Intended use of Reference Standards: key role of compendial RS in quality measurements

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PHARMACEUTICAL REFERENCE STANDARDS - INTENDED USE

#1 Reference Standards are part of analytical procedures

Sources:

ICH Q2 R1 Guideline, Glossary

FDA *Analytical Procedures and Methods Validation for Drugs and Biologics,* Guidance for Industry, IV.B, V July 2015

#2 Analytical procedures must be validated

Sources:

ICH Q2 R1 Guideline

EU GMP 6.15

#3 Analytical Procedure Validation: demonstration of suitability for the intended use

Source: ICH Q2 R1 Guideline

PHARMACEUTICAL REFERENCE STANDARDS - INTENDED USE

Reference Standards must be suitable for their intended use

Sources:

Ph. Eur. Chapter 5.12. paragraph 3

FDA *Analytical Procedures and Methods Validation for Drugs and Biologics,* Guidance for Industry, V July 2015

ISO 17034:2016 3.3

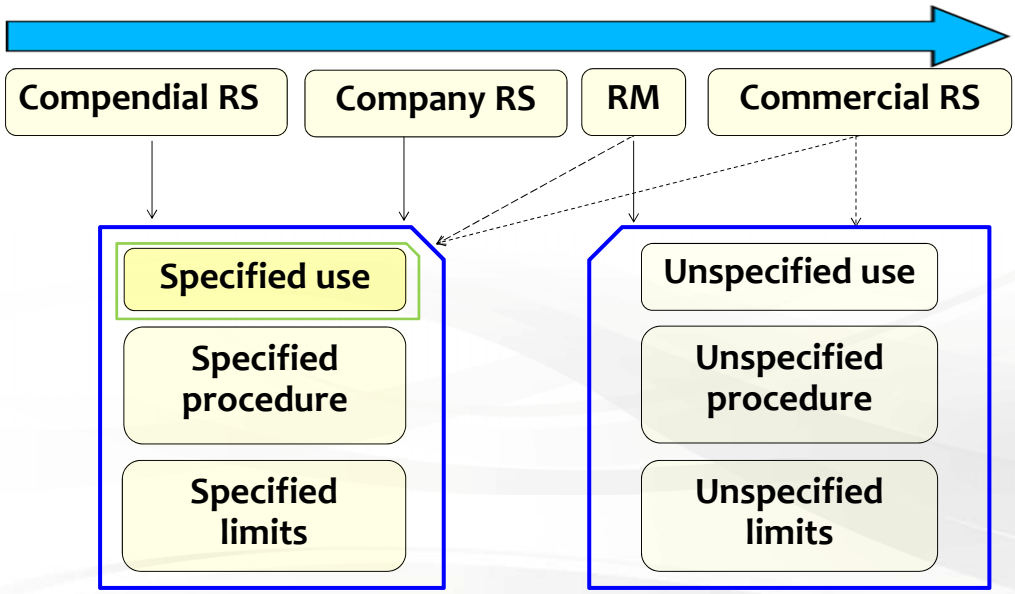
INTENDED USE OF PHARMACEUTICAL REFERENCE STANDARDS

Categories of RS

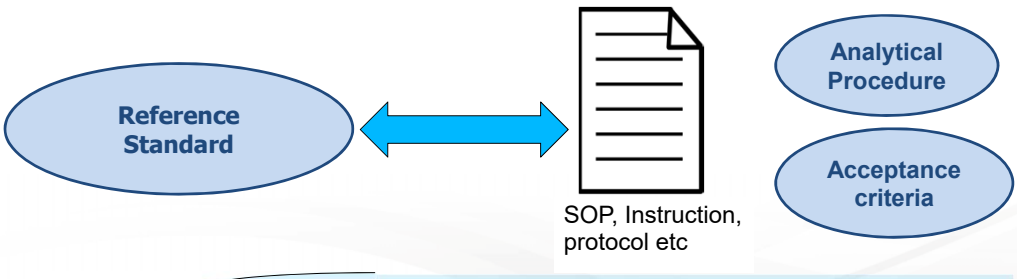
Compendial RS	**Pharmacopoeias (all types)**
International RS	**WHO international standards**
Company RS	**In-house, working, R&D standards**
Commercial RS	**Reagents, chemicals, herbal standards**
Reference materials	**General use**

Types of RS: where they belong

Compendial RS	**Corresponding compendium**
International RS	**WHO report** (ex. biological standardisation)
Company RS	**Company document** (SOP, instruction etc)
Commercial RS	**Info provided to users**
Reference materials	**RM document** (ISO Guide 17034 3.6)

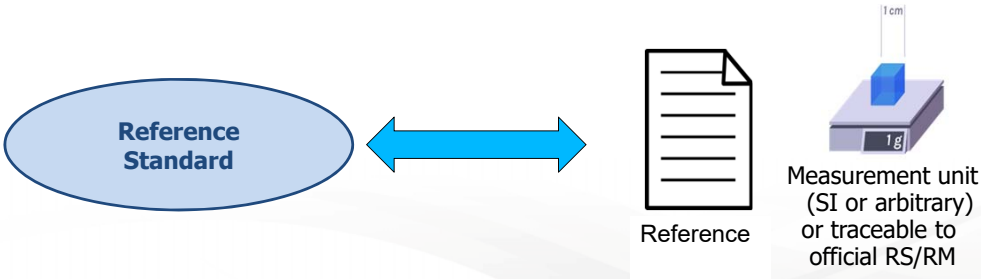


Company Reference Standards



Quality Control
Development (method, product, etc)
Stability studies
Method validation
Method transfer
Creating Working Standards
....

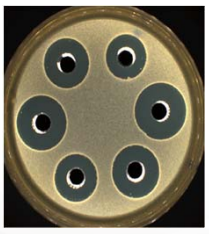
Commercial Reference Standards



Quality Control
Development (method)
Stability studies
Method validation
...

International Reference Standards

WHO Int. Reference Standard



Arbitrary unit

Reference document

Creating Working Standards
Quality Control

Compendial Standards

normally consist of

- documentary standards
  i.e. monographs (general and specific), general chapters;

- physical standards
  i.e. reference standards, reference reagents, reference spectra.

Monographs, chapters

Reference standards

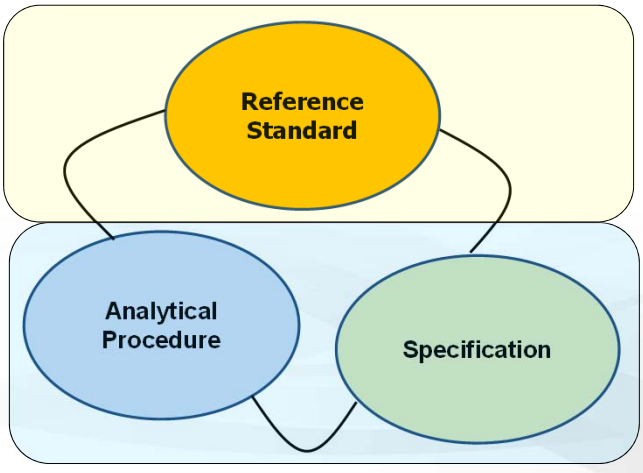
A Ph. Eur. reference standard referred to in a monograph or general chapter represents the official standard that is alone authoritative in case of doubt or dispute.

Ph. Eur. General Chapter 5.12.

Where USP or NF tests or assays call for the use of a USP Reference Standard, only those results obtained using the specified USP Reference Standard are conclusive.

USP–NF General Notices Section 5.80

Compendial Reference Standards



To test and interpret result according to compendium

Compendial standards, what is unique?

For a given test article (substance to be tested), they encompass and link:

- the analytical measurement procedure,
- the analytical benchmark (reference standard)
- the way to interpret the test results (limits).

