THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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Use of RS for impurity control

System suitability, peak identification and quantification

2019 Training Session
"The European Pharmacopoeia"
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EDQM Laboratory Department

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SYSTEM SUITABILITY

Technical guide for the elaboration of monographs (7th edition – 2015)

II.5.8.2.a RELATED SUBSTANCES – LC – System suitability criteria

In-situ degradation … offers an alternative approach to define the suitability of the system … to produce decomposition products, the peaks of which can be used to determine a resolution or a peak-to-valley ratio. This may be a useful approach to avoid the use of impurity **reference standards**.

The use of a spiked or impure substance requires procurement of sufficient material to establish the **reference substance** used and in the future, replacement of the system suitability test material with material exhibiting the same characteristics.

SYSTEM SUITABILITY

- **Parameters that are assessed**
  - → selectivity (resolution, peak-to-valley ratio)
  - → repeatability
  - → sensitivity
  - → similarity to chromatogram of RS
- **RS strategy**
  - → nature/composition of RS is key (integral part of system suitability test/validation)
  - → impurities of interest at appropriate level, especially for peak-to-valley ratio
  - → alternative to RS: commercial reagent or *in situ* degradation (*cave* impact)
  - → sometimes also used for peak identification

SYSTEM SUITABILITY

- **RS types**

Type of RS	Pros	Cons
Single substance	Stability Concentration easily controlled	May result in high number of RS
Mixture (normal production batch)	Representative of what user observes	RS batch continuity Peak saturation for API
Mixture (compounded)	Concentration controlled Batch continuity	Stability may be compromised More laborious Not always feasible

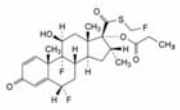
SYSTEM SUITABILITY

- **Example single substance RS**

01/2016:1750

FLUTICASONE PROPIONATE

Fluticasoni propionas



$C_{25}H_{31}F_3O_5S$ [80474-14-2] M_r 500.6

Related substances. Liquid chromatography (*2.2.29*).

Reference solution (a). Dissolve 1 mg of *fluticasone impurity D CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 25.0 mL with the test solution.

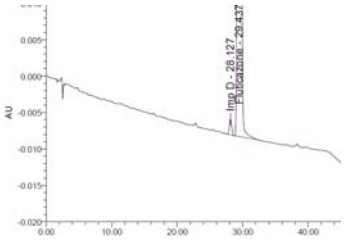
Identification of impurities: use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D; use the chromatogram supplied with *fluticasone*

System suitability: reference solution (a):

– *resolution*: minimum 1.5 between the peaks due to impurity D and fluticasone propionate.

Limits:

– *impurities D, G*: for each impurity, maximum 0.3 per cent;



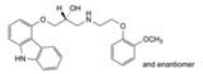
SYSTEM SUITABILITY

- **Example mixture RS (normal production batch)**

04/2012:1745
corrected 8.0

CARVEDILOL

Carvedilolum



$C_{24}H_{26}N_2O_4$
[72956-09-3]

M, 406.5

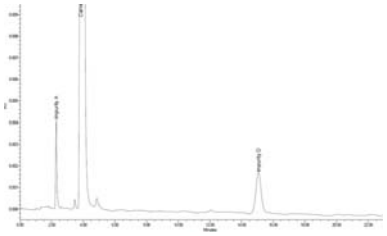
Related substances. Liquid chromatography (*2.2.29*).

Reference solution (c). Dissolve 5 mg of *carvedilol for system suitability CRS* (containing impurities A and D) in the mobile phase and dilute to 50.0 mL with the mobile phase.

Identification of impurities: use the chromatogram supplied with *carvedilol for system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and D; use the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

System suitability:
- *resolution*: minimum 3.5 between the peaks due to impurity A and carvedilol in the chromatogram obtained with reference solution (c);

Limits:
- *correction factor*: for the calculation of content, multiply the peak area of impurity A by 2.0;
- *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *impurity D*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);



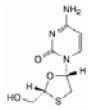
SYSTEM SUITABILITY

- **Example mixture RS (compounded)**

01/2017:2217

LAMIVUDINE

Lamivudinum



$C_8H_{11}N_3O_3S$
[134678-17-4]

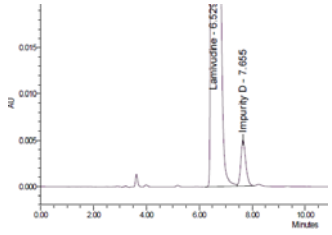
M, 229.3

Enantiomeric purity. Liquid chromatography (*2.2.29*): use the normalisation procedure.

