PURPOSES AND USES OF EUROPEAN PHARMACOPOEIA REFERENCE STANDARDS

Official European Pharmacopoeia Reference Standards (Ph. Eur. RSs) are essential for the application of the quality control tests described in the Ph. Eur. texts.

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QUALITATIVE USE

RS FOR IDENTIFICATION – MAIN SUBSTANCE

Identification of a substance by spectroscopic techniques such as IR absorption spectrophotometry or NMR spectrometry, or by chromatographic separation techniques (LC, GC, TLC)

Example:
Goserelin for NMR identification CRS

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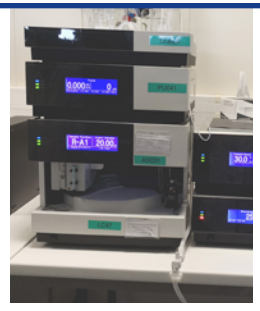

RS FOR PEAK IDENTIFICATION OF IMPURITIES

Identification of impurities in a test for related substances using a liquid chromatographic method (LC)

Example:
Buserelin synthetic peptide

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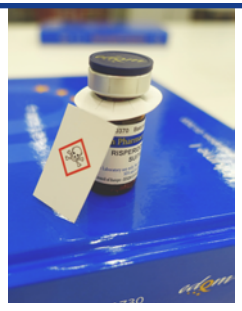

RS FOR SYSTEM SUITABILITY

Verification that a measurement system is operated within the boundaries of its validation scope, often in a test for related substances using a liquid chromatographic method (LC)

Example:
Risperidone for system suitability CRS

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QUANTITATIVE USE

RS FOR PHYSICO-CHEMICAL ASSAY

Quantitative determination of an active pharmaceutical ingredient (API) in an assay by using mostly chromatographic separation techniques (LC, GC)

Example:
Raltegravir potassium CRS

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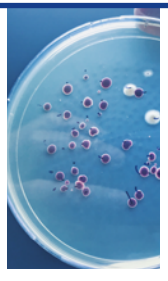

RS FOR MICROBIOLOGICAL ASSAY OF ANTIBIOTICS

Determination of the potency of APIs by comparing the inhibition of growth of sensitive micro-organisms and the corresponding CRS

Example:
Amphotericin B for microbiological assay CRS

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RS USED AS EXTERNAL STANDARD

Quantitative determination of an impurity in a test for related substances by using mostly chromatographic separation techniques (LC, GC)

Example:
Rifamycin B CRS

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RS FOR EQUIPMENT QUALIFICATION

Certified reference material used to qualify equipment according to established quality management system procedures

Example:
Sodium aminosalicylate dihydrate for equipment qualification CRS

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WHO USES THEM?

RS FOR IDENTIFICATION – MAIN SUBSTANCE

Identification of a substance by spectroscopic techniques such as IR absorption spectrophotometry or NMR spectrometry, or by chromatographic separation techniques (LC, GC, TLC)

Example: **Goserelin for NMR identification CRS**

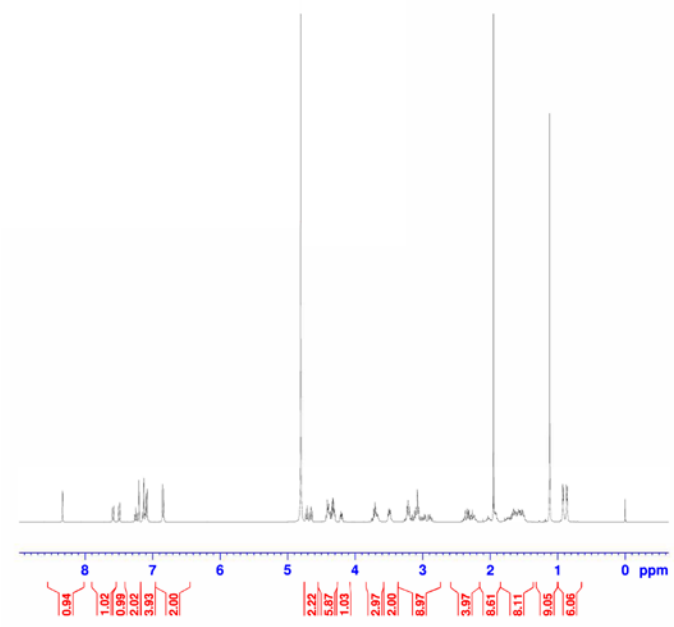
IDENTIFICATION
Carry out either tests A and B or tests B and C.
A. Nuclear magnetic resonance spectrometry (2.2.64).