Compendial RS - intended use

- Identification, Peak identification
- Assay, Potency, External standard
- System suitability / method performance
- Verification of a measurement system

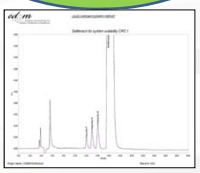
Compendial Reference Standards by purpose

BATCH TESTING

Ex. Assay, Potency, Purity, Identification

VERIFICATION OF SYSTEM SUITABILITY

Ex. in chromatography



VERIFICATION OF A MEASUREMENT INSTRUMENT

Ex. KF equipment

Compendial Reference Standards

- thorough scientific characterisation
- multiple, independent laboratories
- officially approved by an official, authoritative, independent body
- holistic support (leaflet, batch validity statement, helpdesk, training)
- kept in sync with monographs / chapters.

Compendial RS - characterisation and establishment

Suitable for the intended use does not mean *characterised just for the intended use.*

RS for identification
tested against the other sections of the corresponding monograph + non-compendial methods

RS for assay

- **assigned content checked with orthogonal methods**
- **content value (replacement batches) vs previous batch**
- **RS for API suitable (under certain conditions) for finished products.**

Ph. Eur. General Chapter 5.12. Reference Standards

A European Pharmacopoeia reference standard with an assigned content/potency for use in the assay of a substance for pharmaceutical use (…) **may be suitable to determine the content/potency of that substance in a pharmaceutical preparation** provided all of the following conditions are fulfilled:

- the chromatographic assay method described in the active substance monograph is employed;
- the applicability of the method to the particular pharmaceutical preparation (absence of interference) is verified by the user;
- any pre-treatment of the sample (e.g. extraction, filtration) is validated for the particular pharmaceutical preparation.

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – quality, safety and efficacy

Brussels, 28 March 2014

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Part 1
Chapter 6: Quality Control

6.20
Reference standards should be established as suitable for their intended use. Their qualification and certification as such should be clearly stated and documented.

Whenever compendial reference standards from an official source exist, these should preferably be used as primary reference standards unless fully justified

the use of secondary standards is permitted once their traceability to primary standards has been demonstrated and is documented.

Reference Standards in general

- essential part of analytical procedures;
- established for their intended use;
- intended use more or less well-defined depending on the type of RS.

Compendial Reference Standards

- essential part of compendial standards;
- underpin compendial analytical procedures and specification limits
- different role than company RS, commercial RS, RMs and WHO IS
- extensively characterised, using state-of-the-art technology
- ensure ongoing regulatory compliance and risk minimisation.

Thank you very much for your attention.

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Welcome

Empowering a healthy tomorrow

Reference Standards and Traceability (to documentary standards and secondary standards)

Ravi Reddy
Sr. Director, Reference Standards Evaluation

March 13, 2019

Agenda

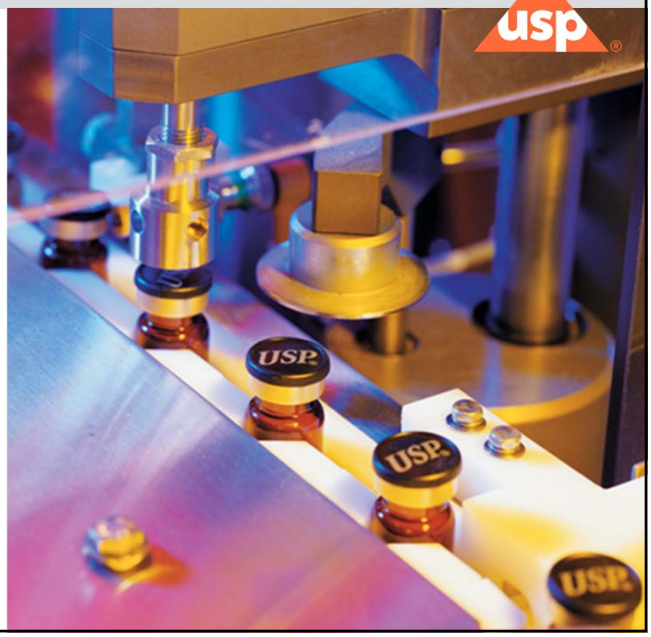
- USP Reference Standards: definition, history and types
- Development of USP Reference Standards
- Reference Standards traceability

1

USP Reference Standards

USP Reference Standards: definition

- Highly characterized specimens of
  - Drug substances
  - Excipients
  - Impurities
  - Biologics
  - Food Ingredients
  - Dietary Supplements
  - Performance Test Tablets



USP Reference Standards

Reference Standards are used as an important part of measurements and establishing comparability and traceability

- Method Validation
- Method Verification
- Method Uncertainty
- Calibration
- Quality Control
- Quality Assurance

USP Reference Standards

- Rigorously tested within USP Labs, Industry, and Government Labs
  - Controlled by internal SOPs, manuals and quality systems
  - Intended for use in Compendial Methods
  - Users are responsible for determining the suitability of use for non-USP compendial use

USP Reference Standards: History

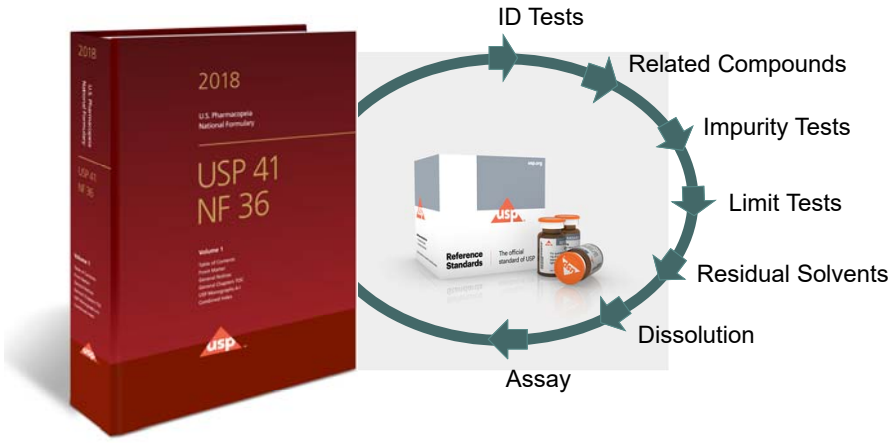
- USP Reference Standards History
  - USP X–1926: First mention of future availability
  - USP XI–1936: First list of USP Reference Standards (6 standards)
  - Over 80 years of history and experience
  - Less than 200 in 1965 to more than 3600 in 2018
  - Several hundred standards are at various stages of development

USP Reference Standards: Types

- Quantitative
  - Assay - Generally > 99.5 % HPLC Purity
  - Impurities - Generally > 98 % HPLC Purity
- Qualitative
  - ID, Resolution, peak identification
  - Chromatographic Purity – Generally > 95%
- Special category
  - Melting point, particle size, dissolution verification tablets
- Non USP Compendial Use
  - Not required for use in compendial methods
  - Service to industry

USP Reference Standards

Directly linked to monographs



2 Development of USP Reference Standards

USP Reference Standards

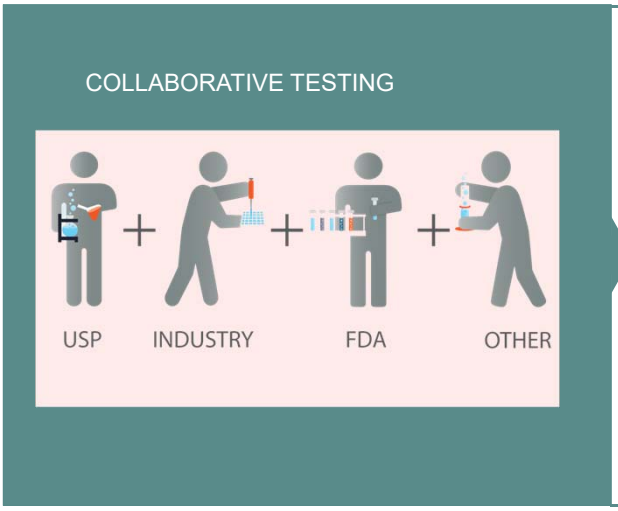
How does the Reference Standards development start?

