Pharmacopeia Standards- Global Teva R&D Perspective

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Presentation Contents

01 Teva R&D

02 Reference Standards Use In Teva

03 USP/EP and TEVA Relationship

04 Challenges

01 - Teva R&D

Global R&D Analytical Representative

- KS IL (Bianca Avramovitch, Dorit Leibler & Svetlana Ginzburg)
- Bio-similar- Netanya, IL (Dan Kenett)
- TAPI (Arina Ceausu)

- Ambernath, Goa, India (Fabian D'souza, Sarvesh Sawant)

- Debrecen, Hungary (Julia Kazlonecsapo)

- Sindan, Romania (Andreea-Iuliana Moise)

- Waterford, Ireland (Clare Doherty)

- Zagreb, Croatia (Tatjana Cindric)

- Runcorn, UK (Kevin Hawkins)
- Larne, UK (Andrew Walker)

- Hafnafjordur, Iceland (Anna Lilja Petursodottir)

- Santiago, Chile (Maria Oyarzun)

- Munro, Argentina (Marcela Carle)

- Mexico (Araceli Garcia)

- SLC,UT (Mamunur Rashid Khan)
- Weston, FL (Zhengjian Chen & Francisco Blanco)
- MS&T – North Wales, PA (Pawan Ratra)
- Sterile QA – Parsipanny, NJ (Richard Thompson)
- Bio-similar- West Chester (Mehran Yazdanian)

Teva Leading Generic Medicines

1 in 7
Rx in the US

1000+
Launches in 2017

Top 3 position
in 25 markets

550+
therapies

1 in 8
Rx in the UK

1800+
Molecules

teva

Teva Leading Specialty Brands

CNS

AJOVY (fremanezumab-vfrm) injection 225 mg/1.5 mL

Austedo (deutetrabenazine)

COPAXONE (glatiramer acetate injection)

Respiratory

ProAir RespiClick (albuterol sulfate) Inhalation Powder

QVAR RediHaler (beclomethasone dipropionate HFA) Breath-Actuated Inhalation Aerosol 40 mcg • 80 mcg

CINQAIR (reslizumab) injection

DuoResp Spiromax budesonide/formoterol

Oncology

BENDEKA (bendamustine HCl) injection

GRANIX (TBO-FILGRASTIM) Injection

LONQUEX lipegfilgrastim

Trisenox (arsenic trioxide) injection

teva

02 - Reference Standards Use In Teva

Primary standards – mandatory requirements

- **Characterization data and documentation**

  Full characterization data should be available. This includes: structure elucidation by ^{1}H-NMR, ^{13}C-NMR, UV spectrum, LCMS analysis, etc.
  The related spectra and chromatograms should be provided.

- **Defined potency**

  The potency of the primary standard should be calculated and stated in the CoA.

- **Impurities analysis**

  LODs and LOQs of all known impurities, down to penultimate step, for the API batch used as reference standard are requested.

- **Impurities response factors**

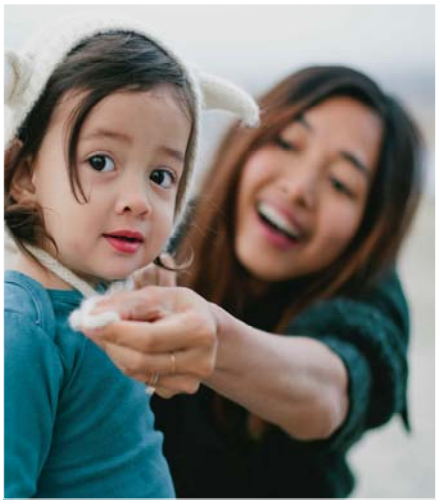
  Response factors of all impurities present at or above their reporting thresholds are requested.

- **Methods and methods validation reports**

  Methods and their validation data for quantitative instrumental analyses, such as: chromatography, water by KF, etc. are requested.

Secondary Standards – Why and How

- **Why:**
  - When availability of primary standard is not ensured
  - High volume of use
  - Steep Price of primary standards
- **How**:
  - Characterization of secondary standards is performed against the primary reference standard.
  - Complete testing according to the relevant monograph is required (based on validated methods), with the exception of characterization test such as NMR, UV or MS which are not required.



Secondary standards – stability

- Retest interval – once a year
- Full testing vs limited testing during retest.
- Stability data collected: Assay (potency), chromatographic purity, water (as appropriate, by KF or TGA) and impurities
- Comparison of retest data with the original data

Note: In case that a significant change in assay value is observed, impact analysis assessment should be performed on the data collected during the last qualification interval.

03 - USP/EP and TEVA Relationship

USP/EP and TEVA relationship

- Ongoing and long term collaboration between Teva and USP/EP:
  - USP/EP standards are found in wide spread use at Teva.

    In Teva R&D KS IL site: during 2018, about 100 standards were purchased from the USP and EP, Which constitute 17% of all standards purchases this year
  - Teva offers to the USP new monographs and update petitions through the pharmacopeial forum.
  - Good bidirectional communication: Immediate reply and data verification when needed.

04 - Challenges

Challenges – quantitative vs qualitative and customer service

- Quantitative vs. qualitative
  - Quantitative data availability is a specific need for our products
  - Assuming the potency is evaluated for the qualitative standards – it is worthwhile to provide the value
- Customer vs. technical service:
  - Ad-hoc clarifications and telephone discussions can improve the service experience and make our investment highly efficient
  - Currently we are lacking a direct communication mechanism

Challenges: Content per vial vs. amount required per analysis

Case Study: The standard packaging does not fit its typical intended use

For chromatography:

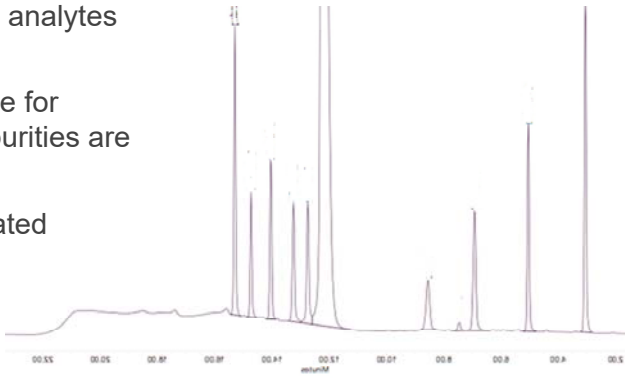
- Vial content: **5mg**
- Required quantity for testing: **20mg (2x10mg)**
- Total number of vials : **4**

For water determination: how many vials?

Recommendation: provide different package sizes as per purpose of use

Challenges – Impurities mix (surrogate standards)

- The accuracy of the impurities profile depends on obtaining similar partition between the phases for the sample (API) as well as for the native analytes (Impurities).
- Often only impurities mix is available while for quantitative use many time individual impurities are required
- Recommendation: Make available separated standards



Challenges – cost and missing documentation

- Cost:
  - USP is more expensive than other suppliers
  - EP is about the same price as other suppliers

- Documentation gap:
  - No characterization package is immediately available. This characterization package (structure, identification spectra, chromatographic typical conditions) is required by most of the regulatory offices

Challenges – stability of standards and calculation value

- Questions regarding stability of standards
  - How is it assessed? Why is it not communicated?
  - How are the replacement timelines are established?

- Why is the below statement not found anymore in the standards CoAs?

> **Calculation Value**
> If a value is not provided on the label or accompanying documentation and the Reference Standard has a quantitative USP compendial application, a value of 100.0% is used. The purity value is not applicable for qualitative uses. Please refer to the specific Reference Standard label for further information.

Thank you.

Case Study

Case Study: Elution order of cis and trans isomers mistakenly assigned

Impact: Investigation was opened in Teva which increased workload in the lab challenging the release timelines

Findings:

1. USP declared the cis/trans isomers order of elution based on the supplier's data without verifying the supplier actual data or proving it at an USP lab.
2. Teva ordered the syntheses and the full characterization of the isomers (due to different ratio of the cis/trans isomers obtained in Teva QC lab vs. USP product profile).
3. Based on the characterization data provided by Teva, USP concluded that the monograph erroneously stated the cis and trans isomers retention times

Conclusions:

1. Teva recognizes the immediate reply and data verification by USP.
2. We recommend to verify the data supplied in order to keep the credibility level of USP.

Use of qNMR and Characterisation of Reference Standards

Dr Torgny Rundlöf, Medical Products Agency, Sweden

13th Int. Symp. Pharmaceutical Reference Standards 13-14 March 2019

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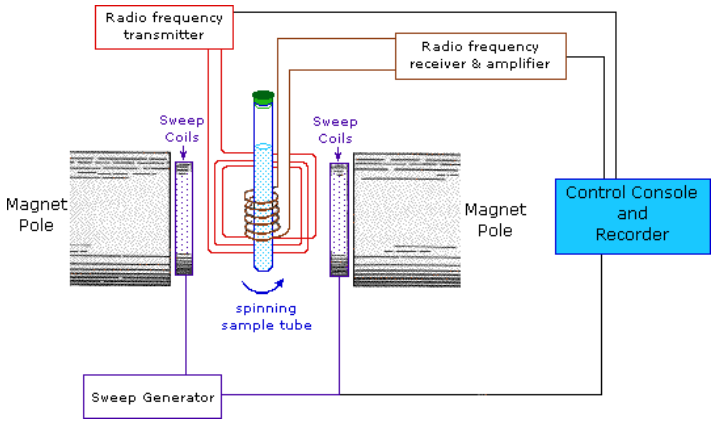
Principle



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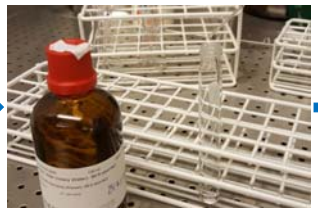
Sample preparation