Preparation: 13 mg/mL solution in *0.2 M deuterated sodium phosphate buffer solution pH 5.0 R* containing 20µg/mL of *deuterated sodium trimethylsilylpropionate R.*

Comparison: 13 mg/mL solution of *goserelin for NMR identification CRS* in *0.2 M deuterated sodium phosphate buffer solution pH 5.0 R* containing 20 µg/mL of *deuterated sodium trimethylsilylpropionate R* (dissolve the contents of a vial of *goserelin for NMR identification CRS* in this solvent to obtain the desired concentration).

Operating conditions:
- *field strength:* minimum 300 MHz;
- *temperature:* 25 °C.

Results: examine the ^{1}H NMR spectrum from 0 ppm to 9 ppm; the ^{1}H NMR spectrum obtained is qualitatively similar to the ^{1}H NMR spectrum obtained with *goserelin for NMR identification CRS.*



^{1}H NMR spectrum of goserelin for NMR identification CRS

RS FOR PEAK IDENTIFICATION OF IMPURITIES

Identification of impurities in a test for related substances using a liquid chromatographic method (LC)

Example: **Buserelin synthetic peptide**

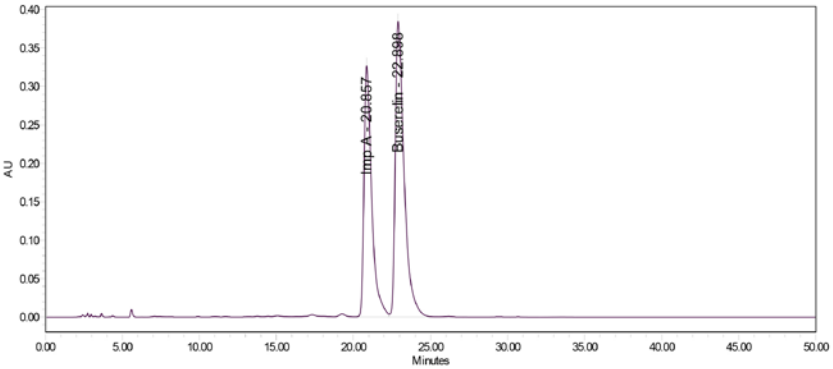
RELATED SUBSTANCES
Liquid chromatography (*2.2.29*).

Test solution. Dissolve 5.0 mg of the substance to be examined in 5.0 mL of the mobile phase.