- Development of a Reference Standard is triggered by a new/revised monograph or inventory depletion
  - Reference Standards are developed as required by the compendial methods
- Types of lots
  - F-Lots: Very first lot of Reference Standard linked to New and Revised Monographs
  - Replacement lots are developed when current lot is depleted
  - Continuation lots
- New Uses for existing Reference Standards
  - Example Qualitative to Quantitative

Development of a USP Reference Standard

High level process

Development of a USP Reference Standard



- Spectroscopic (IR, Raman, UV/Vis)
- Titration or Elemental Analysis (CHN)
- Water or Volatiles (KF or LOD)
- ROI/Sufated Ash
- NMR
- MS
- Chromatographic (HPLC, GC, TLC)
- Thermal (TGA, DSC)
- DVS
- Other techniques as needed

3 Reference Standards traceability

USP Assay Reference Standards traceability

- Traceable to USP monograph methods, particularly API methods and as applicable General Chapters and drug product methods
  - Assigned value on the label is based on mass balance approach for most Reference Standards
- Mass Balance takes into account Impurities, Water, Residual Solvents, Loss on Drying, Inorganic Impurities (Sulfated ash / Residue on Ignition)
- Organic Impurities content used in the mass balance value may also be traceable to methods other than compendial methods

USP Assay Reference Standards traceability

- Some testing for the proposed lots is traceable to the current / previous lots of USP RS for the purpose of confirmation
  - Other compendial standards, e.g. EP Chemical Reference Substances are used
- Mass balance and assay differences are further investigated by orthogonal methods such as qNMR
- Physical traceability, particularly if required by the monograph, is to the polymorph by XRPD

USP Impurity Reference Standards traceability

- Impurity Standards Traceability: Quantitative and Qualitative
- API Methods with modification to concentrations and Organic Impurities HPLC parameters
- Qualitative Standards: No label value is assigned
- Quantitative Impurities Standards are traceable to API methods
- As applicable, current / previous lots of standards are also used
- If Quantitative Impurity Standards are provided as mixtures, for example, x% of Impurity in API or inactive ingredients
  - Label Value is provided based on the assay against pure Reference Standard

USP Antibiotic Reference Standard traceability

- Applicable only to antibiotics Reference Standard with USP <81> testing
- The assigned value is in USP Units against International Standard, when available
- The assigned value is traceable to the current lot International Standard (WHO)
- If an International Standard is not available then testing is performed against the current lot of the USP RS
- Study is conducted using International Standard (WHO) and Current Lot of USP RS
- If available other compendial standards, for example EP, are also used in the study
  - Example

Standard	Mean (µg/mg)	95% CI
WHO IS	671.2	634.0 – 708.4
EP CRS	670.5	636.8 – 704.1
USP Lot M1J001	668.5	634.0 – 694.0

Secondary standards traceability

- USP Reference Standards as pure chemical substances are qualified as primary standards with assigned value based on a mass balance calculation
- Secondary Standards: Label value is assigned based on the assay (%w/w) testing against a standard whose label value was assigned based on mass balance
  - When necessary, the label value may be assigned by comparison to another material
  - Some USP RS are supplied as mixtures, in which case assignments by mass balance is not possible
  - Certain reference materials are available in very limited quantities
  - Botanical extracts and certain food ingredients contain extraneous materials
  - Solution preparations
  - Solvent mixtures
  - Mixtures are tested against pure substances
  - Pure substances are procured, characterized prior to use

Conclusion

- USP Reference Standards are thoroughly characterized physical materials
  - Characterized using the method beyond the monograph methods, particularly with respect to chemical identification
- USP Reference Standards are traceable to analytical method in the monographs
- USP antibiotic reference standards are traceable to IS Standards, if available
- Secondary Standards, when required, are tested against pure materials with assigned mass balance
- USP Reference Standards are suitable for Compendial Use as per the analytical methods defined in the monograph
  - Any non-compendial use is the responsibility of the user
- USP Develops standards for non-USP Compendial use based on the need and/or industry interest

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Questions

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Reference standards for system suitability

Dr Bart Blanchaert

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Outline

- Scope
- Introduction on SST
- Techniques
  - SST criteria in LC / GC
- Types of RS

Scope

- European Pharmacopoeia reference standard
  - Chemical reference substance (CRS)
  - Herbal reference standard (HRS)
- Techniques
  - Chromatographic separation techniques (2.2.46.)
  - Capillary electrophoresis (2.2.47.)
- Miscellaneous (out of scope)
  - Water: micro determination (2.5.32)
  - Atomic absorption spectrometry (2.2.23)
  - …

System suitability: introduction

- Goal: adequate performance of the system
- System: Several components
  - Equipment → qualified
  - Stationary and mobile phase
  - Environment (temperature)
- RS for system suitability typical for compendial methods
  - Actual conditions may vary
  - Data generated under proper experimental conditions
- No results generated
- Integral part of the method

System suitability: introduction

- Ph. Eur. Chapter 2.2.46.: Chromatographic separation techniques:
  - Criteria for all systems:
    - Peak used for quantification in reference solution : symmetry factor between 0.8 – 1.5
    - Maximal RSD for a series of injections of the reference solution

Table 2.2.46.-1. – *Repeatability requirements*

	Number of individual injections			
	3	4	5	6
***B* (per cent)**	**Maximum permitted relative standard deviation**			
2.0	0.41	0.59	0.73	0.85
2.5	0.52	0.74	0.92	1.06
3.0	0.62	0.89	1.10	1.27

CRS !

    - LOQ (S/N = 10) ≤ disregard limit

System suitability: introduction

- Ph. Eur. Chapter 2.2.46.: Chromatographic separation techniques:
- Throughout the chromatographic procedure→ verification scheme
- Criteria specific for individual monograph
- Adjustment of chromatographic conditions
  - Responsive adjustment
  - Within given tolerances
  - For critical parameters: defined in the monograph

Liquid chromatography: isocratic elution

Composition of the mobile phase: the amount of the minor solvent component may be adjusted by ± 30 per cent relative or ± 2 per cent absolute, whichever is the larger (see example above); no other component is altered by more than 10 per cent absolute.

pH of the aqueous component of the mobile phase: ± 0.2 pH, unless otherwise prescribed, or ± 1.0 pH when non-ionisable substances are to be examined.

Concentration of salts in the buffer component of a mobile phase: ± 10 per cent.

Flow rate: ± 50 per cent; a larger adjustment is acceptable when changing the column dimensions (see the formula below).

Temperature: ± 10 °C, where the operating temperature is specified, unless otherwise prescribed.

Detector wavelength: no adjustment permitted.

Injection volume: may be decreased, provided detection and repeatability of the peak(s) to be determined are satisfactory; no increase permitted.

Techniques

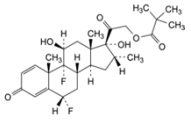
- Thin-layer chromatography (2.2.27)
- Gas chromatography (2.2.28)
- Liquid chromatography (2.2.29)
- Size-exclusion chromatography (2.2.30)

2.2.46

- Capillary electrophoresis (2.2.47)

FLUMETASONE PIVALATE

Flumetasoni pivalas



$C_{31}H_{36}F_2O_6$ [2002-29-1] M_r 494.6

B. Thin-layer chromatography (*2.2.27*).

Reference solution (a). Dissolve 10 mg of *flumetasone pivalate CRS* in *acetone R* and dilute to 10 mL with the same solvent.