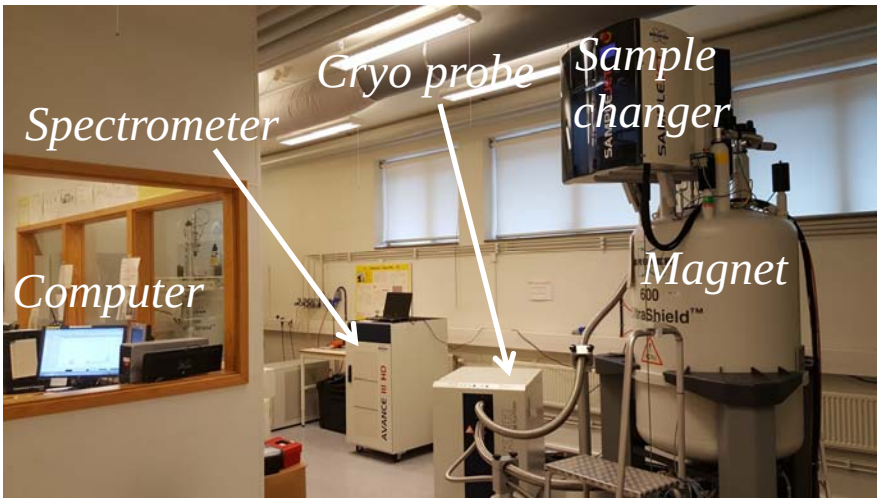
WEIGH
sample 1-10 mg
(internal standard 1 mg)



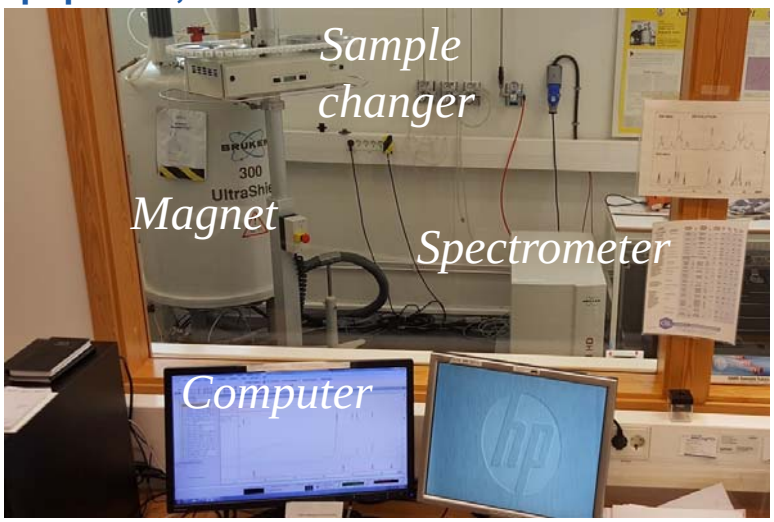
DISSOLVE
Deuterated solvent 0.6ml

NMR tube

Equipment, advanced



Equipment, basic



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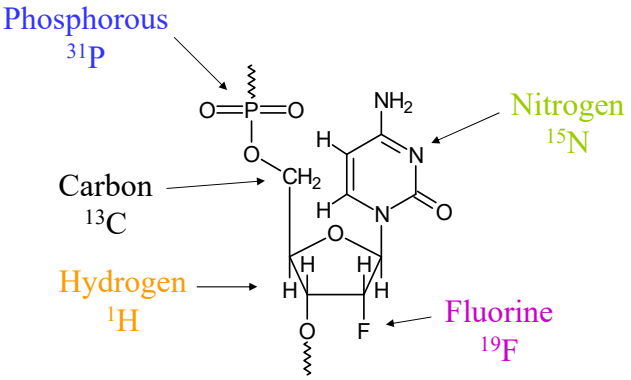
Which nuclei?



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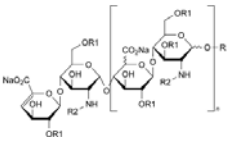
Identity – comparison to reference spectrum
^{13}C NMR

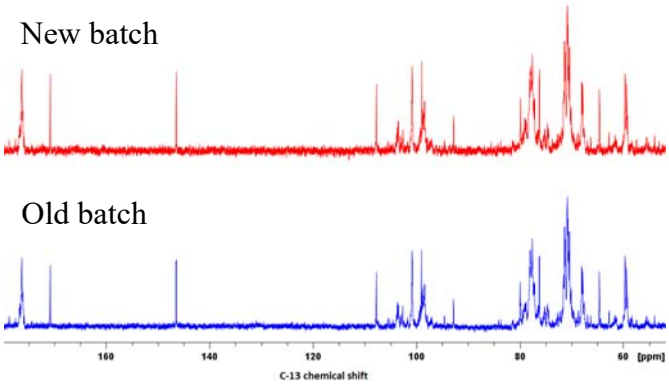
Method: Ph.Eur. 01/2017:0828 Heparins, low-molecular-mass



Enoxaparin sodium

New batch

Old batch



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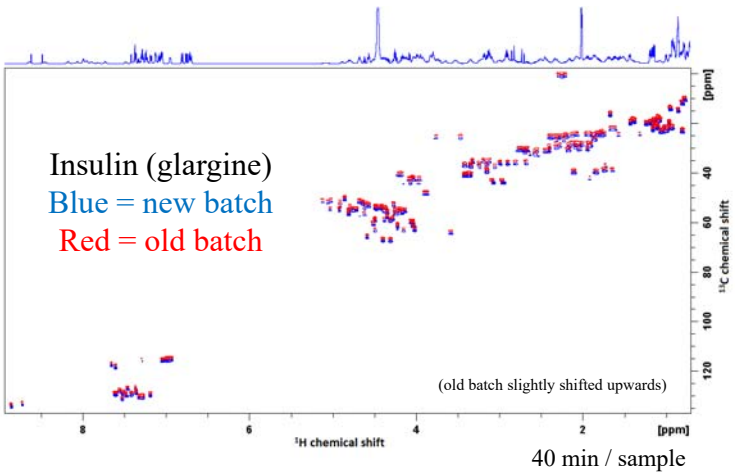
Identity – comparison to reference spectrum
Two-dimensional HSQC



40 min / sample

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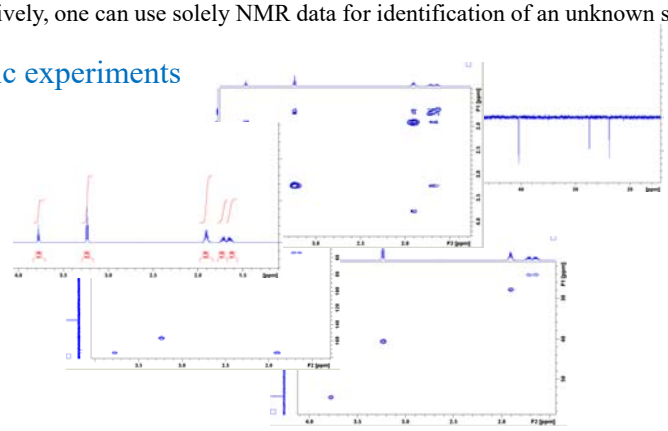
Identity – structure verification and unknowns

Data from various different NMR experiments can be regarded as puzzle pieces.
If there is a proposed structure, it will be easier to find out the NMR puzzle.
Alternatively, one can use solely NMR data for identification of an unknown sample.

Five basic experiments



Identity - five basic experiments

Basic information

- Proton → chemical shifts, splittings, integrals
- Carbon-13 → chemical shifts, type (C, CH, CH_2, CH_3)

Build puzzles

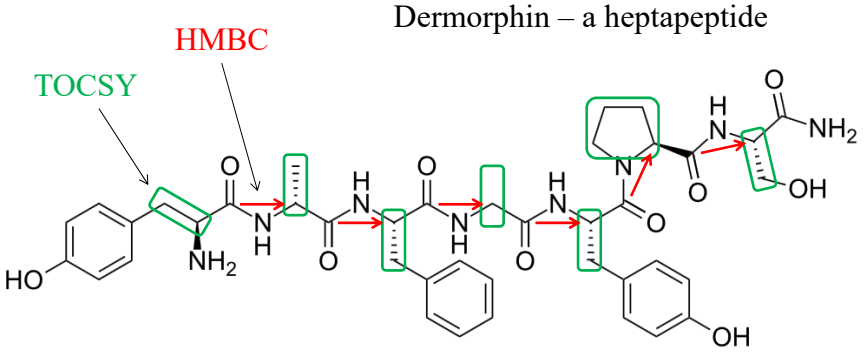
- 2D-COSY or TOCSY → H-H correlation, eg. amino acid side-chains of a peptide
- 2D-HSQC → C-H or N-H correlation
- 2D-HMBC → **C**-C-**H** or **C**-C-C-**H** correlation, eg. amino acid sequence of a peptide

Interpretation of qualitative NMR data

		alpha	beta	gamma	delta	Ar	Ar	Ar	Ar	CO	HMBC	
Tyr(1)	C	54,5	36,3			125,9	130,7	115,7	154,9	169,4	4,14	to Ala
	H	4,01	3,10				7,10	6,88			4,01	
			3,00								3,10	
											3,00	
Ala	C	49,3	16,1							174,4	4,61	to Phe
	H	4,14	0,90								4,14	
											0,90	
Phe	C	54,8	36,9			136,3	129,1	128,6	128,6	173,5	4,61	
	H	4,61	3,16				7,24	7,36	7,36		3,86	to Gly
			2,89								3,77	to Gly
											3,16	
											2,89	
Gly	C	42,1								170,5	4,85	to Tyr
	H	3,86									3,86	
		3,77									3,77	
Tyr(2)	C	52,9	35,5			127,8	130,7	115,4	154,4	171,5	4,85	
	H	4,85	3,10				7,17	6,86			4,49	to Pro
			2,87								3,10	
											2,87	
Pro	C	60,7	29,0	24,4	47,7					174,1	4,49	
	H	4,49	2,31	2,03	3,82						4,42?	to Ser?
			1,98		3,57						2,31	
											1,98	
Ser(1)	C	55,3	61,0							174,3	4,42	
	H	4,42	3,88								3,88	