Reference solution. Dissolve the contents of a vial of *lamivudine for system suitability 2 CRS* (containing impurity D) in 1.0 mL of *water R*.

System suitability: reference solution:
- *peak-to-valley-ratio*: minimum 15, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to lamivudine.

Limit:
- *impurity D*: maximum 0.3 per cent.



PEAK IDENTIFICATION

Technical guide for the elaboration of monographs (7th edition – 2015)

II.5.8. RELATED SUBSTANCES

Monographs should provide a reliable means of locating all specified impurities on the chromatogram. Identification of unspecified impurities is necessary if a correction factor is to be applied. Peaks may be located using:

- a **reference standard** for each impurity;
- a **reference standard** of the substance to be examined containing some or all of the specified impurities, provided with a chromatogram.

Location by relative retention is not generally considered sufficient for pharmacopoeial purposes, notably for gradient elution.

PEAK IDENTIFICATION

- **RS strategy**
  - → nature/composition of RS is less critical, compared to system suitability
  - → impurities of interest at detectable levels
  - → alternative to RS: commercial reagent or *in situ* degradation (more than for system suitability)
  - → types of RS: cfr. system suitability
  - → impurities are specified; therefore, normal production batches expected to be suitable
  - → a chromatogram is often supplied in the RS leaflet

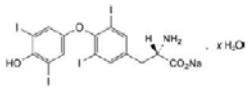
PEAK IDENTIFICATION

- **Example mixture RS (normal production batch)**

01/2013:0401

LEVOTHYROXINE SODIUM

Levothyroxinum natricum



$C_{15}H_{10}I_4NNaO_4xH_2O$ ($x \approx 5$) M_r 799 (anhydrous substance)
[25416-65-3]

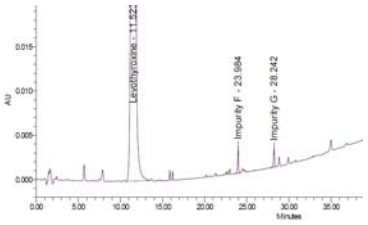
Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Reference solution (d). Dissolve 2.0 mg of *levothyroxine for peak identification CRS* (containing impurities F and G) in 10.0 mL of the solvent mixture and sonicate for 10 min.

System suitability: reference solution (a):
- *resolution*: minimum 5.0 between the peaks due to impurity A and levothyroxine.

Identification of impurities: use the chromatogram supplied with *levothyroxine for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities F and G.

Limits:
- *impurity F*: not more than 5 times the area of the peak due to levothyroxine in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *impurity G*: not more than 3 times the area of the peak due to levothyroxine in the chromatogram obtained with reference solution (b) (0.3 per cent);



QUANTIFICATION

Technical guide for the elaboration of monographs (7th edition – 2015)

II.5.8. RELATED SUBSTANCES

External standard. A dilution of the test solution/substance to be examined is used, unless there is a large difference in the detector response of a specified (or exceptionally an unspecified) impurity that necessitates the use of a specific external standard, which may be:

- a solution of the impurity, normally in form of a **reference standard** (preferred option);
- a solution of the substance to be examined containing a known amount of the impurity.

QUANTIFICATION

- **RS strategy**
  - → purity of RS is critical:
    - * ≥ 95.0 % (preferred) no content assigned (considered 100 % pure)
    - * < 95.0 % content is assigned and given in RS leaflet
  - → salt form has impact on use
  - → alternative to RS: use of a commercial reagent may be considered, if available sufficiently pure and well defined in corresponding Ph.Eur. Chapter
  - → types of RS: single substance RS only
  - → higher amount of candidate material is required: extensive characterisation and increased amount per vial (sufficient for preparation of two solutions)
  - → sometimes also used for system suitability/peak identification

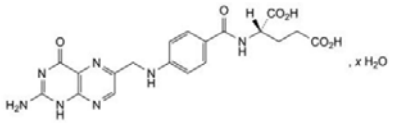
QUANTIFICATION

- **Example**

07/2018:0067
corrected 10.0

FOLIC ACID HYDRATE

Acidum folicum hydricum



$C_{19}H_{19}N_7O_6,xH_2O$ M_r 441.4 (anhydrous substance)
Anhydrous folic acid: [59-30-3]

Related substances. Liquid chromatography (*2.2.29*).

Reference solution (e). Dissolve 4.0 mg of *folic acid impurity D CRS* in solution A and dilute to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Calculation of percentage contents:
- for impurity A, use the concentration of impurity A in reference solution (d);
- for impurity D, use the concentration of impurity D in reference solution (e);
- for impurities other than A and D, use the concentration of folic acid hydrate in reference solution (c).

Limits:
- *impurity D*: maximum 0.4 per cent;

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