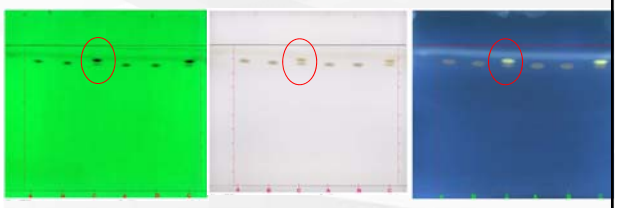
Reference solution (b). Dissolve 10 mg of *desoxycortone acetate CRS* in *acetone R* and dilute to 10 mL with the same solvent. Dilute 5 mL of this solution to 10 mL with reference solution (a).

Techniques

Results B: the principal spot in the chromatogram obtained with the test solution is similar in position, colour in daylight, fluorescence in ultraviolet light at 365 nm and size to the principal spot in the chromatogram obtained with reference solution (a).

System suitability: reference solution (b):

– the chromatogram shows 2 clearly separated spots.



Techniques

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DEXTRAN 1 FOR INJECTION

Dextranum 1 ad iniectabile

Molecular-mass distribution. Size-exclusion chromatography (*2.2.30*).

Test solution. Dissolve 6.0-6.5 mg of the substance to be examined in 1.0 mL of the mobile phase.

Reference solution (a). Dissolve 6.0-6.5 mg of *dextran 1 CRS* in 1.0 mL of the mobile phase.

Reference solution (b). Dissolve the contents of a vial of *isomaltooligosaccharide CRS* in 1 mL of the mobile phase, and mix. This corresponds to approximately 45 µg of isomaltotriose (3 glucose units), approximately 45 µg of isomaltononaose (9 glucose units), and approximately 60 µg of sodium chloride per 100 µL.

Identification of peaks: use the chromatogram obtained with reference solution (b) to identify the peaks due to isomaltotriose, isomaltononaose and sodium chloride.

Determine the peak areas. Disregard any peak due to sodium chloride. Calculate the average relative molecular mass M_w and the amount of the fraction with less than 3 and more than 9 glucose units, of *dextran 1 CRS* and of the substance to be examined, using the following expression:

$$M_w = \sum w_i \times m_i$$

M_w = average molecular mass of the dextran;

m_i = molecular mass of oligosaccharide i;

w_i = weight proportion of oligosaccharide i.

System suitability: the values obtained for *dextran 1 CRS* are within the values stated on the label.

2.2 Analytical information related to intended use

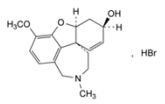
The "as is" content is : **Average molecular mass: 930 - 1000**
Fraction with less than 3 glucose units: 8.0 to 10.5%
Fraction with more than 9 glucose units: 10.0 to 12.5%

Techniques

01/2017:2366
corrected 9.6

GALANTAMINE HYDROBROMIDE

Galantamini hydrobromidum



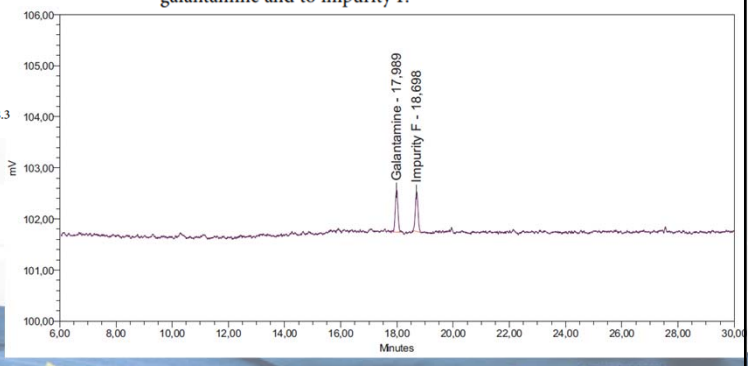
$C_{17}H_{21}BrNO_3$ [1953-04-4] M_r 368.3

Enantiomeric purity for galantamine produced by a synthetic process. Capillary electrophoresis (*2.2.47*). *Prepare the solutions immediately before use.*

Reference solution (a). Dissolve 5 mg of *galantamine racemic mixture CRS* in 10.0 mL of *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*. Filter through a membrane filter (nominal pore size 0.22 µm).

System suitability: reference solution (a):

– *resolution*: minimum 2.5 between the peaks due to galantamine and to impurity F.



SST criteria in LC/GC

- Selectivitiy
  - Resolution
  - Peak-to-valley ratio
  - Baseline separation
- Repeatability of response
- Sensitivity: S/N
- Similarity to reference chromatogram

SST criteria in LC/GC

Resolution (R_s)

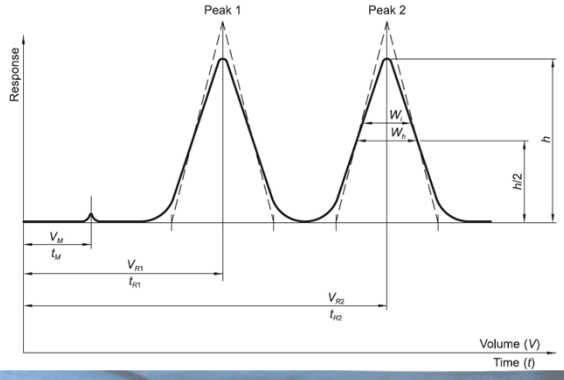
The resolution between peaks of 2 components (Figure 2.2.46.-1) may be calculated using the following equation:

$$R_s = \frac{1.18\,(t_{R2} - t_{R1})}{w_{h1} + w_{h2}}$$

$t_{R2} > t_{R1}$

t_{R1}, t_{R2} = retention times of the peaks;

w_{h1}, w_{h2} = peak widths at half-height.



SST criteria in LC/GC

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VALPROIC ACID

Acidum valproicum

$C_8H_{16}O_2$ [99-66-1] M_r 144.2

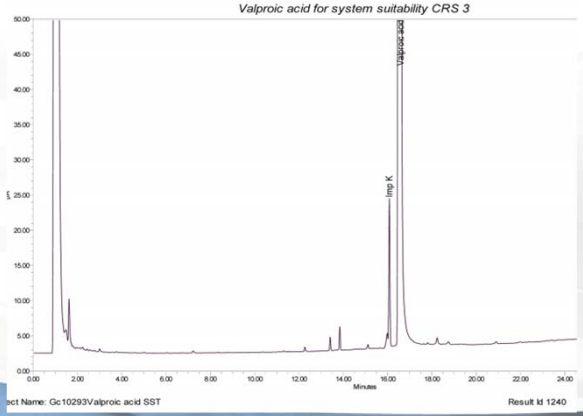
Related substances. Gas chromatography (*2.2.28*).

Reference solution (a). Dissolve 5 mg of *valproic acid for system suitability CRS* (containing impurity K) in 1.0 mL of *heptane R*.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the peaks due to impurity K and valproic acid.

Valproic acid for system suitability CRS 3



p/v ratio

- Definition (2.2.46.):

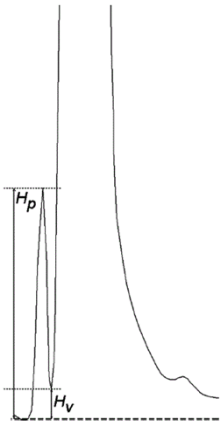
Peak-to-valley ratio (p/v)

The peak-to-valley ratio may be employed as a system suitability criterion in a test for related substances when baseline separation between 2 peaks is not achieved (Figure 2.2.46.-6).

$$p/v = \frac{H_p}{H_v}$$

H_p = height above the extrapolated baseline of the minor peak;

H_v = height above the extrapolated baseline at the lowest point of the curve separating the minor and major peaks.