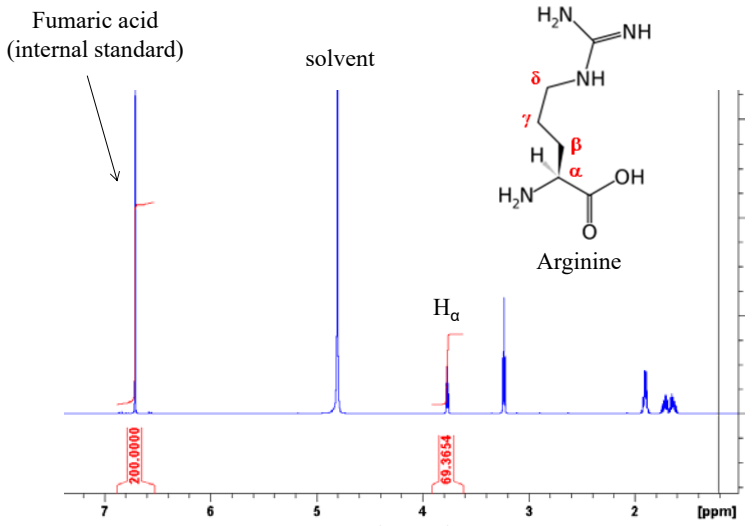
Structure elucidation

Dermorphin – a heptapeptide



Tyr – Ala – Phe – Gly – Tyr – Pro – Ser-NH_2

Assay: quantitative ^{1}H NMR (qNMR)



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Quantitative NMR – calculation

$$P(sample) = P(std) \cdot \frac{MW(sample)}{MW(std)} \cdot \frac{nH(std)}{nH(sample)} \cdot \frac{m(std)}{m(sample)} \cdot \frac{A(sample)}{A(std)}$$

		Standard (Fumaric acid)	Sample (Arginine)
Constants:	MW (g/mol)	116.07	174.2
	Purity (%)	100	
	NMR signal (ppm)	6.74	6.34
	No of protons	2	1

		Standard	Sample	Purity(%)
Analysis 1				
	m (mg)	1.9657	3.7979	
	Integral area	200	128.248	
				99.62
Analysis 2				
	m(std)	1.1000	1.1423	
	Integral area	200	69.365	
				100.25
Analysis 3				
	m(std)	1.5614	1.2521	
	Integral area	200	53.125	
				99.43

Results		
	Mean value, purity (%)	**99.77**
	Standard deviation	**0.43**
	RSD %	**0.43**

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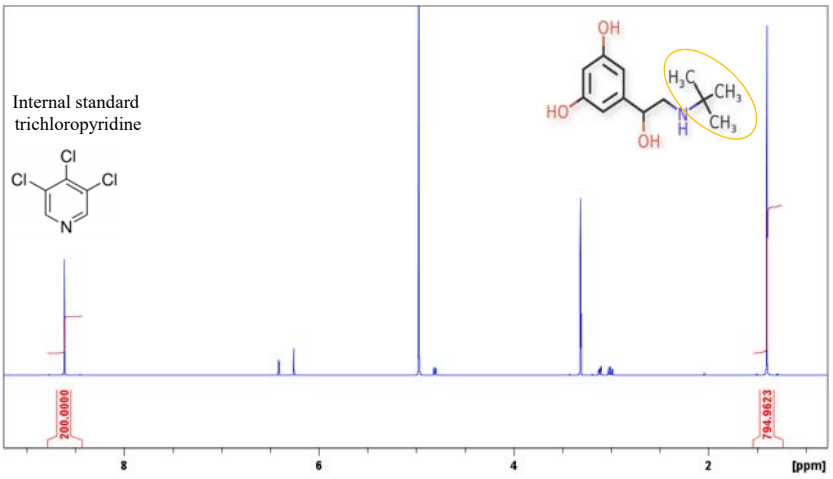
qNMR – example Terbutaline sulphate



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Terbutalin sulphate – quantification by titration, HPLC-UV, and qNMR

	TITRATION PhEur 01/2008:0690		HPLC QC method		qNMR# Generic method	
Batch	Assay, %	SD (n=3)	Assay, %	SD (n=2)	Assay, %	SD (n=3)
1	99,5	0,1	99,6	0,1	99,6	0,9
2	99,5	0,1	99,6	0,0	100,1	0,4
3	99,5	0,1	99,5	0,0	100,0	1,0
4	99,5	0,1	100,0	0,4	99,8	0,5
Ref. std	-	-	-	-	99,5	0,3

qNMR assay calculated assuming [terbutalin * 1/2 H_2SO_4]

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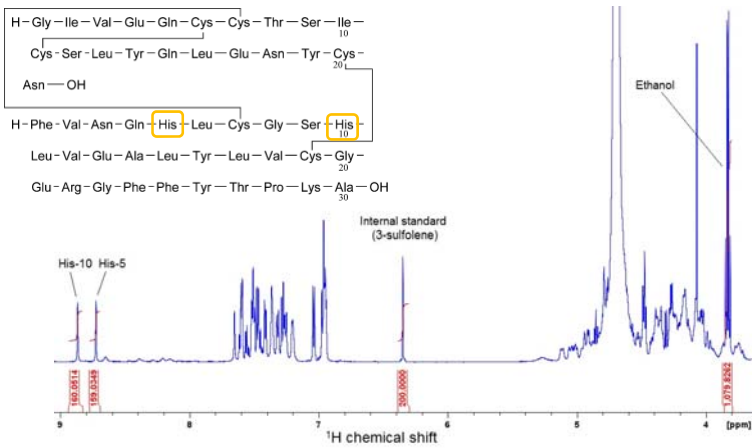
qNMR – insulin (porcine)



In addition: identification and quantification of residual ethanol

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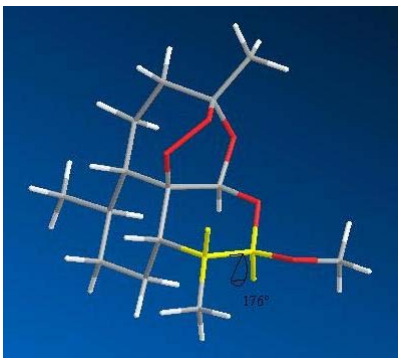
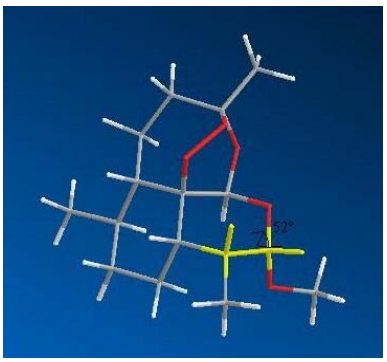
Stereochemical isomers

Which 3-dimensional structure corresponds to my sample?





1 *or* 2

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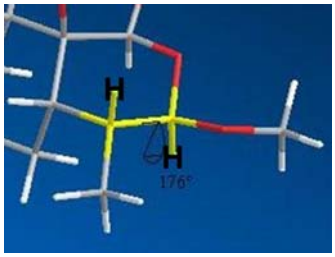
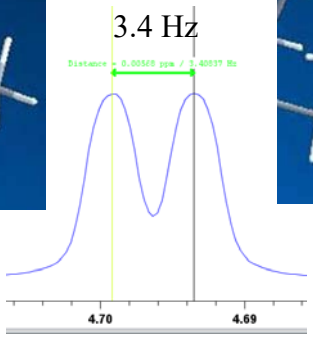
3D structure by NMR: coupling constants

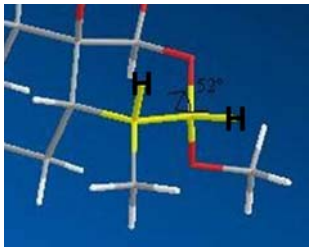
Different geometry!



~~7-10 Hz~~

Measured:
3.4 Hz





3-4 Hz

Structure 2

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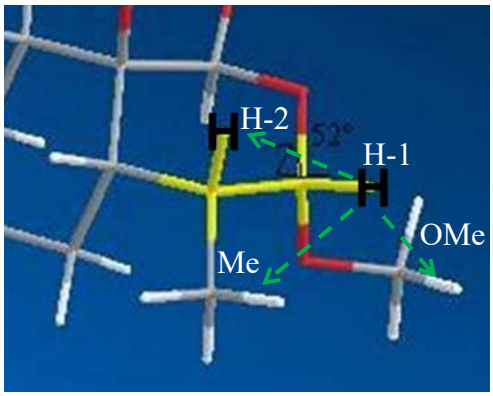
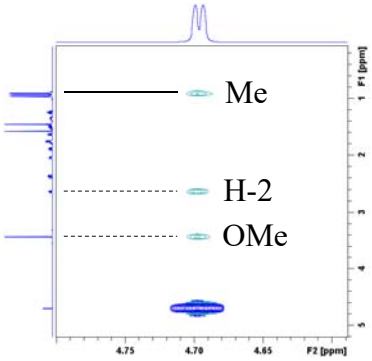
3D structure by NMR: NOE – through space interactions

Three strong NOE interactions observed



Structure 2



H-1

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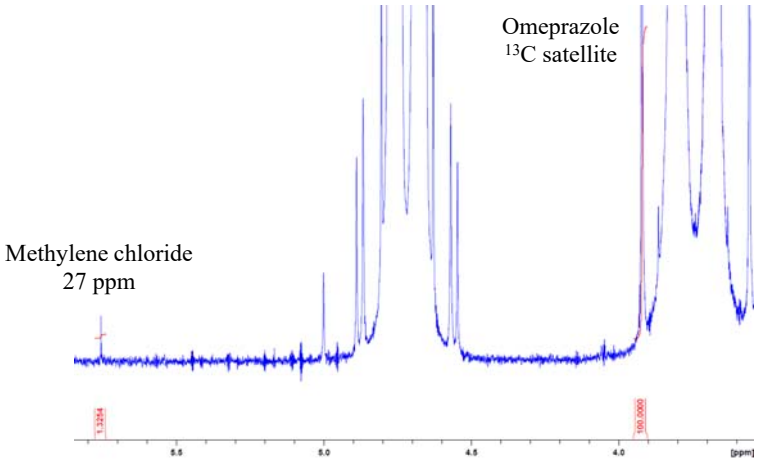
Residual solvents – identification and quantification



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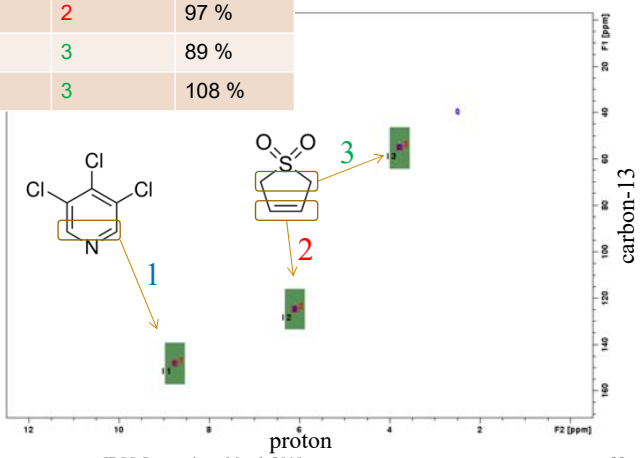
Improved ”resolution”: 2D-HSQC qNMR

