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Verification of Compendial Procedures acc. to Ph.Eur.

12.07.2023

About us

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Key facts

- 90 chemists, biologists, engineers and laboratory technicians
- Laboratory building completed in 2008, 2’640 m^2 of laboratory floor space
- 1’000 national & international regular clients – from local farmers to big pharma
- Independent: all of Interlabor shares owned by management
- Accredited according to ISO 17025 / GMP certified

Our field of activity

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INTERLABOR – analytics with passion

Pharma
Routine analysis for raw materials / finished products, stability studies, ICHQ3D, cleaning validation

Phytopharmaceuticals
Residuals (pesticides, toxins, heavy metals), microbiological tests

Cosmetics
Microbiological / preservative challenge tests

Food and Dietary supplements
Residuals (pesticides, toxins, heavy metals), microbiological tests, vitamins, mineral elements

Medical devices
Residuals from production (e.g., lubricating oil or abrasives), bioburden, endotoxins

Environment
Airborne germs for indoor air, aldehydes / ketones, micropollutants

Water
Drinking, spring, or mineral water / Pharma and process water

Special analytics
Troubleshooting, leachables & extractables studies, LC-(HR)MS/MS analytics

Validation vs. Verification

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Why either?

- Production of pharmaceutical products worldwide →comparability of quality required
- Ultimate goal / responsibility: ensure patient safety

Validation

- Non-compendial methods
- Compendial methods applied for non-compendial products
- Usually based on ICH Q2R1 Guideline

Verification

- Public methods: → e.g. Pharmacopoeia, ISO norm, methods published by governmental bodies (e.g. EU, FDA) [1]
- Validated methods of analytical test kits (e.g. ELISA test)

[1] SAS-Leitfaden 324dw, 2017-11, Rev. 03

Verification: Literature

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Literature

- USP-NF <1226>: Verfication of compendial procedures, official as of 01-Dec-2019
- Ph.Eur. 01/2023: 52600 – Implementation of pharmacopeial procedures
- EDQM, “Examples of implementation of pharmacopeial procedures according to chapter 5.26 “Implementation of pharmacopeial procedures” ”, Edition 2022

Verification: USP vs. Ph.Eur.

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Similarities

- Compendial methods regarded as validated
- Scope = establish suitability of available personnel, equipment, reagents etc. [2]
- Performance prior to implementation of test
- Reduced testing scope compared to validation → assessment of selected performance characteristics
  - Tests dependent on complexity of analysis and test matrix
  - Extent of implementation work responsibility of user [3]
  - No critical factors identified → no laboratory testing required
- Microbiological tests covered by different chapter (e.g. USP-NF <51>, <61>, <1227> or Ph.Eur. 2.612, 2.6.13)

[2] USP-NF <1226>, official as of 01-Dec-2019

[3] Ph.Eur. 01/2023: 52600

Verification: USP vs. Ph.Eur.

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Differences

USP	Ph.Eur.
Stability of sample / standard preparation = responsibility of user	n/a
No verification for • routinely performed basic compendial procedures (LoD) • wet chemical tests (acid value) • simple instrumental test (pH)	Assessment case-by-case
Production route of test matrix taken into account	n/a
n/a	Verification parameter = sensitivity instead of DL / QL (verify lower range limit)

Verification – How to proceed

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Ph.Eur. 01/2023: 52600

- Step 1 – assessment for factors impacting performance of test
- Step 2 – determine APPCs (analytical procedure performance characteristics), acceptance criteria → verification plan; perform experiments
- Step 3 – re-evaluation in case of monograph update

Intended use / APPCs	Identification	Testing for impurities		Assay - content/potency - dissolution (measurement only)	Other quantitative tests
		Limit test	Quantitative test		
Accuracy	○	○	○	◗	◗
Precision					
- Repeatability	○	○	●	●	●
- Intermediate precision	○	○	◗	◗	◗
Specificity/Selectivity	◗	●	●	●	◗
Sensitivity	○	●	●	○	◗
Linearity	○	○	○	◗	◗
Range	○	○	○	◗	◗
Robustness	○	○	◗	◗	◗

Verification – Examples

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Example from the lab – Ph.Eur. 07/2019:1235

ASSAY

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

Injection: test solution and reference solution (a).