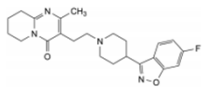


p/v ratio

01/2011:1559
corrected 7.4

RISPERIDONE

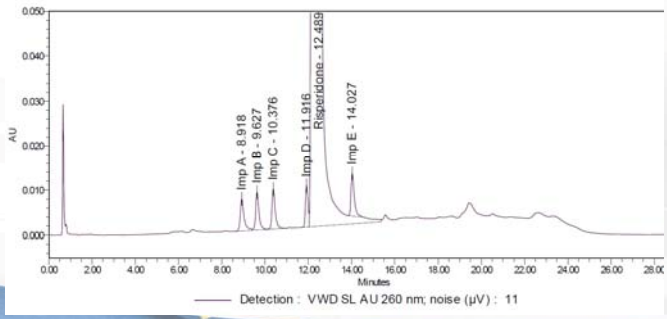
Risperidonum



$C_{23}H_{27}FN_4O_2$ M_r 410.5
[106266-06-2]

Related substances. Liquid chromatography (*2.2.29*).
Test solution. Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.
Reference solution (a). Dissolve 10 mg of *risperidone for system suitability CRS* (containing impurities A, B, C, D and E) in 1.0 mL of *methanol R*.

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.

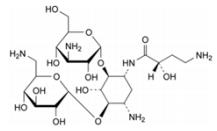


SST criteria in LC/GC

07/2014:1289

AMIKACIN

Amikacinum



$C_{22}H_{43}N_5O_{13}$ M_r 585.6
[37517-28-5]

Content: 96.5 per cent to 102.0 per cent (anhydrous substance).

ASSAY

Liquid chromatography (*2.2.29*).

Reference solution. Dissolve 50.0 mg of *amikacin CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase.

System suitability: reference solution:

- *repeatability*: maximum relative standard deviation of 1.5 per cent after 6 injections.

Table 2.2.46.-1. – *Repeatability requirements*

	Number of individual injections			
	3	4	5	6
B (per cent)	Maximum permitted relative standard deviation			
2.0	0.41	0.59	0.73	0.85
2.5	0.52	0.74	0.92	1.06
3.0	0.62	0.89	1.10	1.27

SST criteria in LC/GC

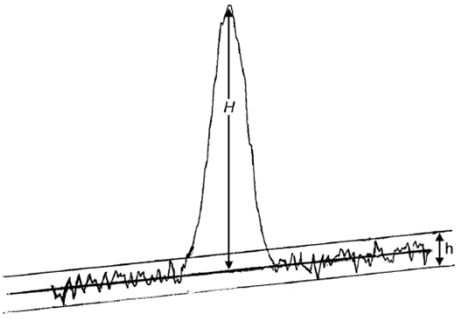
Signal-to-noise ratio (*S/N*)

The short-term noise influences the precision of quantification. The signal-to-noise ratio is calculated using the following equation:

$$S/N = \frac{2H}{h}$$

H = height of the peak (Figure 2.2.46.-7) corresponding to the component concerned, in the chromatogram obtained with the prescribed reference solution, measured from the maximum of the peak to the extrapolated baseline of the signal observed over a distance equal to at least 5 times the width at half-height;

h = range of the noise in a chromatogram obtained after injection or application of a blank, observed over a distance equal to at least 5 times the width at half-height of the peak in the chromatogram obtained with the prescribed reference solution and, if possible, situated equally around the place where this peak would be found.

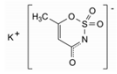


SST criteria in LC/GC

01/2017:1282

ACESULFAME POTASSIUM

Acesulfamum kalicum



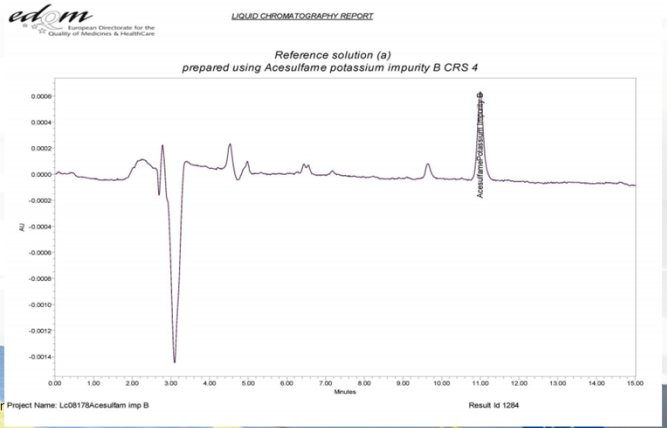
Impurity B. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (a). Dissolve 4.0 mg of *acesulfame potassium impurity B CRS* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of the solution to 200.0 mL with *water R*.

System suitability:

– *signal-to-noise ratio*: minimum 10 for the peak due to impurity B in the chromatogram obtained with reference solution (a);



SST criteria in LC/GC

07/2018:2571

INSULIN GLARGINE

Insulinum glarginum

$C_{267}H_{404}N_{72}O_{78}S_6$ M_r 6063

B. Peptide mapping (*2.2.55*).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution. Prepare a 10.0 mg/mL solution of the substance to be examined in a 1 g/L solution of *hydrochloric acid R* and transfer 5 µL of the solution to a clean tube. Add 1.0 mL of *1 M tris-hydrochloride buffer solution pH 7.5 R* and 100 µL of a 20 U/mL solution of *Staphylococcus aureus strain V8 protease, type XVII-B R* in *1 M tris-hydrochloride buffer solution pH 7.5 R*. Mix and incubate at 45 °C for about 2 h. Stop the reaction by adding 2 µL of *phosphoric acid R*.

Reference solution. Prepare at the same time and in the same manner as for the test solution but using *insulin glargine CRS* instead of the substance to be examined.

CHROMATOGRAPHIC SEPARATION. Liquid chromatography (*2.2.29*).

System suitability:

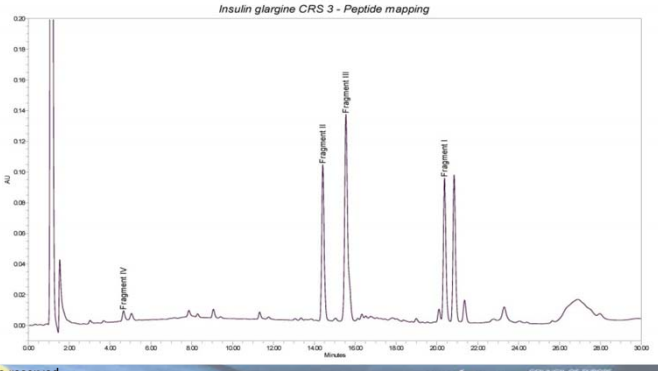
- the chromatograms obtained with the test solution and the reference solution are qualitatively similar to the chromatogram of insulin glargine digest supplied with *insulin glargine CRS*;
- in the chromatogram obtained with the reference solution, identify the peaks due to digest fragments II and III:

symmetry factor: maximum 1.5 for the peaks due to fragments II and III;

resolution: minimum 3.4 between the peaks due to fragments II and III.

LIQUID CHROMATOGRAPHY REPORT

Insulin glargine CRS 3 - Peptide mapping



Types of RS

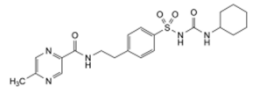
- Pure reference standard
  - Subject of a monograph or impurity
  - Key attribute:
    - Fitness for purpose (in case of SST use)
  - Compliance with monograph if applicable
  - Advantages:
    - + Stability: less likely to have incompatibilities (compared to mixture)
    - + Control of concentration
    - + Batch continuity and sustainability
  - First choice

Types of RS

04/2019:0906

GLIPIZIDE

Glipizidum



$C_{21}H_{27}N_5O_4S$ [29094-61-9] M_r 445.5

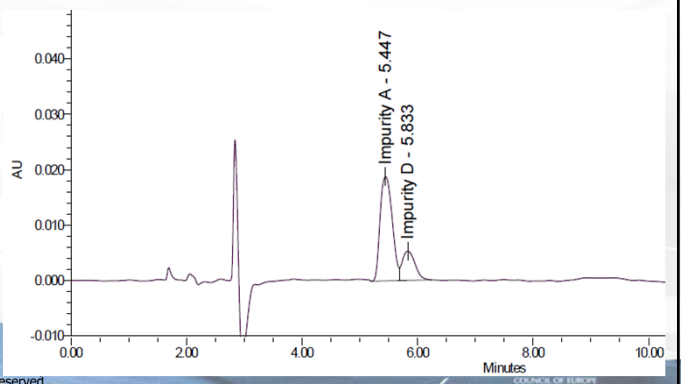
Related substances. Liquid chromatography (*2.2.29*).

