Kontrolle von Verunreinigungen mittels HPLC im Europäischen Arzneibuch - Anforderungen und Entwicklungen

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INHALT

- Kontrolle von Verunreinigungen im E.P.
- Akzeptanzkriterien für Verunreinigungen
- Revisionsprogramm TLC- HPLC
- Peakidentifizierung
- Säulenauswahl und -beschreibung
- Systemeignungstests
- Anforderungen der EP für chromatographische Trennungen, neue Entwicklungen

IMPURITIES CONTROL: RECENT REVIEW

- Reflect regulatory practice in monographs
- Application of ICH guideline Q3A to pharmacopoeial substances --> focus on quantitative aspects
- Adaptation to globalisation
- Revise general texts for impurity control
- Revise monographs , in particular progressive replacement of TLC by LC, GC or CZE

General monograph: Substances for Pharmaceutical Use

- To be read in conjunction with the individual monographs
- The general monograph for substances for pharmaceutical use does not apply to herbals and herbal drug products

General monograph: Substances for Pharmaceutical Use

Related substances

Unless otherwise prescribed, organic impurities in active substances are to be reported, identified wherever possible, and qualified as indicated in Table 2034.-1.

Specific thresholds may be applied for impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects.

Substances for Pharmaceutical Use (2)

Use	Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
Human or human and veterinary	≤ 2 g /day	> 0.05 per cent	> 0.10 per cent or daily intake > 1.0 mg (whichever is the lower)	> 0.15 per cent or daily intake > 1.0 mg (whichever is the lower)
Human or human and veterinary	> 2 g/day	> 0.03 per cent	> 0.05 per cent	> 0.05 percent
Veterinary only	Not applicable	> 0.1 per cent	0.2 per cent	> 0.5 per cent

Thresholds do not apply for*

- Biological and biotechnological products
- Peptides
- Oligonucleotides
- Radiopharmaceuticals
- Products of fermentation and semi-synthetic products derived therefrom
- Crude products of animal or plant origin or herbal products

*see chapter 5.10 Control of impurities in substances for pharmaceutical use

Standard requirements in an E.P. monograph

- **Limits for:**
  - ✓ Specified impurities
  - ✓ Unspecified impurities
  - ✓ Total impurities
  - ✓ Disregard limit
- **Impurities section (transparency list)**
  - ✓ Specified impurities
  - ✓ Other detectable impurities
- **If the impurities section is not divided, all the impurities cited are specified**

Specified impurities

- Specified impurities are those in specifications for approved products
- Specifications for approved products and batch analysis data for approved products
- Specified impurities are qualified at or above the level indicated in the monograph

Other detectable impurities (ODIs)

Specific EP category

- Impurities sections in monographs may have a list of ODIs
- Analytical information only: the impurity is detected by the monograph method
- ODIs are limited in the monograph by the limit for "unspecified impurities" (or *Substances for Pharmaceutical Use*)

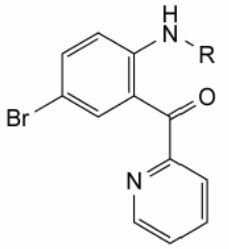
Transparency list

Bromazepam

IMPURITIES

Specified impurities: *A, B, E.*

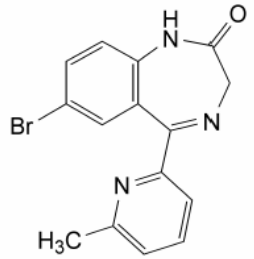
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034).* It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *C, D.*



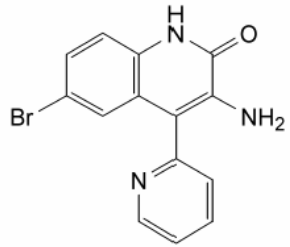
A. R = H: (2-amino-5-bromophenyl)(pyridin-2-yl)methanon

B. R = CO-CH_2-Cl: *N*-[4-bromo-2-(pyridin-2-ylcarbonyl)phenyl]-2-chloroacetamide,

E. R = CO-CH_2-Br: 2-bromo-*N*-[4-bromo-2-(pyridin-2-ylcarbonyl)phenyl]acetamide,



C. 7-bromo-5-(6-methylpyridin-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one,



D. 3-amino-6-bromo-4-(pyridin-2-yl)quinolin-2(1*H*)-one.

General chapter 5.10 (E.P. 5.5)

Control of impurities in substances for pharmaceutical use (E.P. 5.10)

Defines:

- Basis for the elaboration of monographs with regards to the control of impurities
- Terminology
- Interpretation of related substances tests
- Other aspects of impurities control

ESSENTIAL READING!