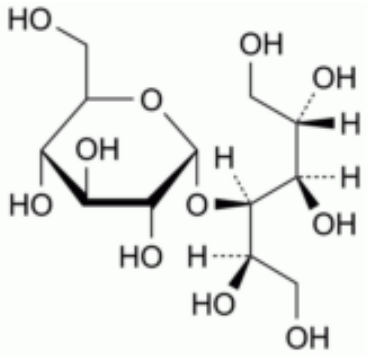
Calculate the percentage content of $C_{12}H_{24}O_{11}$ taking into account the assigned content of maltitol CRS.

- Isocratic chromatography
- Mobile phase: water
- Sample dissolved and diluted in water

MALTITOL

Maltitolum

- Step 1 – assessment of critical factors
  - sample → specificity / selectivity
  - sample preparation → no impact
  - reagents → no impact
  - lab equipment→ basic equipment → no impact on test
    → LC with RI detector → precision, SST
    → column →specificity / selectivity
  - lab conditions → no impact



Verification – Examples

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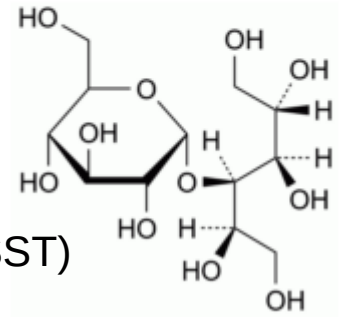
Example from the lab – Ph.Eur. 07/2019:1235

MALTITOL

Maltitolum



- Assay by LC-RID

- Step 2 – verification parameters
  - Specificity / selectivity
    → selectivity blank, reference and sample solution
  - Precision
    → system repeatability (repeat injection of reference solution, SST)
    → repeatability (recommened acc. to Ph.Eur. 5.26)

- Step 2 – acceptance criteria
  - Selectivity / specificity → no interference in blank @ RT of analyte
  - Precision → RSD (n = 6) ≤ 0.7 %
  - System repeatability → SST: RSD (n = 6) ≤ 0.85 %, peak symmetry 0.8 – 1.8
  - Additional: mean value precision experiment in specification (98.0 – 102.0 %)

Verification – Examples

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Example from the lab – Ph.Eur. 01/2017:1647, Identification B

B. Thin-layer chromatography (2.2.27).

Test solution. Dissolve 10 mg of the substance to be examined in water R and dilute to 1 mL with the same solvent.

Reference solution. Dissolve 10 mg of lactobionic acid CRS in water R and dilute to 1 mL with the same solvent.

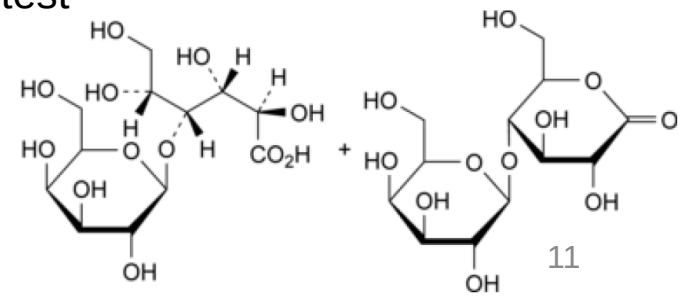
Plate: TLC silica gel plate R.

Mobile phase: concentrated ammonia R1, ethyl acetate R, water R, methanol R (2:2:2:4 *V/V/V/V*).