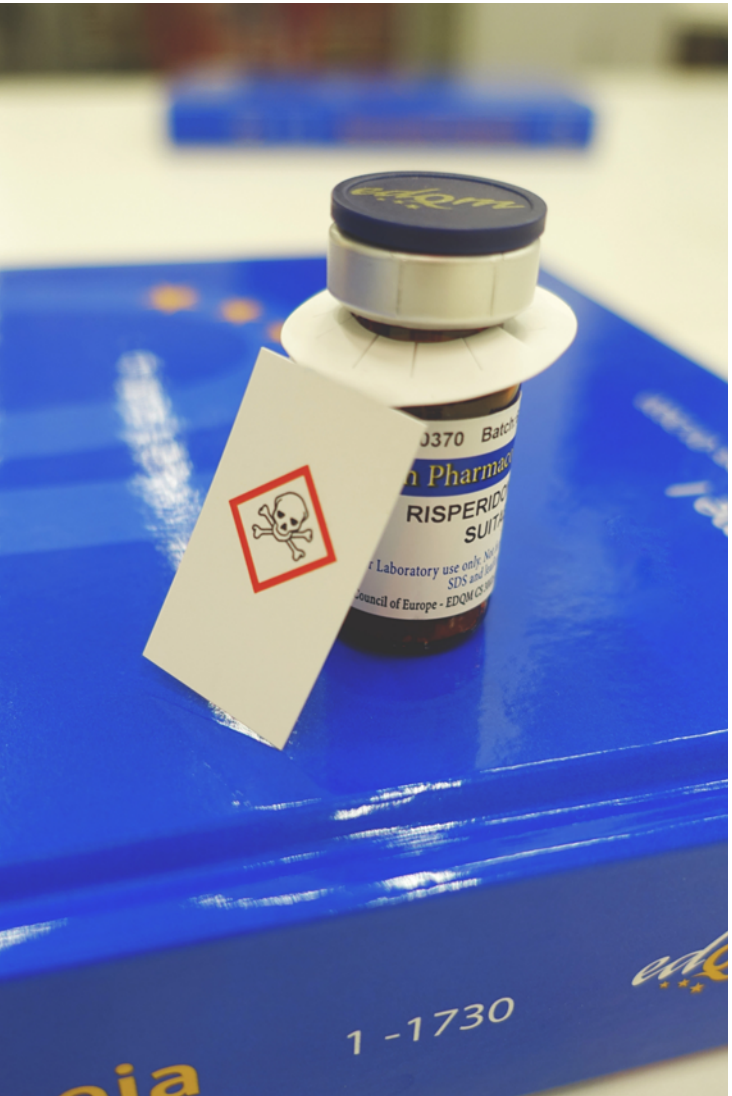
Reference solution (a). Dissolve the contents of a vial of *D-His-buserelin* CRS (impurity A) in the mobile phase. Dilute an appropriate volume of this solution in the mobile phase to obtain a final concentration of 1 mg/mL. Add 1.0 mL of the test solution to 1.0 mL of this solution.

Reference solution (b). Dissolve the contents of a vial of *buserelin CRS* in the mobile phase. Dilute an appropriate volume of this solution in the mobile phase to obtain a final concentration of 1.0 mg/mL.

Reference solution (c). Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase.



Chromatogram obtained with reference solution (a)



RS FOR SYSTEM SUITABILITY

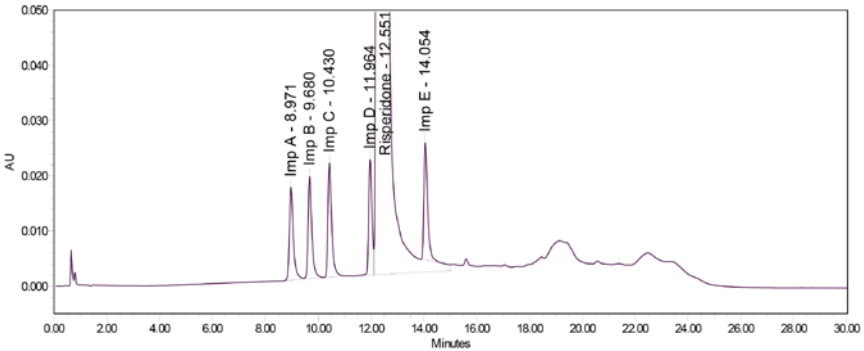
Verification that a measurement system is operated within the boundaries of its validation scope, often in a test for related substances using a liquid chromatographic method (LC)

Example: **Risperidone for system suitability CRS**

SYSTEM SUITABILITY
Reference solution (a):

– the chromatogram obtained is similar to the chromatogram supplied with *risperidone for system suitability CRS;*

– *peak-to-valley ratio:* minimum 1.5, 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 risperidone.



In this example, the system suitability test contains both qualitative and quantitative aspects.

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RS FOR PHYSICO-CHEMICAL ASSAY

Quantitative determination of an API in an assay by using mostly chromatographic separation techniques (LC, GC)

Example: **Raltegravir potassium CRS**

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 $C_{20}H_{20}FKN_6O_5$ taking into account the assigned content of *raltegravir potassium CRS.*


INFORMATION LEAFLET Ph. Eur. Reference Standard

Raltegravir potassium CRS batch 1

The "as is" content of the reference standard is usually assigned by mass balance based on data generated in an inter-laboratory study.