Control of impurities in substances for pharm. use

The tests are intended to cover organic and inorganic impurities that are relevant in view of the sources of active substances in authorised medicinal products.

Control of residual solvents is provided by the general monograph Substances for pharmaceutical use and general chapter 5.4 Residual solvents.

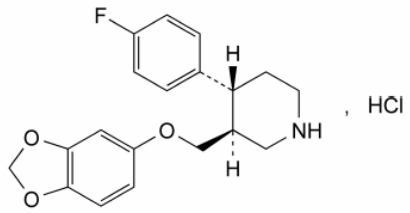
Instructions for the control of impurities may be included in the Production section of a monograph, for example where the only analytical method appropriate . . . is to be performed by the manuf. since the method is technically too complex for general use . . .

Example: Anhydrous paroxetine HCl

04/2007:2283

PAROXETINE HYDROCHLORIDE, ANHYDROUS

Paroxetini hydrochloridum anhydricum



$C_{19}H_{21}ClFNO_3$ M_r 365.8

Specified impurities:
A, B, C, D, E, F, G, H, I, J

PRODUCTION

Impurity G: maximum 1 ppm, determined by liquid chromatography, coupled with tandem mass spectrometry using a suitable, validated method.

Interpretation of the related substances test

A specific monograph on a substance for pharmaceutical use is to be read in conjunction with the general monograph on substances for pharmaceutical use.

Where a monograph has no related substances test (or equivalent) but only specific tests, the user of a substance must nevertheless ensure that there is suitable control of organic impurities.

Where an impurity other than a specified impurity is found in an active substance, it is the responsibility of the user of the substance to check whether it has to be identified / qualified

edqm

Interpretation of the related substances test

Acceptance criteria for the related substances test are **presented in different ways** in existing monographs.

A decision tree is given to be used as an aid in the interpretation of the of the general acceptance criteria and their relation with the Impurities section of the monograph.

General acceptance criteria for "other" impurities are currently expressed in various ways in the monographs:

"any other impurity", "other impurities", "any impurity", "any spot", "any band", etc.

Pending editorial adaption of already published monographs, the decision tree may be used to determine the acceptance criteria to be applied.

Revision needs

- Replace TLC by LC, GC or CZE
- Add a limit for total of impurities
- Allow unambiguous peak identification
- Bring general acceptance criterion in line with "Substances for pharmaceutical use"
- Introduce impurity section (transparency list)

Special revision programme

About 60 monographs revised since 2004

Identification of impurities

Ph. Eur. - Reference Substances for peak identification

The identification of a given impurity is needed

- when the impurity has an individual limit, and/or
- when a correction factor must be applied.