Std peak	Sample peak	Recovery
1	2	97 %
1	3	89 %
2	3	108 %

Promising, but optimization required…



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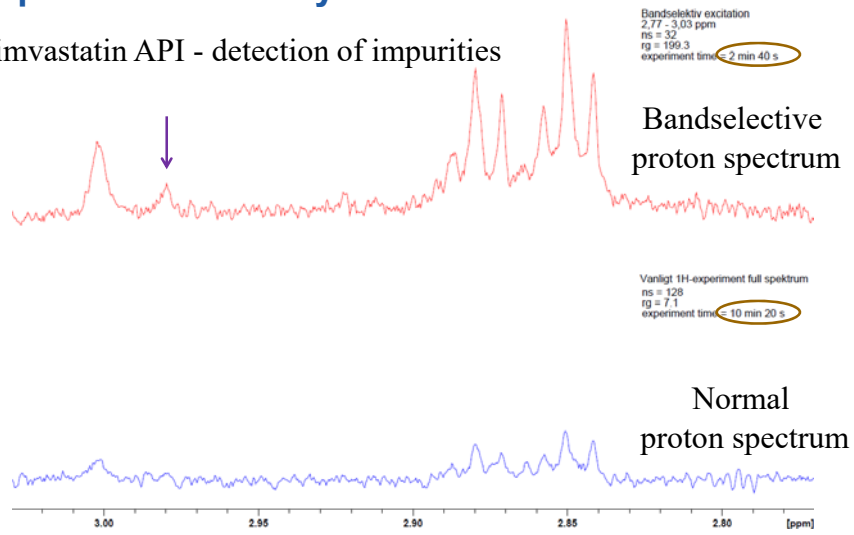
Improved sensitivity: band-selective excitation

Simvastatin API - detection of impurities



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Why NMR?

Positive	Negative
•**Quick** sample preparation •**Automated** analysis •**Non-destructive** (samples may be re-used) •**Much information** in a single analysis •**Quantitative** – equal response for any compound •**Robust**, a minimum of calibration and maintenance required •Many different NMR-experiments available in order to obtain qualitative and/or quantitative data	•**Expensive** equipment •**Trained** operators required •Sometimes **complicated** data interpretation •Need for regular N_2(l) and He(l) **refills** •Equipment may require a dedicated room

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Acknowledgements

My NMR colleagues:

Andreas Blomgren

Karl-Henrik Jönsson

Birgit Hakkarainen

EMA Guideline on Antibiotics Reference Standards

Semi-Synthetic Products

Strassburg, 13 – 14 March 2019

Topics of the Presentation

- Fermentation and Semisythetic Synthesis
- Manufacturnig Processes of Antibiotics
- Substances for Pharmaceutical Use Ph.Eur. 5.10
- EMA Guideline QWP/199250/2009
- Identification / Quantification of Related Substances
- Consequences of EMA Guideline for Antibiotic Monographs
- Assay of Antibiotics

Fermentation Process

Pharma
Consulting & Services

Products of Fermentation are:

Indirect gene products (primary or secondary metabolites)
of microorganisms such as bacteria, yeast, fungi and micro algae,
irrespective of whester or not the microorganisms have been
modified by tradional procedures or by recombinant DNA technology.

Fermentation and Semisythetic Synthesis

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Consulting & Services

Fermentation manufacturing processes

- biological systems are involved
- processes less stable than chemical ractions
- complex mixtures of related substances may be formed
- degradation products, by-products, intermediates having biological activity may result

Semi-synthetic manufacturing processes

- fermentation products are starting materials
- subsequent chemical reactions

Production of Antibiotics

by Fermentation or Semisynthetic

- Penicillins/Cephalosporins
- Carbapenems
- Aminoglycosides
- Macrolides
- Polymyxins
- Tetracyclins

by Chemical Synthesis

- Sulfonamids
- Gyrase Inhibitors

Meropenem

DEFINITION

Semi-synthetic product derived from a fermentation product, or synthetic product

RELATED SUBSTANCES

Limits:
– *unspecified impurities*: for each impurity, not more 0.10 %
– disregard limit: 0.05 %

For meropenem trihydrate produced by a fully synthetic process:
– unspecified impurities: for each impurity, 0.05 %
– disregard limit: 0.03 %

5.10. CONTROL OF IMPURITIES IN SUBSTANCES FOR PHARMACEUTICAL USE

The provisions of the Related substances section of the general monograph Substances for pharmaceutical use (2034), notably those concerning thresholds, do not apply to …….

fermentation products and semi-synthetic products derived therefrom.

Thresholds for impurities in drug substances (Q3A)

Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
≤ 2g/day	0.05 %	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
>2g/day	0.03 %	0.05%	0.05%

EMA guideline (30. June 2013) (EMA/CHMP/CVMP/QWP/199250/2009 corr.)

Guideline on setting specifications for related impurities in antibiotics

Active substances	**Semi-synthetic ***	**Fermentation, single**	**Fermentation, family**	**Peptides**
Reporting	0.05%/0.03%	0.10%	0.10%	0.1%
Identification	0.10%/0.05%	0.15%	0.15%	0.5%
Qualification	0.15%/0.05%	0.15%	0.50%**/0.2%	1.0%

Definitions

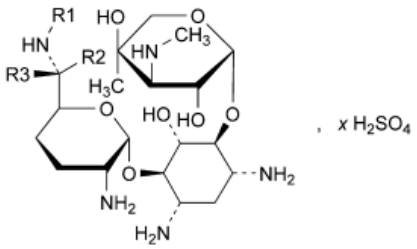
Fermentation, Single:

The active substance consists of only one compound

Fermentation, Family:

The active substance consists of a mixture of compounds. The composition regarding names and amounts of relevant components is defined in the active substance specification……
The composition will appear in any Ph.Eur. monograph available.

Gentamicin sulfate



Gentamicin	Mol. Formula	R1	R2	R3
C1	$C_{21}H_{43}N_5O_7$	CH_3	CH_3	H
C1a	$C_{19}H_{39}N_5O_7$	H	H	H
C2	$C_{20}H_{41}N_5O_7$	H	CH_3	H
C2a	$C_{20}H_{41}N_5O_7$	H	H	CH_3
C2b	$C_{20}H_{41}N_5O_7$	CH_3	H	H

EMA guideline (30. June 2013) (EMA/CHMP/CVMP/QWP/199250/2009 corr.)

Guideline on setting specifications for related impurities in antibiotics

Active substances	**Semi-synthetic ***	**Fermentation, single**	**Fermentation, family**	**Peptides**
Reporting	0.05%/0.03%	0.10%	0.10%	0.1%
Identification	0.10%/0.05%	0.15%	0.15%	0.5%
Qualification	0.15%/0.05%	0.15%	0.50%**/0.2%	1.0%

Identification / Quantification of Related Substances

Pharma
Consulting & Services

Related Substances:

- Identification
  - Relative retention times
  - Peak identification solution → CRS
  - External standards → CRS

- Quantification
  - Area normalisation
  - Dilution of main component
  - External standards (Impurity > 5.0 %) → CRS

Consequences of EMA Guideline

Pharma
Consulting & Services

Ph.Eur. 9.8.

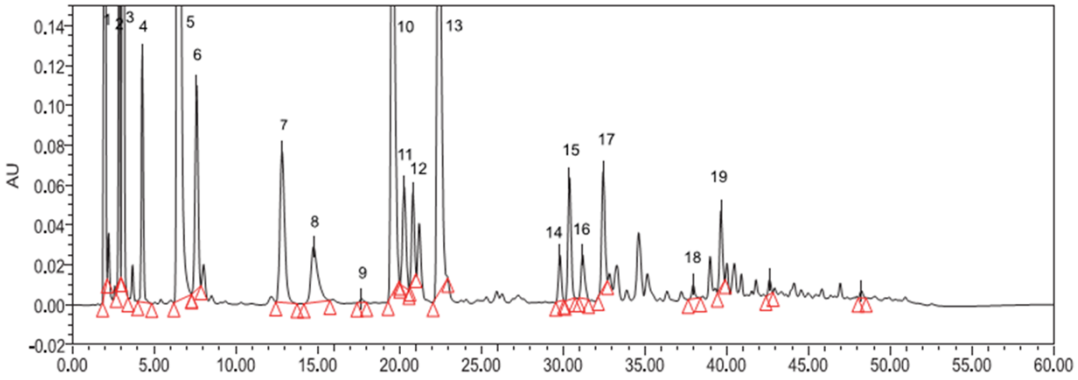
Limits of Impurities for Amoxicillin Sodium

	Limit
impurity J	≤ 3 %
any other impurity	≤ 2 %
total	≤ 9 %
disregard limit	0,1 %

Consequences of EMA Guideline

Pharma
Consulting & Services

Improved chromatographical separation of the impurities of Amoxillin sodium



Consequences of EMA Guideline

Pharma
Consulting & Services

Limits according to EMA Guideline

	Limit
Impurity J	≤ 2.0 %
Impurity D (sum of isomers D1, D2)	≤ 1.5 %
Impurity C (sum of isomers C1, C2) Impurity E (sum of isomers E1, E2) Impruity G	for each impurity ≤ 1.0 %
Impurity K (sum of isomers K1, K2)	≤ 0.8 %
sum of impurities F and P	≤ 0.6 %
Impurity L	≤ 0.5%
Impurity N	≤ 0.4%
Impurities A, B, H, I, M, O, U, V	for each impurity ≤ 0.3 %
Any other impurity	≤ 0.15 %
Total	≤ 4.0 %
Reporting threshold	≤ 005 %

- 21 impurities to be identified and quantified

Consequences of EMA Guideline

Last Proposal of the Experts of Group 7

	Limit
Impurity J	≤ 2.0 %
Impurity D (sum of isomers D1, D2)	≤ 1.5 %
Impurity C (sum of isomers C1, C2) Impurity E (sum of isomers E1, E2) Impruity G	for each impurity ≤ 1.0 %
sum of impurities F and P	≤ 0.6 %
Impurity K, L	each impurity ≤ 0.5%
Impurity N	≤ 0.4%
Any other impurity	≤ 0.30 %
Total	≤ 4.0 %
Reporting threshold	≤ 005 %