RS FOR MICROBIOLOGICAL ASSAY OF ANTIBIOTICS

Determination of the potency of APIs by comparing the inhibition of growth of sensitive micro-organisms and the corresponding CRS

Example: **Amphotericin B for microbiological assay CRS**

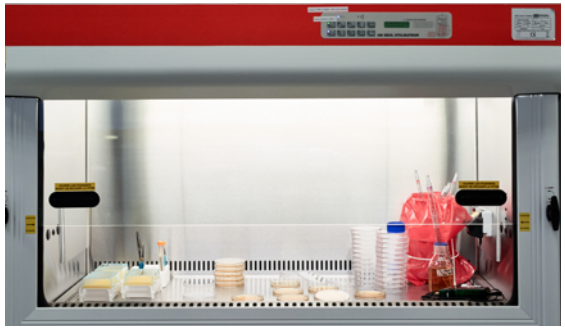


Table 2.7.2.-1 - Diffusion assay

Antibiotic	Reference substance	Solvent to be used in preparing the stock solution	Buffer solution (pH)	Micro-organism	Medium and final pH (± 0.1 pH unit)	Incubation temperature
Amphotericin B	*Amphotericin B for microbiological assay CRS*	*Dimethyl sulfoxide R*	pH 10.5 (0.2 M)	*Saccharomyces cerevisiae* ATCC 9763 IP 1432-83	F - pH 6.1	35-37 °c
Bacitracin zinc	*Bacitracin zinc CRS*	*0.01 M hydrochloric acid*	pH 7.0 (0.05 M)	*Micrococcus luteus* NCTC 7743 CIP 53.160 ATCC 10240	A - pH 7.0	35-39 °c
Bleomycin sulfate	*Bleomycin sulfate CRS*	*Water R*	pH 6.8 (0.1 M)	*Mycobacterium smegmatis* ATCC 607	G - pH 7.0	35-37 °c

RS USED AS EXTERNAL STANDARD

Quantitative determination of an impurity in a test for related substances by using mostly chromatographic separation techniques (LC, GC)

Example: **Rifamycin B CRS**

INFORMATION LEAFLET Ph. Eur. Reference Standard

Rifamycin B CRS batch 4

Unit Quantity: ca 25 mg

1. **Identification**
Catalogue code: R0900000

2. **Scientific information**

2.1 Intended use
Reference Standard for laboratory tests as prescribed in the European Pharmacopoeia only.
Established for use with the monograph(s): 0432.

2.2 Analytical information related to intended use, when applicable
The "as is" content is : **86.0% of $C_{39}H_{49}NO_{14}$**

Rifamycin B CRS 4 is supplied as the free acid.

Prepare reference solution (a) in the following way:
Reference solution (a): Dissolve 10.0 mg of rifamycin B CRS (impurity A) and 40.0 mg of rifamycin S CRS (impurity B) in mobile phase A [instead of the solvent mixture] and dilute to 200.0 mL with mobile phase A [instead of the solvent mixture]. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase A [instead of the solvent mixture].

2.3 Uncertainty of the assigned value, when applicable
The uncertainty of the assigned value is not stated since it is considered to be negligible in relation to the defined limits of the method specific assays for which the reference standard is used. Please also refer to Ph. Eur. chapter 5.12.

2.4 Validity
Ph. Eur. RS are periodically tested to ensure their continuous fitness for purpose. For each valid Ph. Eur. RS, a Batch Validity Statement at the time of use can be downloaded and printed from the EDQM website (Reference Standards Database).

2.5 Instructions for use
The container should not be opened until required for use. Allow the closed container to equilibrate at ambient temperature before opening to avoid uptake of moisture. Use "as is". Do not dry/decarbate before use. Ph. Eur. RS are for immediate use. Once the container has been opened, its entire content must be used immediately. Any further storage and re-use are not warranted.

3. **Storage conditions**
In the original container at +5°C ± 3°C, protected from light. Re-instate promptly upon receipt.