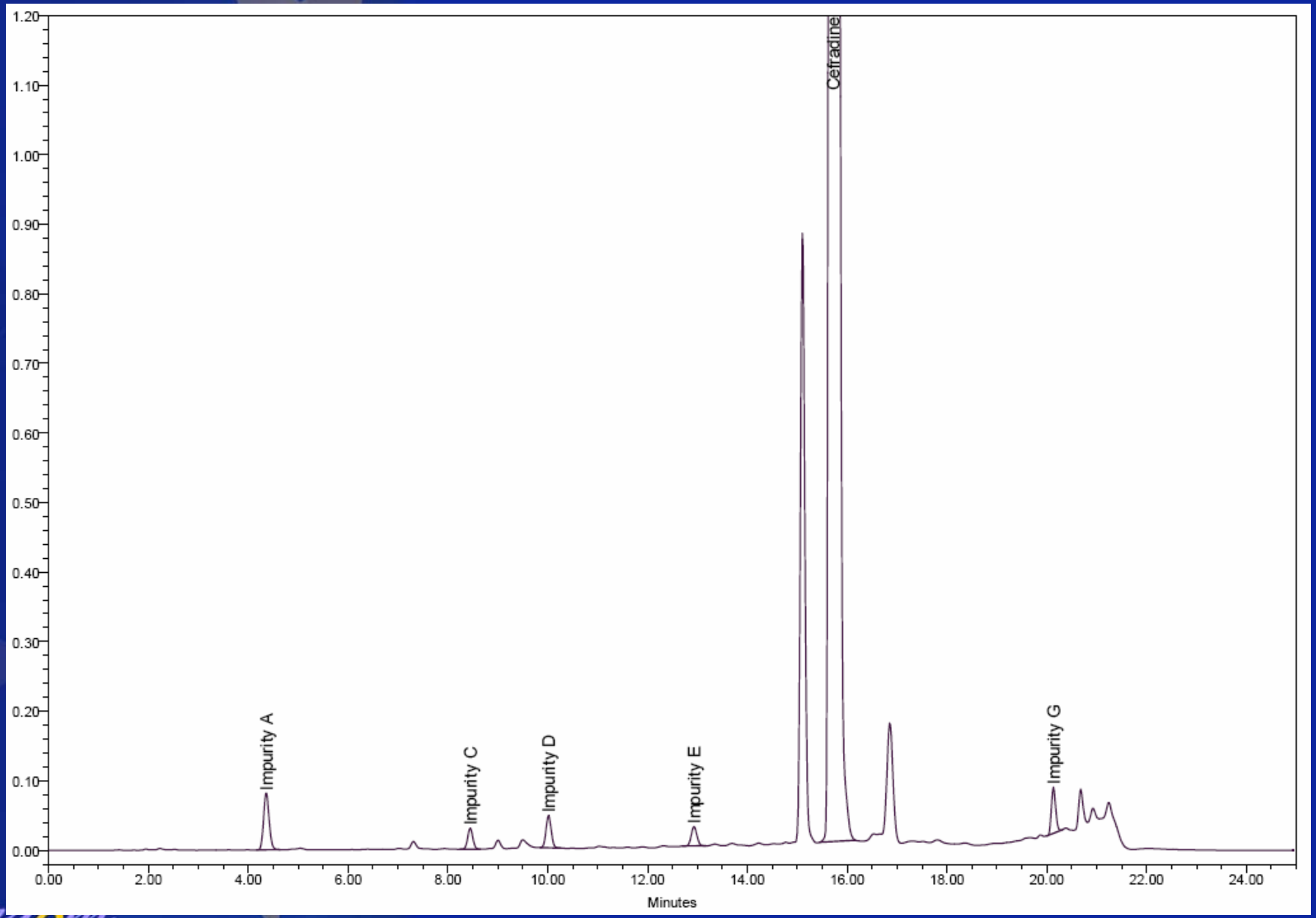
- In all the other cases although desirable, the identification is not required.

- The method of choice to identify an impurity in a chromatogram is by comparison with an authentic sample.

Ph. Eur. - Reference Substances

CONSTRAINT: an impurity is available in scarce quantity

CRS: a samples containing the impurity of interest (a "bad batch", a spiked batch, a mixture of substance and its impurities).