Reference solution (b). Dissolve 6.0 mg of *glipizide impurity A CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (d). Dissolve 2 mg of *glipizide impurity D CRS* in the solvent mixture and dilute to 250 mL with the solvent mixture. Dilute 1 mL of the solution to 20 mL with reference solution (b).

System suitability: reference solution (d):

- *peak-to-valley ratio*: minimum 2.0, 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 impurity A.



Types of RS

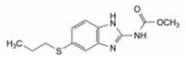
- Mixture (normal production batch)
  - … for system suitability CRS
  - Key attribute: fitness for purpose
  - Impurities spiked for identification
  - Leaflet chromatogram may be provided
  - Advantages:
    - + Representative for what user will observe
  - Drawback
    - – Batch continuity
    - – Sustainability
    - – Linked to monograph which may evolve

Types of RS

04/2018:1386
corrected 9.6

ALBENDAZOLE

Albendazolum



$C_{12}H_{15}N_3O_2S$ [54965-21-8] M_r 265.3

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solvent mixture: *sulfuric acid R, methanol R* (1:99 *V/V*).

Test solution. Dissolve 25.0 mg of the substance to be examined in 5 mL of the solvent mixture and immediately dilute to 50.0 mL with the mobile phase.

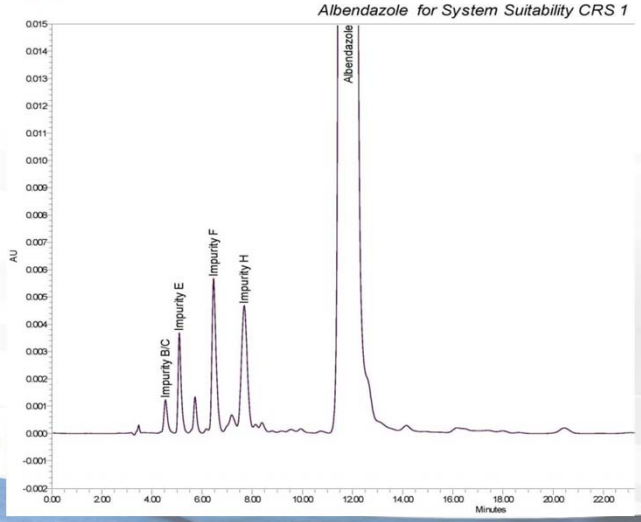
Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *albendazole for system suitability CRS* (containing impurities B, C, E, F and H) in 1 mL of the solvent mixture and dilute to 10 mL with the mobile phase.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to impurities B + C and E.

Albendazole for System Suitability CRS 1



Types of RS

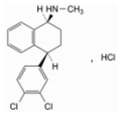
- Mixture (compounded)
  - With or without substance subject of monograph
  - Key attribute: fitness for purpose
  - Leaflet chromatogram may be provided
  - Advantages:
    - + Better control of concentration
    - + Batch continuity
  - Drawback
    - – Increased likelyhood of stability issues (high surface, residual solvents, amorphous)
    - – Linked to monograph which may evolve

Types of RS

04/2019:1705

SERTRALINE HYDROCHLORIDE

Sertralini hydrochloridum



$C_{17}H_{18}Cl_3N$ [79559-97-0] M_r 342.7

Related substances. Gas chromatography (*2.2.28*): use the normalisation procedure.

Test solution. Introduce 0.250 g of the substance to be examined into a 15 mL stoppered centrifuge tube, add 2.0 mL of *methanol R* and 0.20 mL of a 25 per cent solution of *potassium carbonate R* and mix in a vortex mixer for 30 s. Add 8.0 mL of *methylene chloride R*, stopper the tube and mix in a vortex mixer for 60 s. Add 1 g of *anhydrous sodium sulfate R*, mix well and then centrifuge for about 5 min.

Reference solution (a). Dissolve the contents of a vial of *sertraline for peak identification CRS* (containing impurities A, B, C and F) in 0.2 mL of *methylene chloride R*.

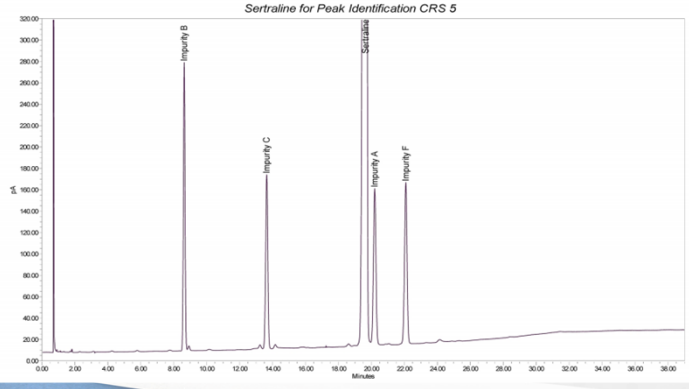
System suitability: reference solution (a):

- *peak-to-valley ratio*: minimum 15, where H_p = height above the baseline of the peak due to impurity A and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to sertraline.

edqm European Directorate for the Quality of Medicines & HealthCare

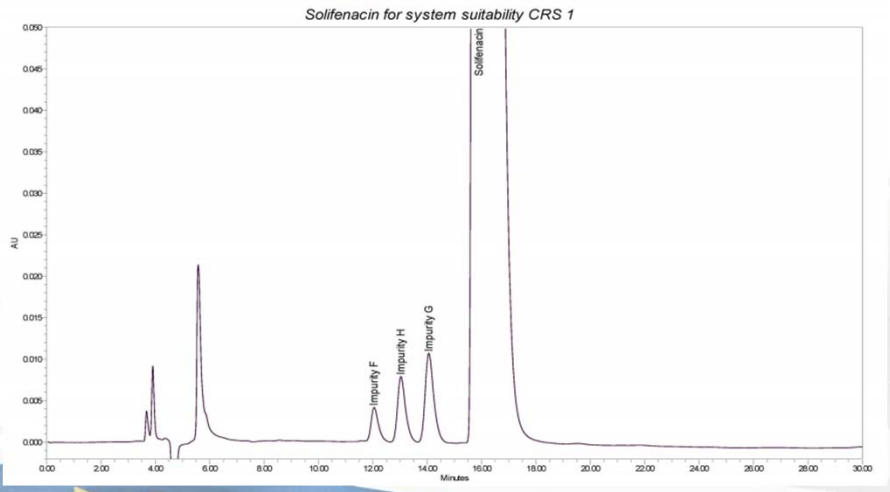
GAS CHROMATOGRAPHY REPORT

Sertraline for Peak Identification CRS 5



Types of RS

Solifenacin for system suitability CRS 1



Thank you very much for your attention.

