISO 8655.

It is recommended, at Level II of the qualification of pipettes (Installation and release for use), to check if all requirements set during the selection of the instrument and supplier are met by the pipette supplier and all necessary aspects are covered in the provided certificate.

FREQUENCY OF CALIBRATION

The recommended minimum calibration frequency is as follows:

- At reception (unless already calibrated by the supplier).
- Once a year during the use of the pipette.
- After any repair or adjustment.

GLOSSARY

The following terms and definitions are extracted from the EN ISO 8655-Part 1, chapter 3: Terms and definitions.

Systematic error ***(accuracy)***

(piston-operated volumetric apparatus) Difference between the dispensed volume and the nominal volume or selected volume of the piston-operated volumetric apparatus.

Random error ***(repeatability)***

(piston-operated volumetric apparatus) Scatter of the dispensed volumes around the mean of the dispensed volumes.

Nominal volume

(piston-operated volumetric apparatus) Volume specified by the manufacturer and used for identification and for indication of the measuring range.

NOTE: for a variable-volume piston-operated volumetric apparatus, the nominal volume corresponds to the maximum volume that can be set by the user and that is specified by the manufacturer.

OMCL Network of the Council of Europe
QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (14) 18 3R

SUB-CONTRACTING OF TESTS

Full document title and reference	Guideline "Sub-Contracting of Tests" *PA/PH/OMCL (14) 18 3R*
Document type	Guideline for the General European OMCL Network (GEON) of the Council of Europe
Legislative basis	Council Directive 2001/83/EC and 2001/82/EC, as amended
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Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
Concerned Network	GEON

OMCL Network of the Council of Europe
QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (14) 39

SUB-CONTRACTOR QUALIFICATION

Full document title and reference	**"Sub-contractor Qualification"** *PA/PH/OMCL (14) 39* Annex I to the Guideline "Sub-Contracting of Tests"
Document type	Guideline for the General European OMCL Network (GEON) of the Council of Europe
Legislative basis	Council Directive 2001/83/EC and 2001/82/EC, as amended
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OMCL Network of the Council of Europe
QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (14) 40

OMCL MODEL CONTRACT FOR SUB-CONTRACTING

Full document title and reference	**"OMCL Model Contract for Sub-contracting"** *PA/PH/OMCL (14) 40* Annex II to the Guideline "Sub-Contracting of Tests"
Document type	Guideline for the General European OMCL Network (GEON) of the Council of Europe
Legislative basis	Council Directive 2001/83/EC and 2001/82/EC, as amended
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QUALITY ASSURANCE DOCUMENT

PA/PH/OMCL (07) 105 DEF

ARCHIVING

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Document type	Guideline
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Ontwikkelingen Ph. Eur.

- Grondstof monografieën
- Product monografieën
- Documenten voor kwaliteitssysteem
- Basis is ISO17025= overeenkomstig met ISO 15189