Cefradine
Impurity A
Impurity C
Impurity D
Impurity E
Impurity G
1.20
1.10
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
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2.00
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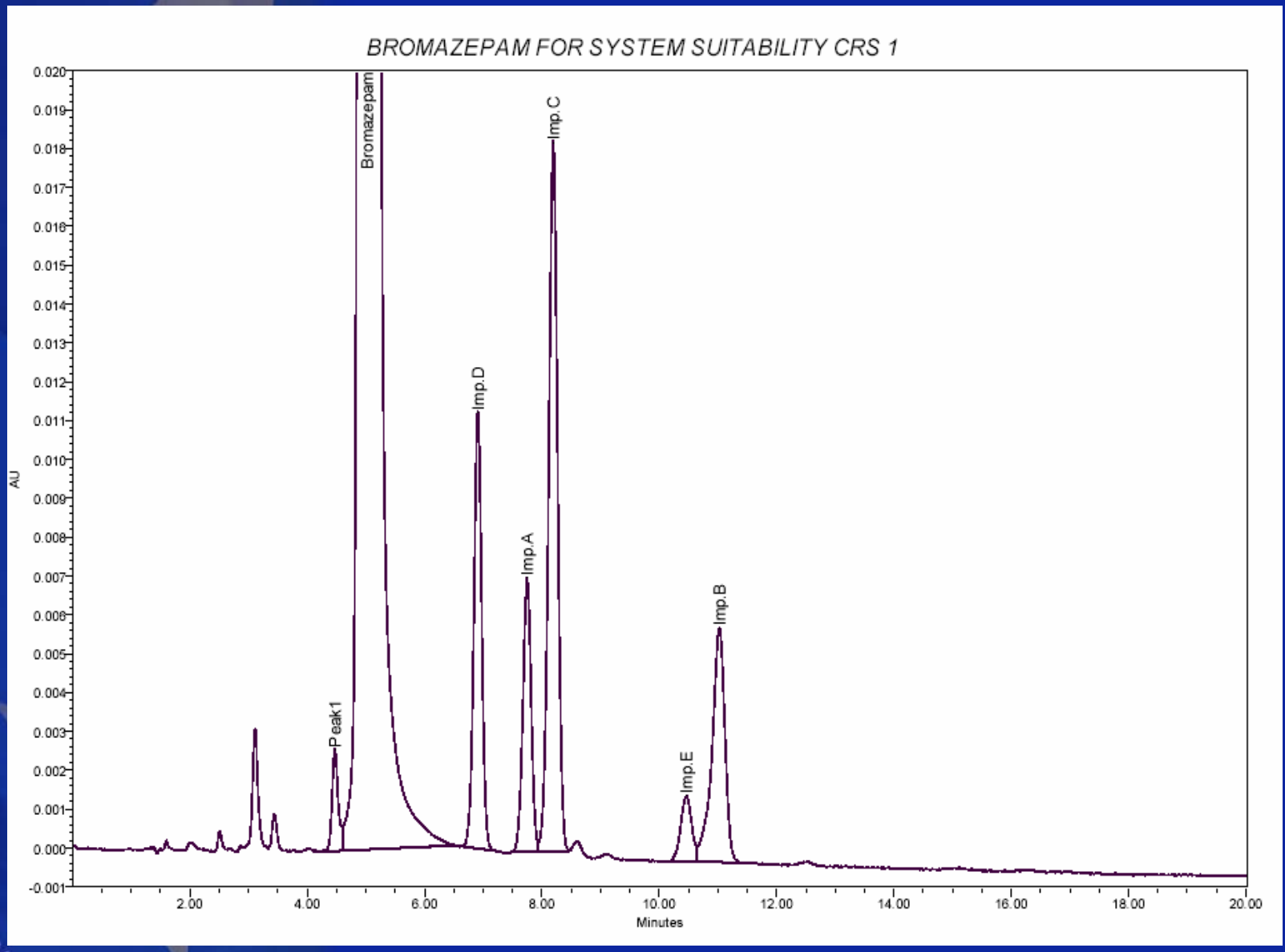
14.00
16.00
18.00
20.00
22.00
24.00
Minutes


BROMAZEPAM FOR SYSTEM SUITABILITY CRS 1
AU
Minutes
Peak1
Bromazepam
Imp.D
Imp.A
Imp.C
Imp.E
Imp.B
0.020
0.019
0.018
0.017
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0.015
0.014
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0.009
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2.00
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16.00
18.00
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Is retention time a system suitability requirement ?