- 13 impurities to be identified and quantified

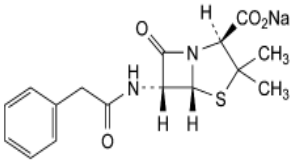
Assay of Antibiotics

Assay:

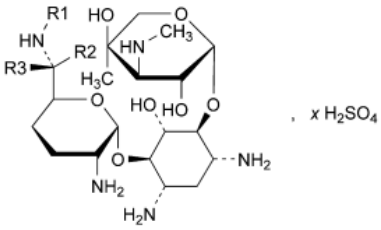
- Single component ➡ CRS
- Main component < 80 % ➡ CRS for microbiolocial assay
- Mixture of component ➡ CRS for microbiolocial assay

Reference standards for Antibiotic assays

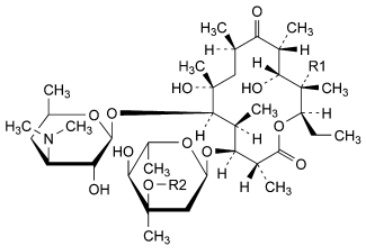
- CRS for microbiolocial assays regularly are secondary standards
- Property values for these CRS are assigned by comparison to primary WHO standards
- 26 monographs for antibiotics using microbiological assays
- Colistin Sulfate: Microbiological assay reintroduced (Ph.Eur. 7.6)
- Polymyxin B sulfate: Microbiological assay reintroduced (Ph.Eur. 9.7)



Benzylpenicillin Sodium



Gentamicin Sulfate



Erythromycin

Thank You for Your Attention

Microbiological Reference Standards

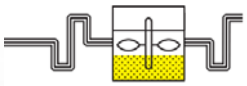
13th International Symposium on Pharmaceutical Reference Standards

13-14 March 2019, Strasbourg, France

Dr Sylvie JORAJURIA
Head of the Biology Section
Laboratory Department
EDQM – Council of Europe

Antibiotics in Ph. Eur. monographs

Production process of antibiotics
- Synthetic
- Semi-synthetic
- Fermentation



→ Single compound
Mixture of compounds

Specific quality requirements

Related substances
- limit for unspecified impurities
- total impurities
- disregard limit

Assay
- LC: content in %m/m determined against a CRS with assigned value
- microbiological: different type of RS and arbitrary units valid wordwide

Heterogeneity of antibiotic assay units

- RS for antibiotic assay may be expressed in:

International system of units (SI)

mg

- applicable to chemically homogeneous (pure) substances
- CRS established using mass balance approach based on monograph methods
- traceable to a higher order standard

-> content

LC improved

Arbitrary units

International Units

- essential for substances of complex and heterogeneous chemical structure
- unitage assigned by WHO
- traceable to a higher order standard

-> potency
determined by measuring antibiotic inhibitory effect on a microorganism

Other arbitrary units

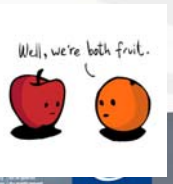
"unit" of antibiotic

- more than one active compound in the antibiotic

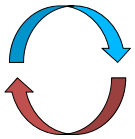
"µg" of activity

- thought to consist of a single chemical entity

Discrepancy in arbitrary units:
- legacy of the past
- questioned by users
- risk of misuse of RS and units



Lost in conversion



- **Principle:**
  - quantity of substance is measured in mass
  - potency is estimated in units defined by a reference standard

-> potency of complex antibiotics (mixtures) cannot be measured in terms of mass

- **Definition of IU:**
  - activity contained in a given amount (mg or vial) of a particular batch of a reference standard expressed in an assay system -> **≠ mass unit**
  - IU depends on the activity of the substance and therefore varies from substance to substance

Example: 1st ISA for Gentamicin
The IU was defined in 1968 as the activity contained in 0.00156 mg of the preparation

1 IU ≠ 0.00156 mg and 1 IU ≠ 1.56 µg
but in this case 1 IU = 1"µg" of activity

-> Do not use conversion factor
Use the RS established for the intended purpose in the corresponding Pharmacopoeia

Reference standards for microbiological assay of antibiotics at EDQM

Primary standard: International Standard for Antibiotic (ISA)

- Use: establishment of national/regional secondary standards
- Established, kept, distributed by EDQM, approved by WHO

Secondary standard: Ph. Eur. CRS for microbiological assay of antibiotic

- Use: routine quality control
- Established by EDQM against the ISA, approved by the Ph. Eur. Commission

➡ Advantages of Ph. Eur. CRS:
Traceability is ensured
Same unitage: International Unit (IU)

Adoption of WHO ISA and spread of IU

- 1950-1990: rapid increase in number of antibiotics needing standards
  -> **wide use of IU**
- today 23 of the 50 ISA established are in distribution
- characterization of many antibiotics by physico-chemical means improved
  -> discontinuation of some ISA
  -> however IU continue to be used in the clinical setting

W.H.O. ECBS 1967

Transitioning from microbiological assay to LC in Ph. Eur.

Introduction of LC can be envisaged when:
- **purity** of antibiotic is high e.g. > 90 %
- structure of the substance is known
- selective and accurate chromatographic methods are available

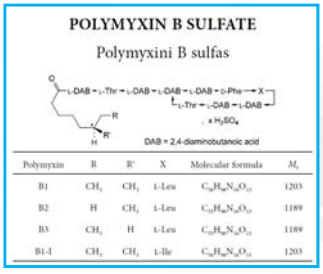
Examples in the Ph. Eur.:

Antibiotic	CRS for LC assay	CRS for microbiological assay	ISA
Tobramycin	yes	no	yes
Erythromycin	yes	yes	yes
Dihydrostreptomycin sulfate	yes	no	yes
Netilmicin sulfate	yes	yes	yes

Re-introducing microbiological assay

Challenges of LC assay for mixtures:
- preparation and the establishment of the required reference substance can be technically difficult
- biological activity of the different physicochemical entities might not be identical

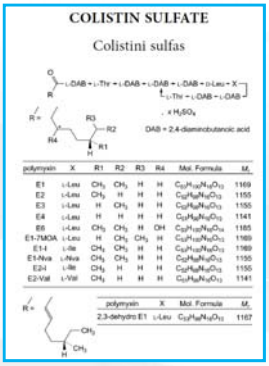
Example: mixture of polypeptide sulfates


POLYMYXIN B SULFATE

Polymyxini B sulfas

DAB = 2,4-diaminobutanoic acid

Polymyxin	R	R'	X	Molecular formula	M_r
B1	CH_3	CH_3	L-Leu	$C_{56}H_{98}N_{16}O_{13}$	1203
B2	H	CH_3	L-Leu	$C_{55}H_{96}N_{16}O_{13}$	1189
B3	CH_3	H	L-Leu	$C_{55}H_{96}N_{16}O_{13}$	1189
B1-I	CH_3	CH_3	L-Ile	$C_{56}H_{98}N_{16}O_{13}$	1203


COLISTIN SULFATE

Colistini sulfas

DAB = 2,4-diaminobutanoic acid

polymyxin	X	R1	R2	R3	R4	Mol. Formula	M_r
E1	L-Leu	CH_3	CH_3	H	H	$C_{53}H_{100}N_{16}O_{13}$	1169
E2	L-Leu	CH_3	H	H	H	$C_{52}H_{98}N_{16}O_{13}$	1155
E3	L-Leu	H	CH_3	H	H	$C_{52}H_{98}N_{16}O_{13}$	1155
E4	L-Leu	H	H	H	H	$C_{51}H_{96}N_{16}O_{13}$	1141
E6	L-Leu	CH_3	CH_3	H	OH	$C_{53}H_{100}N_{16}O_{14}$	1185
E1-7MOA	L-Leu	H	CH_3	CH_3	H	$C_{53}H_{100}N_{16}O_{13}$	1169
E1-I	L-Ile	CH_3	CH_3	H	H	$C_{53}H_{100}N_{16}O_{13}$	1169
E1-Nva	L-Nva	CH_3	CH_3	H	H	$C_{52}H_{98}N_{16}O_{13}$	1155
E2-I	L-Ile	CH_3	H	H	H	$C_{52}H_{98}N_{16}O_{13}$	1155
E2-Val	L-Val	CH_3	H	H	H	$C_{52}H_{98}N_{16}O_{13}$	1141

polymyxin	X	Mol. Formula	M_r
2,3-dehydro-E1	L-Leu	$C_{53}H_{98}N_{16}O_{13}$	1167

-> In view of difficulties with the expression of the content of the substance after replacement of the microbiological titration by an LC assay, **the microbiological titration has been re-introduced**

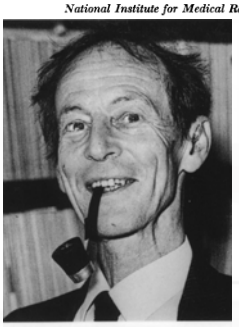
Towards standardisation: the diffusion method

HUMPHREY, J. H. & LIGHTBOWN, J. W. (1952). *J. gen. Microbiol.* 7, 129–143

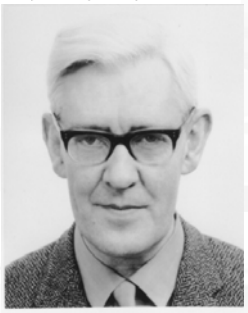
A General Theory for Plate Assay of Antibiotics with some Practical Applications

BY J. H. HUMPHREY AND J. W. LIGHTBOWN

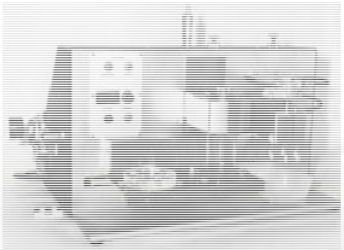
National Institute for Medical Research, Mill Hill, London, N.W. 7



J H Humphrey



J W Lightbown



Diffusion assay by an automated procedure - 1979

- Same assay system for most antibiotics
- Since 1952 the plate diffusion assay has remained technically the same, each assay takes 2 days

Towards harmonisation: general chapters

- **Ph. Eur.** general chapter
  2.7.2. Microbiological assay of antibiotics
- **USP** general chapter
  <81> Antibiotics – Microbial assays
- **JP** general chapter
  4.02 Microbial assay for antibiotics
- **International Pharmacopoeia** general chapter
  3.1 Microbiological assay of antibiotics

- Same methods described: diffusion, turbidimetry
- Procedure highly similar, design may differ
- Same intended purpose of reference standard
- Slight differences in the antibiotics listed

Towards harmonisation: reference standard units?