- Step 1 – assessment of critical factors
  - sample → specificity / selectivity
  - sample preparation → no impact
  - reagents → no impact
  - lab equipment→ basic equipment → no impact on test
  - lab conditions → specificity / selectivity

LACTOBIONIC ACID

Acidum lactobionicum



Verification – Examples

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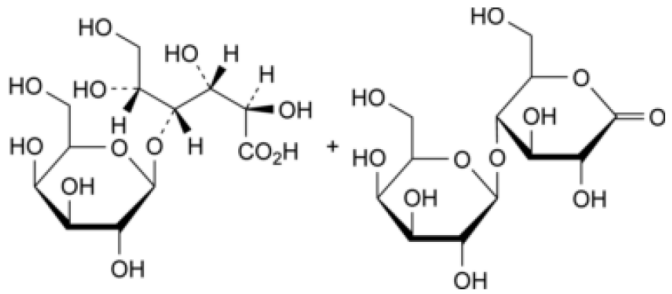
Plate: TLC silica gel plate R.

Mobile phase: concentrated ammonia R1, ethyl acetate R, water R, methanol R (2:2:2:4 *V/V/V/V*).

- Step 2 – verification parameters
  - Specificity / selectivity
    → blank, reference and sample solution
- Step 2 – acceptance criteria
  - Selectivity / specificity → all expected spots present, no unexpected spots in blank

LACTOBIONIC ACID

Acidum lactobionicum



Verification – Examples

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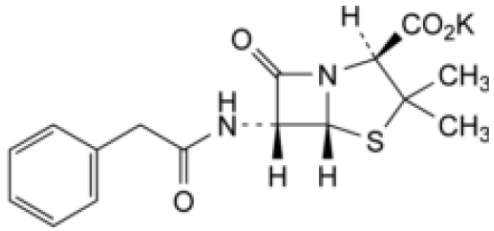
Example from EDQM Guidance document [4] – Ph.Eur. 07/2017:0113

- Assay by LC-UV
  - Isocratic chromatography
  - Mobile phase: phosphate buffer, water, methanol
  - Sample dissolved and diluted in water
  - All solution to be prepared immediately before use

BENZYLPENICILLIN POTASSIUM

Benzylpenicillinum kalicum



- Step 1 – assessment of critical factors
  - sample → Specificity / selectivity
  - sample preparation → Stability of solutions
  - reagents → no impact on test
  - lab equipment→ basic equipment → no impact on test
    → LC with UV detector → linearity, precision
  - lab conditions → no impact

[4] EDQM, "Examples of implementation of pharmacopeial procedures according to chapter 5.26", Edition 2022

Verification – Examples

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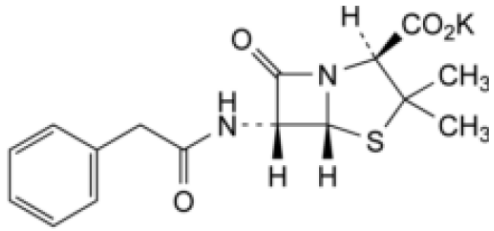
Example from EDQM Guidance document [4] – Ph.Eur. 07/2017:0113

- Assay by LC-UV

BENZYLPENICILLIN POTASSIUM

Benzylpenicillinum kalicum



- Step 2 – verification parameters
  - Specificity / selectivity
    → symmetry factor reference solution (SST)
    → selectivity blank, reference and sample solution
  - Stability of solutions
    → tested during validation (by EDQM)
  - Linearity
    → linearity of detector range (instrument qualification)
  - Precision
    → system repeatability (repeat injection of reference solution, SST)
    → repeatability (recommened acc. to Ph.Eur. 5.26)

[4] EDQM, “Examples of implementation of pharmacopeial procedures according to chapter 2.26”, Edition 2022

Thank you

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- In case of questions:
  - Visit www.interlabor.ch/en/
  - Contact lydia.stucki@interlabor.ch for issues related to verification
  - Contact martina.lingg@interlabor.ch for other inquiries
  - Publication by Interlabor: https://interlabor.ch/en/news-detail/validation-of-methods-but-the-right-way