Collaborative study to valuate a LC method for Dicloxacillin sodium

Lab	Column	Dimensions (mm)	Source	Symmetry	Resolution	Retention Time (min)	Repeatability (RSD) of Retention Time
1	Hypersil-ODS (5 µm)	4.6 x 250	C	1.3	5.1	17.16	0.55
2	Kromasil C-18 (5 µm)	4.6 x 250	C	1.4	10.4	18.03	0.64
3	Kromasil 100A C-18 (5 µm)	4.6 x 250	C	1.6	9.0	24.95	0.14
4	Nucleosil C18 (5 µm)	4.6 x 250	C	1.2	8.0	16.81	1.03
5	Lichrospher 100 RP18 (5 µm)	4.6 x 250	C	1.2	9.5	24.69	1.15
6	Hichrom C-18 (5 µm)	4.6 x 250	C	1.0	6.7	7.78	0.59
7	Lichrospher 100 RP18 (5 µm)	4.6 x 250	C	1.0	10.2	28.55	0.13
8	Altima C18 (5 µm)	4.6 x 250	C	1.5	10.4	39.26	0.45
9	Hypersil-ODS (5 µm)	4.6 x 250	C	1.9	6.2	12.76	0.31

C = Commercial.

But: Relative retention is more stable and may be used !

edqm

System suitability and column description

LC methods in the Ph. Eur. originally developed and validated by manufacturers, i.e. well-defined equipment and column(s).

Robustness challenged by the fact that only a general description of the column can be given. The chromatographic behaviour with the variety of commercially available "C 18" columns is very often too variable, esp. with gradients.

→ need to provide CRS **and** chromatogram

→ need to set appropriate criteria (SST)

→ info on the columns used

edqm

Related substances:

- LC gradient elution, UV detection (ex: Amiodarone HCl)

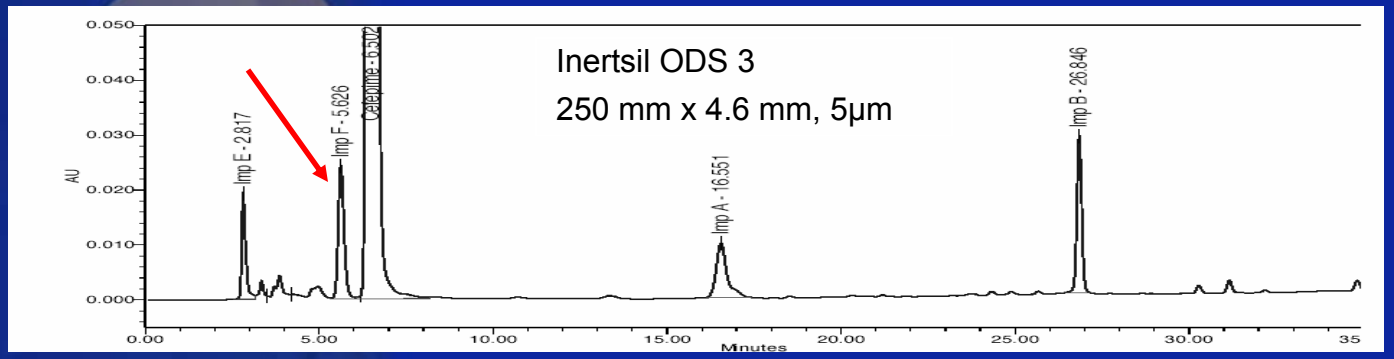
Stationary phase

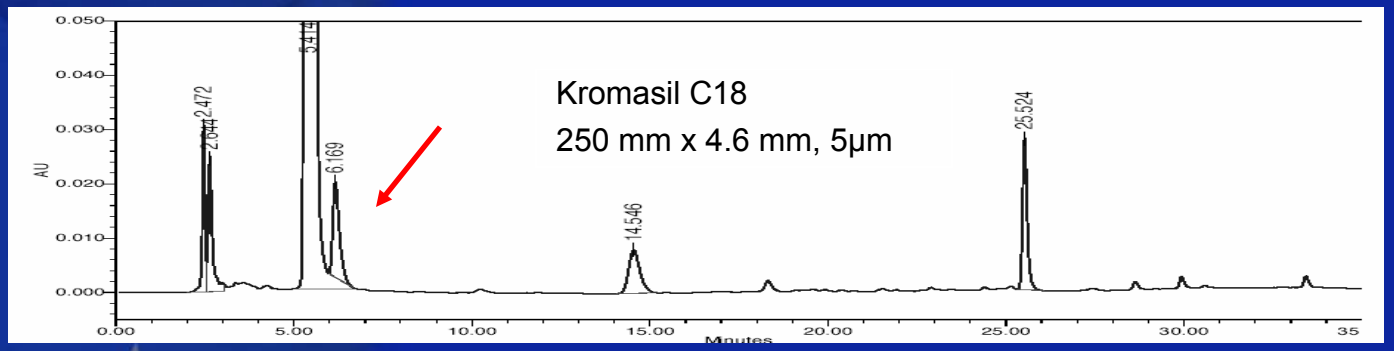
Column:
— *size*: *l* = 0.15 m, Ø = 4.6 mm,
— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm),
— *temperature*: 30 °C.