European Pharmacopoeia

- Use of **IU**:
  - per vial when CRS is freeze-dried
  - per mg when CRS is a powder
- Use of **Ph. Eur. Unit**:
  - only in the absence of ISA
    ex: Josamycin

US Pharmacopoeia

- Use of **µg/mg**
- Use of **Unit of antibiotic**
- **Use of µg/mg traceable to Ph. Eur. CRS or ISA**

ex: Amphotericin B:
USP RS: 994 µg amphotericin B/mg, "when tested against the Amphotericin B CRS 2, the value is 994 IU/mg"

ex: Vancomycin:
USP RS: 98800 µg vancomycin, "when tested against the WHO Vancomycin 2nd IS, the value is 98800 IU per vial"

Perspective

- Widespread and increasing resistance to antibiotics worldwide
- New antibiotics in development: it is not known if they are effective against the most dangerous forms of antibiotic-resistant bacteria
- Improvement of existing antibiotics and acceleration of the entry of new antibiotic drugs needed
- Recent recommendation that current WHO listing of international standards for antibiotics be reviewed

1923 Meeting on Standards

Edinburgh, 1st international meeting on standardization of biologicals

Thank you for your attention

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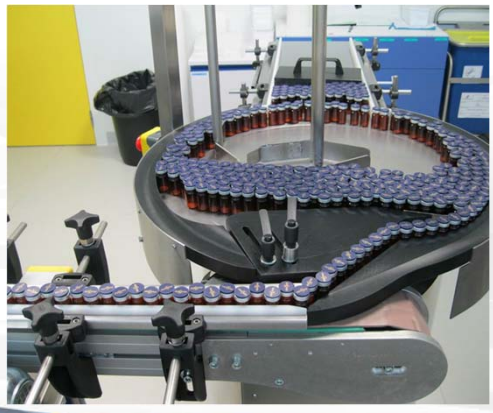
RS for general chapters

Dr Stefan Almeling

Deputy Head of Laboratory Department,

EDQM, Council of Europe



Background

Traditionally Ph.Eur. reference standards were established in relation to specific monographs rather than for equipment performance control.

In the recent years the situation has slightly changed in that some reference standards used for equipment or method performance control were described:

Recent examples:

- Sodium Aminosalicylate dihydrate for equipment qualification CRS
- Amoxicillin trihydrate for equipment verification CRS
- Paracetamol for equipment qualification CRS
- Nicotinic acid for equipment qualification CRS
- *EI Standards (Cd, As, Pb, Hg)*

WHERE ARE WE TODAY?

Ph.Eur. Chapter 2.2.48. Raman Spectroscopy

Paracetamol for equipment qualification CRS

Material thoroughly characterised for identity, purity, homogeneity

Table 2.2.48.-1. – *Wavenumber shifts (and acceptable tolerances) of polystyrene, paracetamol and cyclohexane*

	Wavenumber shifts[a] [cm^{-1}]	Tolerances	
		Benchtop [cm^{-1}]	Hand-held [cm^{-1}]
Polystyrene[b]	620.9	± 1.5	± 2.5
	1001.4	± 1.5	± 2.0
	1031.8	± 1.5	± 2.0
	1602.3	± 1.5	± 3.0
	3054.3	± 3.0	NA[c]
Paracetamol[c]	797.2	± 1.5	± 2.5
	857.9	± 1.5	± 2.0
	1168.5	± 1.5	± 2.0
	1236.8	± 1.5	± 2.0
	1323.9	± 1.5	± 2.5
	1648.4	± 1.5	± 3.0
	2931.1	± 2.0	NA[c]

NICOTINIC ACID FOR EQUIPMENT QUALIFICATION CRS

Control of absorbance accuracy. Control the absorbance accuracy at an appropriate number of wavelengths in the intended spectral range using suitable solid or liquid filters to check that the absorbance measured at the test wavelength matches the certified absorbance of the filter or the absorbance value that is calculated from a certified specific absorbance. *Nicotinic acid for equipment qualification CRS* may be used.

Acceptance criteria

The difference between the measured absorbance and the absorbance of the certified material is ± 0.010 or ± 1 per cent, whichever is greater, for each combination of wavelength and absorbance assessed (applies to absorbance values not greater than 2). Tolerances for higher absorbance values should be defined on the basis of a risk assessment.

NICOTINIC ACID FOR EQUIPMENT QUALIFICATION CRS

CRS leaflet info:

2.2 Analytical information related to the intended use
Specific absorbance:
213 nm: = 430.7
261 nm = 422.5

2.3 Uncertainty of the assigned property values
Uncertainty of the assigned specific absorbance values, expressed as expanded uncertainty (95% confidence interval, coverage factor of k=2): U_{213nm}: ±3.5, U_{261nm} :±2.8

SODIUM AMINOSALICYLATE DIHYDRATE FOR EQUIPMENT QUALIFICATION CRS

Ph.Eur. 2.5.12. Water: Semi-micro determination

… Instrument qualification is carried out according to established quality system procedures, for example using a suitable certified reference material (**sodium aminosalicylate dihydrate for equipment qualification CRS** may be used).

SODIUM AMINOSALICYLATE DIHYDRATE FOR EQUIPMENT QUALIFICATION CRS

2.2 Analytical information related to intended use, when applicable

2.2.32. – Loss on drying

Certified loss on drying value[1)]: 169.6 mg/g
Uncertainty[2)]: 0.4 mg/g

Test procedure: Determine the loss on drying in triplicate using 1000 mg of substance per determination. Drying conditions: 105 °C until constant mass (Ph. Eur. method 2.2.32. d))

Container dimensions (recommended): diameter about 50 mm; height about 30 mm.

2.5.12. – Semi-micro determination of water

Certified water content[1)]: 171.6 mg/g
Uncertainty[2)]: 1.0 mg/g

Test procedure: Carry out the test in triplicate using 100 mg of substance per determination.

Hydranal composite 5 was found suitable. If other solvents/titrants are used, carry the suitability test described in Ph. Eur. 2.5.12.

SODIUM AMINOSALICYLATE DIHYDRATE FOR EQUIPMENT QUALIFICATION CRS

Additional leaflet info:

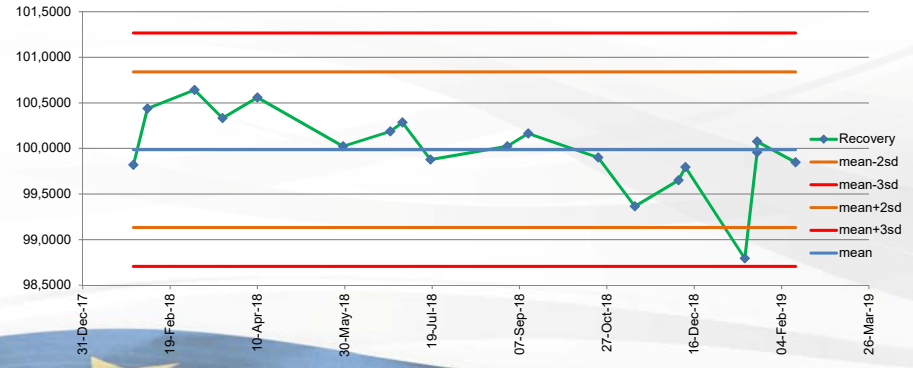
Suggested acceptance criteria:
Taking into account inter-laboratory standard deviation as well as the mean intra-laboratory standard deviation obtained the inter-laboratory study for the value assignment, the result of a measurement performed (following the above experimental conditions) is considered 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):	167.3 mg/g to 173.7 mg/g

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

SODIUM AMINOSALICYLATE DIHYDRATE FOR EQUIPMENT QUALIFICATION CRS

KF statistical equipment control chart



ELEMENTAL IMPURITIES SOLUTION CRS

Ph.Eur. 2.4.20. DETERMINATION OF ELEMENTAL IMPURITIES

ACCURACY

Verify the accuracy using a certified reference material or by performing a test for recovery. *Elemental impurity solutions CRS* may be used.

INFORMATION LEAFLET Ph. Eur. Reference Standard

Lead solution CRS batch 1

1. **Identification**

Catalogue code: Y0001996 Unit Quantity: ca 10 mL

2. **Scientific Information**

2.1 Intended use

Reference Standard for laboratory tests as prescribed in the European Pharmacopoeia.
Established for use with chapter: 20420.

2.2 Analytical information

Mass fraction of lead in the solution:	0.9996 mg/g
Associated expanded uncertainty:	U = 0.0050 mg/g, k = 2
Density of the solution:	1.013 g/mL at 21.6 °C
Solvent composition:	about 2.5 % m/m nitric acid

Traceability to the SI base units kilogram and mole is achieved through an uninterrupted chain of calibration measurements that link lead solution CRS 1 to a primary material characterised by a National Metrology Institute at the highest metrological level (High purity lead BAM-Y004).
The IUPAC standard atomic weight for lead shall be applied.
Dilutions of lead solution CRS 1 should be made with 2.5 % nitric acid.

CRS may also be suitable for other purposes, e.g.:
-standard for quantification
-for spiking / recovery testing

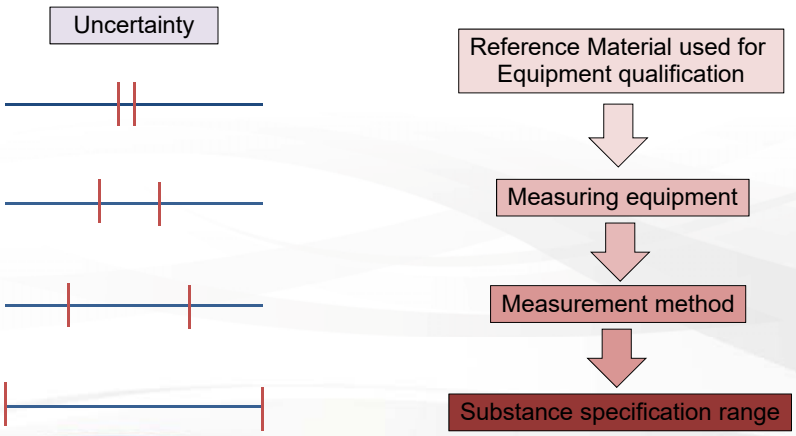
AND TOMORROW ?!

