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Use of RS for finished products
Identification, assay, related substances and dissolution test

2019 Training Session
"The European Pharmacopoeia"
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GENERAL CONSIDERATIONS

- **Specific challenges of RS strategy for finished product (FP) monographs**
  - → experience being gathered to develop guiding principles
  - → privilege use of existing RS portfolio
- **Addition to general RS strategy principles for API monographs**
  - → new RS in FP monographs: apply existing general principles
  - → use (or not) of existing RS in FP monographs: apply specific FP principles
- **Use existing RS where possible**
  - → benefits for users and EDQM
  - → assuming viability as far as amount per vial, stock, quality attributes (e.g. assigned content)
  - → avoid upgrade of use of existing RS from qualitative to quantitative (describe new RS)

IDENTIFICATION

It does not depend on the method

- Use existing substance RS

(also if method is different)

- Identity already certified

(hence, suitable)

07/2018:2938

RALTEGRAVIR TABLETS

Raltegraviri compressi

IDENTIFICATION

Carry out either tests A, B or tests B, C.

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 in the range of 190-400 nm.

Results: the UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

Reference solution (a). Dissolve 22.0 mg of *raltegravir potassium CRS* in the solvent mixture and dilute to 200.0 mL with the solvent mixture.

ASSAY

RS strategy depends on the assay and related substances methods

- Same methods as substance's monograph

  Use existing assay RS with its assigned content

- Different methods from substance's monograph (assay and/or related substances)

  Compare selectivity:

✓Similar	Use existing assay RS and its assigned content
✓Not similar + low impact	Use existing assay RS and its assigned content
✓Not similar + high impact	Use a different RS
✓Unknown	Risk assessment

  One assay RS = one assigned content!

RELATED SUBSTANCES

RS strategy may depend on the method

- RS presented as mixtures (system suitability / peak identification)

  → no change in composition of existing RS

  → specific, additional related substances for FP (degradation products): separate RS

  → same related substances in API and FP monograph: use existing RS

* identical methods	use existing chromatogram in leaflet
* different methods	add new chromatogram in leaflet

- Impurity RS (quantification)

  → existing RS and its assigned content can generally be used for FP monograph, even when methods are different

RELATED SUBSTANCES

RS strategy may depend on the method

- RS strategy for FP-specific impurities
  - → impurities not specified in API monograph but needed in FP monograph (degradation products)
  - → dirty batch of API normally not an option (conceptual difference)
  - → explore *in situ* generation of degradation products
  - → if not feasible, try to procure/establish individual degradation products

07/2018:2938

RALTEGRAVIR TABLETS

Raltegraviri compressi

Reference solution (c). Dissolve 2 mg of *raltegravir impurity E CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the test solution.

Reference solution (d). In order to prepare impurities C and D *in situ*, dissolve 20 mg of *raltegravir potassium R* in a 40 g/L solution of *sodium hydroxide R* and dilute to 10 mL with the same solvent. Stir the solution for 2 h at room temperature. To 5 mL of the solution add 5 mL of a 103 g/L solution of *hydrochloric acid R* and dilute to 50 mL with the solvent mixture.

DISSOLUTION TEST

RS strategy depends on the method

- UV

  Use of RS not required (technique is aspecific, limits are broad, additional cost)

  Specific absorbance, where possible, is the preferred way

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DRONEDARONE TABLETS

Dronedaroni compressi

Dissolution (2.9.3, Apparatus 2). *Use sinker devices and carry out the test protected from light.*

Analysis. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Measure the absorbances of the solutions at the absorption maximum at 288 nm.

Calculate the amount of dissolved dronedarone ($C_{31}H_{44}N_2O_5S$), expressed as a percentage of the content stated on the label, taking the specific absorbance to be 316.

Note: if an RS cannot be avoided, use dedicated RS (and not assay RS)

DISSOLUTION TEST

RS strategy depends on the method

- LC-UV

  Use assay RS and its assigned content

07/2018:2938

RALTEGRAVIR TABLETS

Raltegraviri compressi

Dissolution (*2.9.3, Apparatus 2*). The tablets comply with the test, unless otherwise justified and authorised. Use sinker devices.

Analysis. Liquid chromatography (*2.2.29*).

Reference solution. Using sonication, dissolve a suitable quantity of *raltegravir potassium CRS* in a suitable quantity of a mixture of 30 volumes of *acetonitrile R*

Calculate the amount of dissolved raltegravir, expressed as a percentage of the content of raltegravir ($C_{20}H_{21}FN_6O_5$) stated on the label, taking into account the assigned content of *raltegravir potassium CRS* and a conversion factor of 0.9210.

Note: assigned content for assay deemed valid for dissolution test unless reason for concern (selectivity difference)

Thank you for your attention

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