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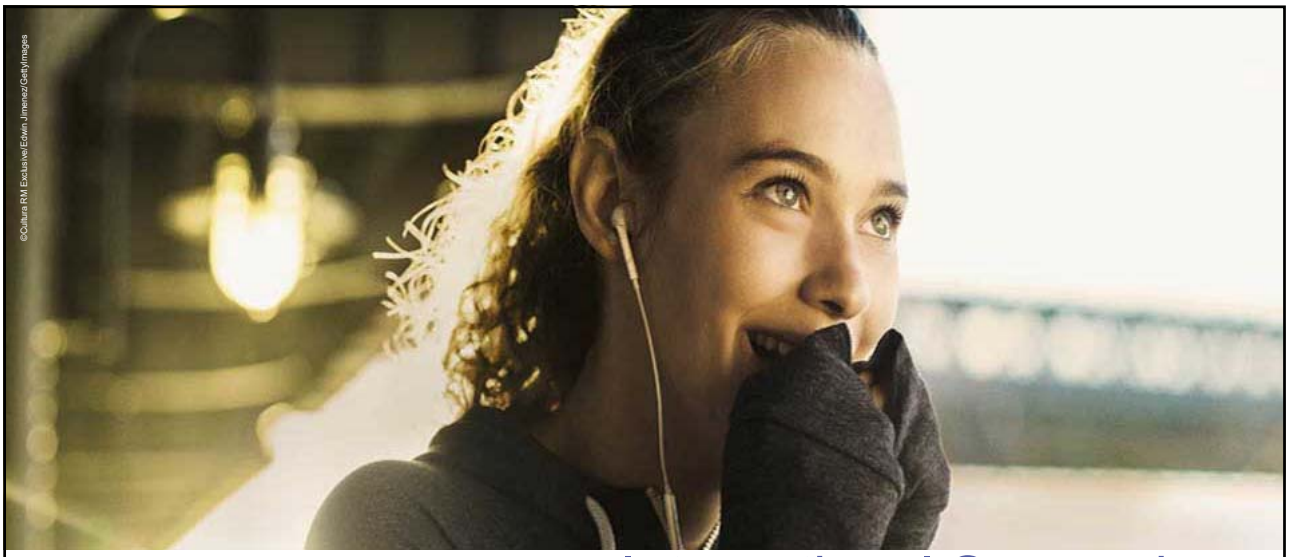

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International Symposium
on Pharm. Reference Standards
13-14 March 2019, Strasbourg, France

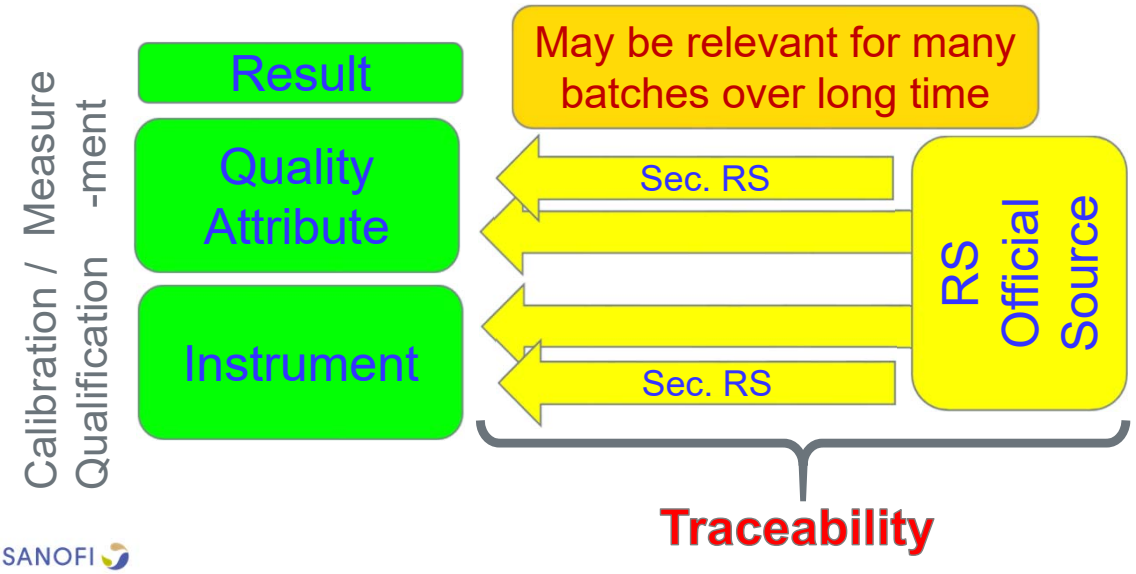
INTERNATIONAL SYMPOSIUM ON PHARMACEUTICAL REFERENCE STANDARDS

Use of Reference Standards and Quality Control: Experiences and Unmet Needs

Joachim Ermer

Industrial Quality & Compliance, Chemistry Frankfurt

Impact of Reference Standards (RS)



Use of Official Reference Standards

- **ICH Q7, 11.17: If obtained from an officially recognized source, normally used without testing if stored under prescribed conditions.**
- **FDA: Reference standards from USP/NF and other official sources do not require further characterization.**
- **Responsibility of Compendia / official source**
  - Accuracy of characterisation and provided information (e.g. assigned content)
  - Ongoing suitability (stability)
- **Minimisation of risk when using official RS**

Official RS: Responsibility of User

- **Correct use**
  - Identification (qualitative) or content (quantative)
  - According to instructions (e.g. „immdiate use“)
  - Use of content as declared („as is“ or e.g. „anhydrous“)
- **Correct storage (including controls)**
- **Check of validity at time of use**
- **Any further use must be assessed and justified**
- **Prevention of cross-contamination in case of multiple use (USP RS)**

Unmet Needs: Assignment of Content

- **USP General Chapter <11> USP Reference Standards**
  - „For Reference Standards that do not bear a property value or calculation value on the label or in accompanying documentation, assume the Reference Standard is 100.0% pure for compendial quantitative applications.“
- **Ph.Eur. 5.12: Reference Standards**
  - Impurity CRS: “.. Where (the preferred minimum content of 95%) is achieved the assigned content of the CRS is not given and it is considered to be 100.0 %.”
- **Some CRS for quantification have no assigned content.**
  - E.g. Clobazam impurity A, Metamizol imp. A, Fexofenadine imp. B
- **Risk of misinterpretation of use ➔**
  All RS for quantification should have an assigned content

Unmet Need: Instruction for Immediate Use

- **Ph.Eur. CRS Information Leaflet**
  - "Once the container has been breached, stability of the contents cannot be guaranteed. It is for immediate use."
- **Is this always justified by substance properties?**
- **Permission of multiple use is certainly justified in some cases, e.g.**
  - RS for qualitative use (e.g. identification)
  - No relevant water uptake and degradation for quantitative RS
- **Should be differentiated according to RS stability and use**
  - As in USP <11>: "Some standards (mainly materials with significant handling requirements or materials that are available only in small amounts) are provided in single-use containers."

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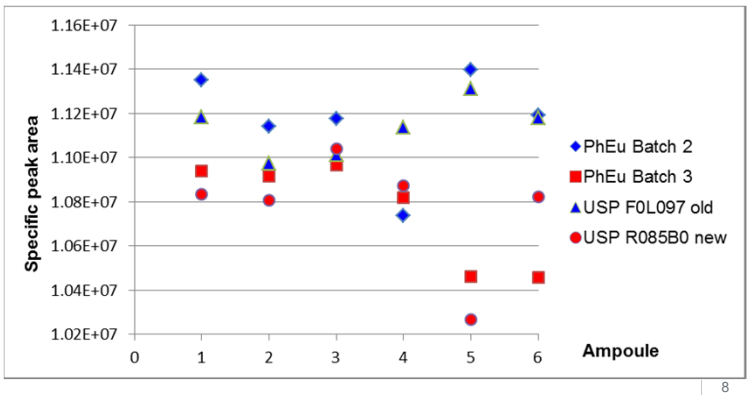
Replacement of Batches with Assigned Content

- **Challenge: Potential shift of results**
  - In case of use of different RS-batches for API and finished product
  - Monitoring of batch release results and/or analytical control samples
- **Example: Insulin Aspart**
  - Direct comparison of old/new Ph.Eur. and USP RS
  - 6 ampoules each, accord. to monograph method, same series
  - Difference
    CRS 2 – 3: - 3.6%
    USP old – new: - 3.2%



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What is an Acceptable Uncertainty?