ARE YOU CERTAIN OF YOUR RESULT?

Neither the production nor measurement processes are devoid of error, there will always be some dispersion in the observed product value either for repeated measurements of one item or for measurements of a series of items.

Conformity assessment is focused on determining actual product errors: **apparent dispersion due to limited measurement capability should normally be small.**

ARE YOU CERTAIN?

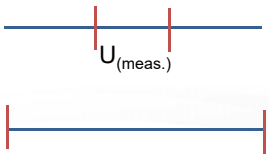


HOW "SMALL" IS SMALL ENOUGH?

ISO GUIDE 98-3 (GUM) – Type B evaluation of uncertainty
Method of evaluation of uncertainty by means other than statistical analysis of a series of observations, e.g.:
- Previous measurement data
- **Manufacturer`s specifications**
- Data provided in calibration and other certificates
- …

Ph.Eur. limit setting
Limits are based on data obtained in normal analytical practice; they take account of **normal analytical errors**, of **acceptable variations in manufacture** and compounding and of **deterioration** to an extent considered acceptable...

PRODUCT SPECIFICATION AND MEASUREMENT UNCERTAINTY



Measurement method

Substance specification range

GUIDE 98-3 (GUM)
Assuming that a two-sided specification limit correspond to the mean ± 3sd (i.e. 99.73%), and a normal (Gaussian) distribution of the measurement results, the related measurement uncertainty can be calculated as follows:

$$u_{(meas.)} = \frac{a}{\sqrt{9}}$$

where *a* is the specification range/2

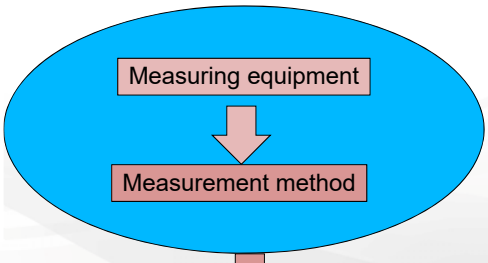
EXAMPLE OPTICAL ROTATION - SUCROSE

Ph.Eur. 2.2.7. Optical Rotation

EQUIPMENT PERFORMANCE

The accuracy of the scale is checked near the value to be measured or over an appropriate range, usually by means of certified quartz plates. Other certified reference materials may also be suitable (e.g. sucrose solutions).

Optical rotation measurements may be used to quantify the amount of an enantiomer or the ratio of enantiomers present in a sample. For that purpose, the linearity must be checked, for example using sucrose solutions.



Ph.Eur. Monograph: 01/2016:0204 Sucrose
Specific optical rotation: +66.3 to +67.0

Substance specification range

EXAMPLE OPTICAL ROTATION - SUCROSE

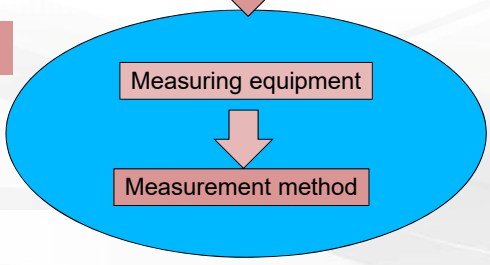
Ph.Eur. Monograph: 01/2016:0204 Sucrose
Specific optical rotation: +66.3 to +67.0

Substance specification range

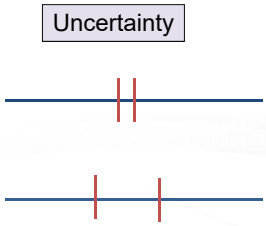
$$u_{(meas.)} \leq \frac{a}{\sqrt{9}} = \frac{{}^{1}/_{2} * (67.0 - 66.3)}{\sqrt{9}} \leq 0.117$$

k=2

$$U_{(exp.)} \leq 0.233$$



REFERENCE MATERIAL REQUIREMENTS



Reference Material used for Equipment qualification

Measuring equipment/method

Reference material (RM): A material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be **fit for its intended use** in the measurement process.

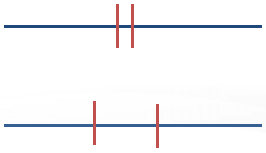
WHAT IS NEGLIGIBLE?

Although different rules (1/3-rule to 1/5-rule) are often applied in metrology, no clear rule could be identified as regards to what can be considered “small” or “negligible”.
Mathematically, the underestimation of the combined standard uncertainty ($u_{(x)}$) is as below, depending on the rule applied:

Omitting an uncertainty contributor of:	Underestimation of the combined standard uncertainty:
1/3	5%
1/4	3%
1/5	2%

REFERENCE MATERIAL REQUIREMENTS

Uncertainty



Reference Material used for Equipment qualification

Measurement equipment/method

$$U_{(exp.RM)} \leq k \times \frac{a}{\sqrt{9}} \div 3 \leq 2 \times \frac{0.35}{9} \leq \pm 0.078$$

NIST Sucrose CRM:
Certified value for specific optical rotation: **+ 65.517° ± 0.134**

EXAMPLE OPTICAL ROTATION - SUCROSE

Calculation of a metrological specification range compatible with the use of Sucrose NIST CRM

$$a = \frac{U_{(exp)} \times 9}{k} = \frac{0.134 \times 9}{2} = 0.603$$

Specific optical rotation: +66.1 to +67.3

CONCLUSION

- Reference standards for equipment qualification and control as described in the Ph.Eur. General methods are a highly relevant tool to ensure reliability off measurement results.
- Reference Standards for equipment qualification are highly characterized specimens that may be employed for additional purposes.
- Education and guidance of the users on the appropriate use of such standards is paramount.
- Suitability of compendial reference standards for equipment qualification is demonstrated, for other standards this must be carefully evaluated.
- Equipment / method capability should be taken into account when setting substance specific limits.

Thank you very much for your attention.

Stay connected with the EDQM

EDQM Newsletter: https://go.edqm.eu/Newsletter

LinkedIn: https://www.linkedin.com/company/edqm/

Twitter:@edqm_news

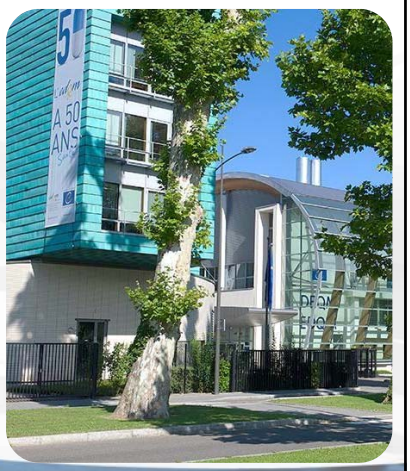
Facebook: @EDQMCouncil of Europe

Joint presentation EDQM and USP on FAQs

Frequently asked questions on EDQM reference standards

13th International Symposium on Pharmaceutical Reference Standards

13-14 March 2019, Strasbourg, France



Dr Matthias Weber
European Directorate for the Quality of Medicines & HealthCare (EDQM),
Council of Europe
Strasbourg, France

Content

- General reference.
- Where to find specific information?
- How to get in contact ?
- FAQs !

General reference

Ph. Eur. Chapter 1. GENERAL NOTICES

The General Notices apply to all monographs and other texts of the European Pharmacopoeia.

…

REFERENCE STANDARDS

Certain monographs require the use of reference standards (chemical reference substances, herbal reference standards, biological reference preparations, reference spectra). See also chapter 5.12. Reference standards. The European Pharmacopoeia Commission establishes the official reference standards, which are alone authoritative in case of arbitration. These reference standards are available from the European Directorate for the Quality of Medicines & HealthCare (EDQM).

General reference

Ph. Eur. Chapter 5.12. REFERENCE STANDARDS

- ✓ Terminology
- ✓ Use of Ph. Eur. Ref. Stds.
- ✓ Establishment (qualitative and quantitative)
- ✓ Manufacturing, Labelling, Storage and Distribution
- ✓ Re-Test Programme

Specific information

EDQM Reference substances online database

https://crs.edqm.eu/

Available since	Cat. No.	Name	Batch No.	Unit Quantity
	S0100000	Salbutamol	2	50 mg
	S0150000	Salbutamol sulfate	4	50 mg
	Y0000030	Salbutamol impurity B	6	5 mg
	Y0000031	Salbutamol impurity F	9	10 mg
	Y0000032	Salbutamol impurity I	4	0.006 mg
	Y0000034	Salbutamol impurity G	4	10 mg
	Y0000071	Salbutamol impurity D	6	10 mg
	Y0001186	Salbutamol impurity J	3	0.00045 mg
	Y0001288	Salbutamol sulfate for system suitability	3	10 mg

Specific information

Catalogue Code	S0150000
Name	Salbutamol sulfate
Current batch number	4
Unit quantity per vial	50 mg
Number of vials per sales unit	1
Used in monograph(s)	0687
Assigned content	
Additional information	
Leaflet	click to download the leaflet
Chemical hazard	Click to download Safety Data Sheet
Biological hazard	none identified
SDS Product Code	201600809
CAS Registry Number	51022-70-9
Presentation	
Origin	click to download Origin Of Goods.pdf
Proposed Import HS code	292250
EDQM long term storage conditions	+5°C ± 3°C
Dispatching conditions	Ambient temp.
UN Code	Not classified
Shipping group	A1A
Price*	79 EUR
Availability	Available
Sales restriction	No

Batches

batch 4 is valid at this date

Print BVS

Batches

batch 3 : validity until 28 February 2019

Print BVS

Specific information

Name	Benzylpenicillin sodium
Catalogue code	B0900000
Batch number*	8
Assigned value	See leaflet
Validity	Batch 8 is valid at the printing date: 2019-2-8
Additional information	
Storage conditions	The standard is intended for immediate use. Recommended EDQM storage conditions for unopened containers : +5°C ± 3°C
Safety data	Safety Data Sheet is available from the detailed view or upon request.
Leaflet	Click on the hyperlink to download the leaflet containing the instructions for use, **if available** (Adobe Acrobat Reader version 5 or higher, or the corresponding browser plug-in is needed to open the file) click to download the leaflet
Origin	Click on the hyperlink to download the origin to check if import permit is required in your country, **if available** (Adobe Acrobat Reader version 5 or higher, or the corresponding browser plug-in is needed to open the file) click to download Origin Of Goods.pdf

European Directorate for the Quality of Medicines & HealthCare
European Pharmacopoeia (Ph. Eur.)
7, Allée Kastner CS 30026, F-67081 Strasbourg (France)
Tel. +33 (0)3 88 41 20 35 Fax. + 33 (0)3 88 41 27 71
For any questions: www.edqm.eu (HelpDesk)

edqm — European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE — CONSEIL DE L'EUROPE

INFORMATION LEAFLET Ph. Eur. Reference Standard

Caffeine CRS batch 4

1. **Identification**

Catalogue code: C0100000 Unit Quantity: ca 70 mg

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): 0267, 0268, 1504, 2412, 2668, 2669, 2678.