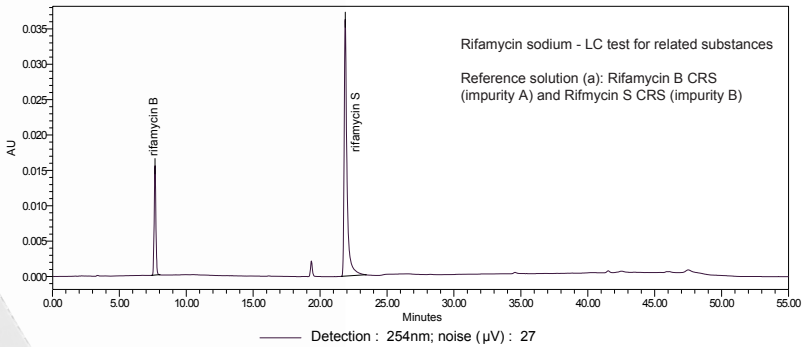
4. **Safety**
For scientific research, development and analysis only. Handle in accordance with good occupational hygiene, safety and laboratory practices and take precautions to avoid exposure. More information is available at the EDQM website (Reference Standards Database); Safety Data Sheet for hazardous chemicals and Safety Data Statement for other materials.

5. **Shipping conditions**
Each Ph. Eur. RS is shipped under conditions that preserve its suitability for use and comply with the relevant regulations. For more details see EDQM website (Reference Standards Database).

6. **Warranties, Liabilities and responsibility**
- Safety
In the event of any safety concerns, please read carefully the safety data sheets or safety data statements available for each product. It is for Purchasers to determine independently the risks associated with the items and

Signed on: 18/10/2019
FORM/597 Rev. 03 (14401/2019)

Rev.3 1/2



RS FOR EQUIPMENT QUALIFICATION

Certified reference material used to qualify equipment according to established quality management system procedures

Example: **Sodium aminosalicylate dihydrate for equipment qualification CRS**

SUGGESTED ACCEPTANCE CRITERIA

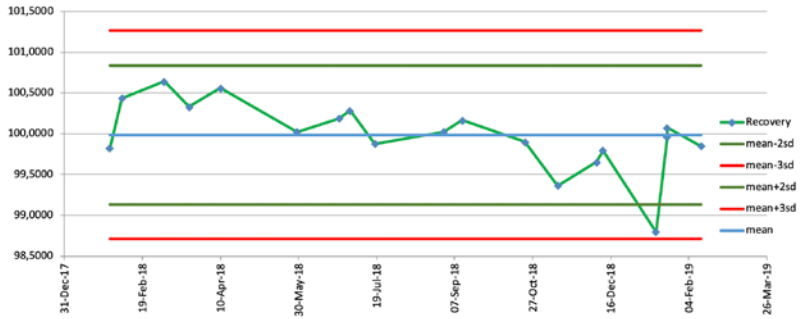
Taking into account inter-laboratory standard deviation as well as the mean intra-laboratory standard deviation obtained in the inter-laboratory study for the value assignment, the result of a measurement performed (following the above experimental conditions) is considered acceptable if the mean of 3 replicate determinations falls within the following limits:

Loss on drying (2.2.32.):
167.2 mg/g to 172.0 mg/g

Semi-micro determination of water (2.5.12.):
165.4 mg/g to 177.8 mg/g

Micro determination of water (2.5.32) – liquid sample introduction:
167.3 mg/g to 173.7 mg/g

It is understood that a laboratory may apply a different approach to set acceptance criteria.



Equipment control chart (example)

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EUROPEAN PHARMACOPOEIA REFERENCE STANDARDS – WHO USES THEM?

QUALITY CONTROL LABORATORIES OF PHARMACEUTICAL COMPANIES

QUALITY CONTROL LABORATORIES OF MANUFACTURERS OF SUBSTANCES FOR PHARMACEUTICAL USE
(E.G. ACTIVE PHARMACEUTICAL INGREDIENTS, EXCIPIENTS, CONTAINERS, CLOSURES, HERBALS, BIOLOGICALS)

OFFICIAL MEDICINES CONTROL LABORATORIES (OMCLS)

COMMUNITY, ARMY OR HOSPITAL PHARMACIES

ACADEMIA