For Establishment or Replacement of an RS

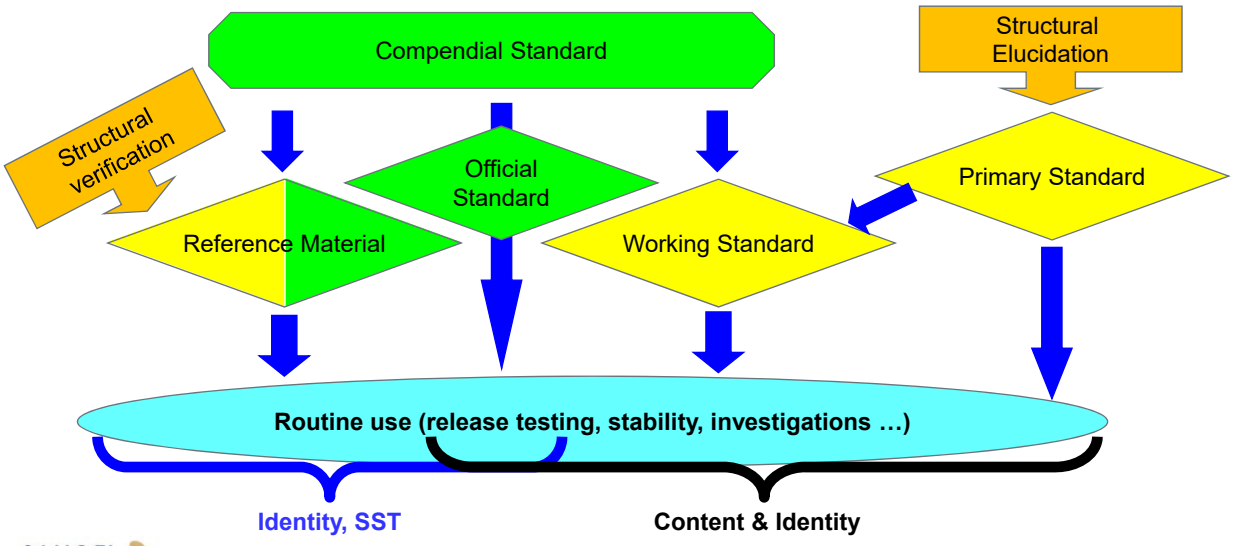
- **Ph.Eur. Chapter 5.12: 4-2-4 Establishment Report**
  - " uncertainty is calculated, and where it is less than a predefined value, which is considered to be negligible in relation to the acceptance criteria for the assay.."
  - What means "negligible"?
- **Publication of rules would be helpful**
  - To improve transparency and understanding
  - To provide orientation for establishment of in-house reference standards

Sanofi Management of Reference Standards

- **Centralised management (subfillings, labelling, certificates, complaints), storage, distribution & coordination by Reference Standards Logistics (RSL) groups**
  - Frankfurt (Germany) and Sisteron (France)
  - Storage facilities: 25°C, 4-8°C, -20°C, -80°C (~120 m^2)
  - ~ 2000 substances ; ~ 400 retests / characterisations per year
  - ~ 2500 orders (~ 22 000 vials); ~ 500 „customers" (in- & external)

- **Decentralised analytical testing by expert laboratories (~25)**
  - QC laboratories responsible for routine testing of the respective API
  - Process Development labs for special analysis (e.g. structural identification)

Traceability: Sanofi RS Types



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Welcome

Empowering a healthy tomorrow

General Chapter <11> USP Reference Standards

Holly Chang
Director, Reference Standards Technical Operations

March 13, 2019

Agenda

- Summary of General Chapter <11> USP Reference Standards
- Summary of revisions
- Revisions to General Notices

1

Summary of General Chapter <11> USP Reference Standards

Summary of <11> USP Reference Standards

- The purpose of USP <11> is to inform on USP policies regarding Reference Standards and instruct on appropriate compendial use
- The chapter has been revised many times over the years as USP's Reference Standards program has grown and changed. The last revision occurred in 2009.
- The intention of the current revision is to update, clarify and expand USP's approach for developing Reference Standards
- The revision was published for public comment in the Pharmacopeial Forum 45(1) issued on January 1, 2019
- Targeted to become official on August 1, 2020

2

Summary of revisions

Summary of revisions

- **Establishment Approaches and Value Assignment**
  - Includes USP's approach to value assignment
    - Typically by a mass balance determination
    - Can also be assigned by comparison to another material
    - The collaborative study (including the number of laboratories used) is primarily driven by the intended use of the Reference Standard
    - The characterization goes beyond establishment of suitability of use
    - Comparison to the previous lot is performed as additional verification of suitability of use

Summary of revisions

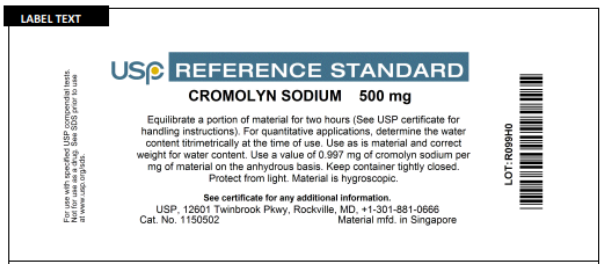
- **USP Reference Standards for *USP* or *NF***
  - Quantitative – includes both *USP* and *NF* articles and impurity standards
    - Used to support measurements on a mass basis or
    - Used for relative determinations of potency or activity
      - Established by calibration to a primary standard
  - Qualitative
    - Identification
    - System suitability
    - Visual (and digital)
  - Performance verification
    - Typically required for use in USP General Chapters
    - Used to ensure the proper operation of instrumentation

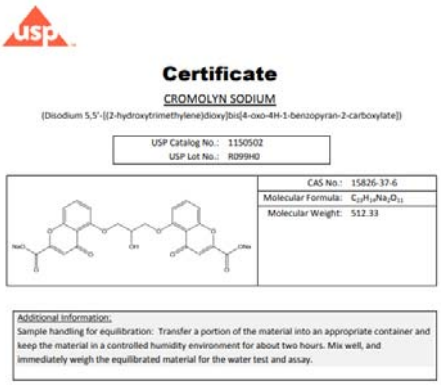
Summary of revisions

- USP Reference Standards for other measurements and determinations
  - USP develops Reference Standards which may not be required in official USP-NF tests or assays including:
    - Food Chemicals Codex (FCC)
    - Herbal Medicines Compendium (HMC)
    - Other regulatory requirements
  - USP may also develop Reference Standards to address common quality issues and challenges which are inherent to technologies which cut across different types of products
  - USP Reference Standards developed for other measurements and determinations are developed under the same Quality Management System as those required in official USP-NF tests or assays

Summary of revisions

- **Labeling**
  - Labeling includes both the label affixed to the vial and the USP Certificate
    - The USP Certificate may contain additional information such as special handling instructions that the affixed label cannot accommodate





Summary of revisions

- **Continued Suitability for Use (CSU)**
  - The CSU section was included to inform of the program
    - All USP Reference Standards are reevaluated throughout their lifecycles to confirm the continued suitability of the material
    - Intervals are established based on collaborative study data, test results from CSU testing and data trending and projections
- **Proper Use**
  - Label terms were added to instruct on appropriate use of the Reference Standards

3

Revisions to General Notices

Changes affecting both <11> and General Notice 5.80

- Delete the text defining USP Reference Standards as “comparison standards in tests and assays”
  - To accommodate USP Reference Standards for performance verification tests
- Delete the following legacy statement
  - “For Reference Standards that do not bear a property value or calculation value on the label or in accompanying documentation, assume the Reference Standard is 100.0% pure for compendial quantitative applications”

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