2.2 Analytical information related to intended use, when applicable

The "as is" content is : **99.9% C8H10N4O2 (for 1504, 2412, 2668, 2669 and 2678)**

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/desiccate 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.

Specific information

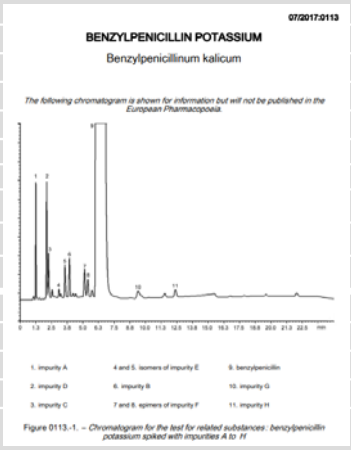
European Pharmacopoeia
Book – Online – Downloadable Version
http://online.edqm.eu

Specific information

The EDQM Knowledge Database

https://www.edqm.eu/en/knowledge-database

Status	In use
Monograph Number	00113
English Name	Benzylpenicillin potassium
French Name	Benzylpénicilline potassique
Latin Name	Benzylpenicillinum kalicum
Pinyin Name	
Chinese Name	
Pharmeuropa	24.3
Published in English Supplement	9.2
Published in French Supplement	9.2
Chromatogram	Available
Additional information	Not available
History	View history
Interchangeable (ICH_Q4B)	NO
Chapter 5.8 Pharmacopoeial harmonisation	NO



Reference standards

Available since	Cat. No.	Name	Batch No.	Unit Quantity	Price	SDS Product Code
	B0700000	Benzylpenicillin potassium	2	100 mg	79 EUR	
	B0900000	Benzylpenicillin sodium	8	200 mg	79 EUR	
	P1100000	Phenoxymethylpenicillin potassium	4	250 mg	79 EUR	
	Y0001889	Benzylpenicillin for system suitability	1	10 mg	79 EUR	

Practical Information

Test(s)	Brand Name/Information
Related substances	From 9.2: YMC Pack-Pro is suitable. D0 (dwell volume used for development of the method) = 1.7mL
Assay	From 9.2: Waters Atlantis T3 is suitable

Get in contact

EDQM FAQ & Helpdesk

https://www.edqm.eu/en/edqm-helpdesk-faqs

Register for the EDQM Helpdesk

https://www.edqm.eu/register/

Interesting questions

Can I use compendial reference standards for method validation or stability studies?

Compendial reference standards are established for the intended use in the correponding monograph(s). The required information is provided in the accompanying leaflet.

The use of compendial reference standards for other purposes is within the reponsibility and justification of the user, not because they are unsuitable, but because we cannot know the specific requirements beyond the monograph.

For example, the availability of the same batch of a reference standard for the duration of a stability study should not be assumed.

[Note: Please see Ph. Eur. Chapter 5.12 Section 3 on the conditions for the use of Ph. Eur. reference standards with an assigned content for determination of content/potency in pharmaceutical preparations.]

Interesting questions

How can we establish a traceable in-house standard?

For qualitative reference standards, it is possible to prepare an in-house standard traceable to the compendial reference standard.

However, for quantitative in-house standards this is more difficult because the uncertainty of the value of the compendial reference standard is not needed for the intended use in the corresponding monograph and so it is not given (see Ph. Eur. Chapter 1.4 General Notices Sub-section Limits).

A suitable approach would be to establish a primary in-house standard thouroughly characterised, and verified against the compendial ref. standard.

Interesting questions

What is the validity of a compendial reference standard?

Compendial reference standards do not come with an expiry date, however their validity is provided to users.

A re-test programme is established and implemented to ensure the continued fitness-for-use of the European Pharmacopoeia reference standards.

The user can document the suitability of the CRS batch at the time of use via our online reference standard database, where a batch-validity-statement (BVS) is available for printing.

Interesting questions

How do you confirm the identity of your reference standards?

A substance, mixture or preparation to be established as compendidal reference standard is characterised using a variety of analytical techniques, in addition to the relevant tests described in the corresponding Ph. Eur. monograph(s).

This may include NMR, MS, IR and elemental analysis as well as other techniques.

[Please see Ph. Eur. Chapter 5.12. Reference standards Sub-chapter 4.4. Ph. Eur. biological reference preparations (BRP) and chemical reference substances for biologicals that are established through the Biological Standardisation programme.]

Interesting questions

How do you assign the content of your reference standards? And what is meant by content 'as is' ?

Quantitative reference standards are tested for the relevant requirements of the correponding monograph(s). Furthermore, water, residual solvents, loss on drying, related substances and inorganic impurities are quantified (mass-balance).

The obtained content is verified by independent methods (e.g. qNMR, DSC, titration, elemental analysis).

The content assigned is 'as is'. Therefore, do not dry or desiccate the reference standard before use. Allow the closed container to equilibrate at ambient conditions before opening to avoid uptake (or loss) of moisture.

More Questions?

FAQ & Helpdesk Refence Standards (RS)

https://www.edqm.eu/en/faq-helpdesk-reference-standards-rs

HelpDesk
Publications Registration

Welcome

Empowering a healthy tomorrow

Joint presentation EDQM and USP on FAQs

Ravi Reddy
Sr. Director, Reference Standards Evaluation

March 13, 2019

Agenda

Topics

- Example Questions
- Resources / References

Example Question - 1

- **How is USP label value calculated?**
  - USP assigns label value only for quantitative standards, both Assay and Impurities
  - USP method of choice for calculating the label value is by mass balance taking into account the impurities, water content, residual solvents, inorganic impurities, Loss on Drying
  - Either Water + Residual solvents or Loss on Drying but not a combination of LOD + Water / Residual Solvents
  - For mixtures the label value is assigned based on the determination against pure standards

Example Question - 2

- **Basis for Use / Handling Conditions**
  - Label states on how to use and must be followed
  - Assigned Label value (typically mg/mg) for quantitative standards should be taken into account
  - “As Is” basis is the preferred approach if supported by the results
  - Handling conditions are added for example use at NMT 40%RH or between 20 and 40% RH
  - Additional details, if applicable, are included in the Certificate
  - Determine water content or loss on drying at the time of use

Example Question – 2 *(Cont.)*

- **Basis for Use / Handling Conditions**
  - Determine Water Content or Loss On Drying at the Time of Use *(Cont.)*
    - Materials for which the water content depends on the %RH at the time of use
    - Results may be different from vial to vial
    - Determination each time even if the same vial is used
    - Results from one vial cannot be used for other vials
    - Monograph acceptance criteria for release of GMP materials to determine compliance are not applicable for Reference Standards
    - Water content / LOD value should be used to correct the weight but the assigned value on the label must not be recalculated

Example Question - 3

- **Use of alternative standards**
  - Users to decide whether or not use alternative standards (secondary standards) or other approaches to achieve compliance
  - Any compliance related matters should be discussed with the applicable authority
  - As per General Notices 5.80: “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”

Example Question - 4

- **Assumption of 100%**
  - Currently 100% assigned value cannot be assumed
  - Under the “Older Process: “*Unless otherwise stated on the Reference Standard label, a value of 100.0% should be used in USP or NF compendial applications for which the use of this Reference Standard is intended.*”
    - The assumption of 100% was meant for quantitative compendial use
  - Under the Current Process: No such statement is in the Certificate. Label Value is assigned for any quantitative use.
    - There is no assigned value for any qualitative use Reference Standards such as System suitability (Resolution), Peak Identification etc.
    - Chapter <11> is currently being updated to clarify

Example Question - 5

- **Back Orders / Out of Stock Items**
  - If expected to be available within 30 days then shipped as per the order
  - If the expected availability exceeds 30 days
    - Notice of Availability (NoA) is sent to determine if customer is still interested
    - If no customer response within 45 days from NoA then order is cancelled
  - Unfortunately exact date of availability cannot be provided due to extenuating circumstances such as timing of bulk receipt, test results availability, approval of Reference Standards Evaluation Package by Expert Committee / standards setting committee etc.
  - Changes to estimated date of availability are mostly due to unforeseen situations that are out of USP control
  - Sign up online store “Notify Me When available”

Example Question - 6

- **Package size**
  - The amount is mentioned on the label of vials / ampoules
  - The amount should be sufficient for one complete analysis for one monograph
  - The amount mentioned on the label is NOT an exact amount, therefore, should not be taken as such
  - For non-Controlled substance, Vials / Ampoules are typically overfilled so that the customers can retrieve at least the stated amount
    - It may be possible that the stated amount on the label cannot retrieved for highly static materials
  - For Controlled Substances, due to stringent DEA monitoring, the amount is very close to the stated amount on the label

Example Question - 7

- **Reference Standards for USP non-compendial use**
  - No label value is provided
  - Handling conditions are included
  - Additional information may be provided in the Certificate
    - Contains approximately x.xx mg/mg or contains xxxx PPM
    - Technique used
  - Examples
    - Melamine in skim milk powder
    - Linezolid Related Compound C

Resources and References

- RSTech@USP.org
- **Certificate**
- **USP Store**
  - Certificate, Safety Data Sheet, Valid use Date if applicable, etc.
- **Frequently Asked Question on the website**
  - http://www.usp.org/frequently-asked-questions/reference-standards

Become a USP Volunteer Expert

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- Share expertise and collaborate with colleagues worldwide
- Add distinction to your career

Currently looking for volunteering candidates with experience in:

- Development and characterization of reference standards
- Metrology and ISO reference standards guidelines
- Chemical medicines, excipients, biologics, and dietary supplements

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Questions

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