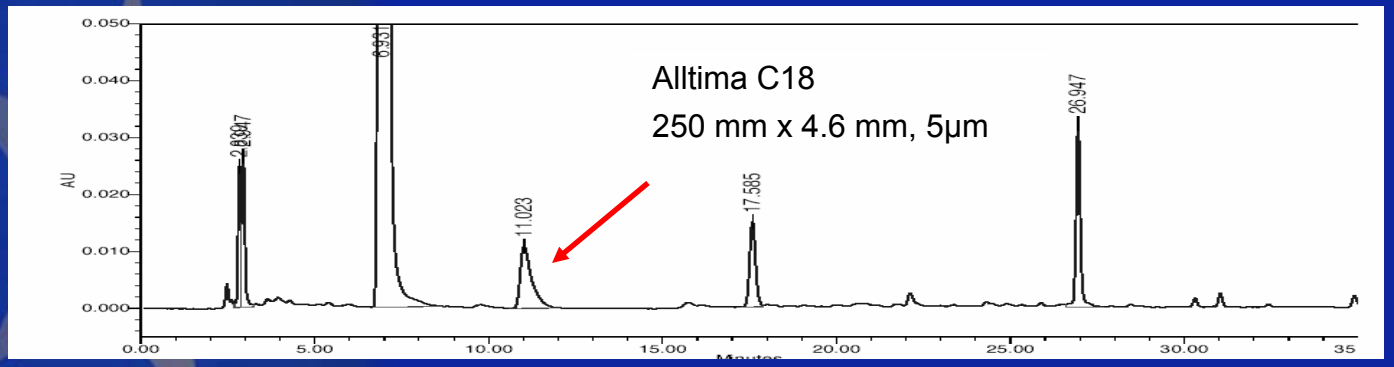
What you will find in the monograph:

- dimensions, particle size, type of stationary phase.

CEFEPIME FOR SST CRS 1







Knowledge database

Search Database online | Knowledge Database

Detailed view of Bromazepamum.

Monograph Number	879
English Name	Bromazepam
French Name	Bromazépam
Latin Name	Bromazepamum
State of Work	5
Pharmeuropa	17.1
Published in Supplement	5.7
Revision in progress	No
Chromatogram	None
Additional information	No pdf, View history

Reference standards

Available since	Cat. No.	Name	Batch No.	Unit Quantity	Price
	B1143000	Bromazepam - * psy	3	60 mg	79 EUR
	T0040000	Temazepam - * psy	1	50 mg	79 EUR
21/09/2006	Y0000645	Bromazepam for system suitability - * psy	1	10 mg	79 EUR

Trade Names

To be used in test(s)	Brand Name
Related substances	Column : l = 0.15 m, diam. = 4.6 mm, 3.5 µm, Zorbax Eclipse XDB-C18

CEP

Substance Number	Substance	Certificate Holder	Certificate Number	Delivery Date	Revision Date	
879	Bromazepam	Centaur Chemicals Private Ltd IND 400 055 Mumbai	R0-CEP 2004-172-Rev 00	17/03/2006		C
879	Bromazepam	Sintefina Industria E Comercio Ltda BR 09990-410 Diadema, Sao Paulo	R1-CEP 1998-150-Rev 01	14/04/2000 14/04/2005	02/12/2005	C

Ranking/classification systems available on the internet

- www.rheodyne.com
- www.pharm.kuleuven.ac.be/pharmchem/columnclassification
- www.acdlabs.com/columnselector

System suitability criteria

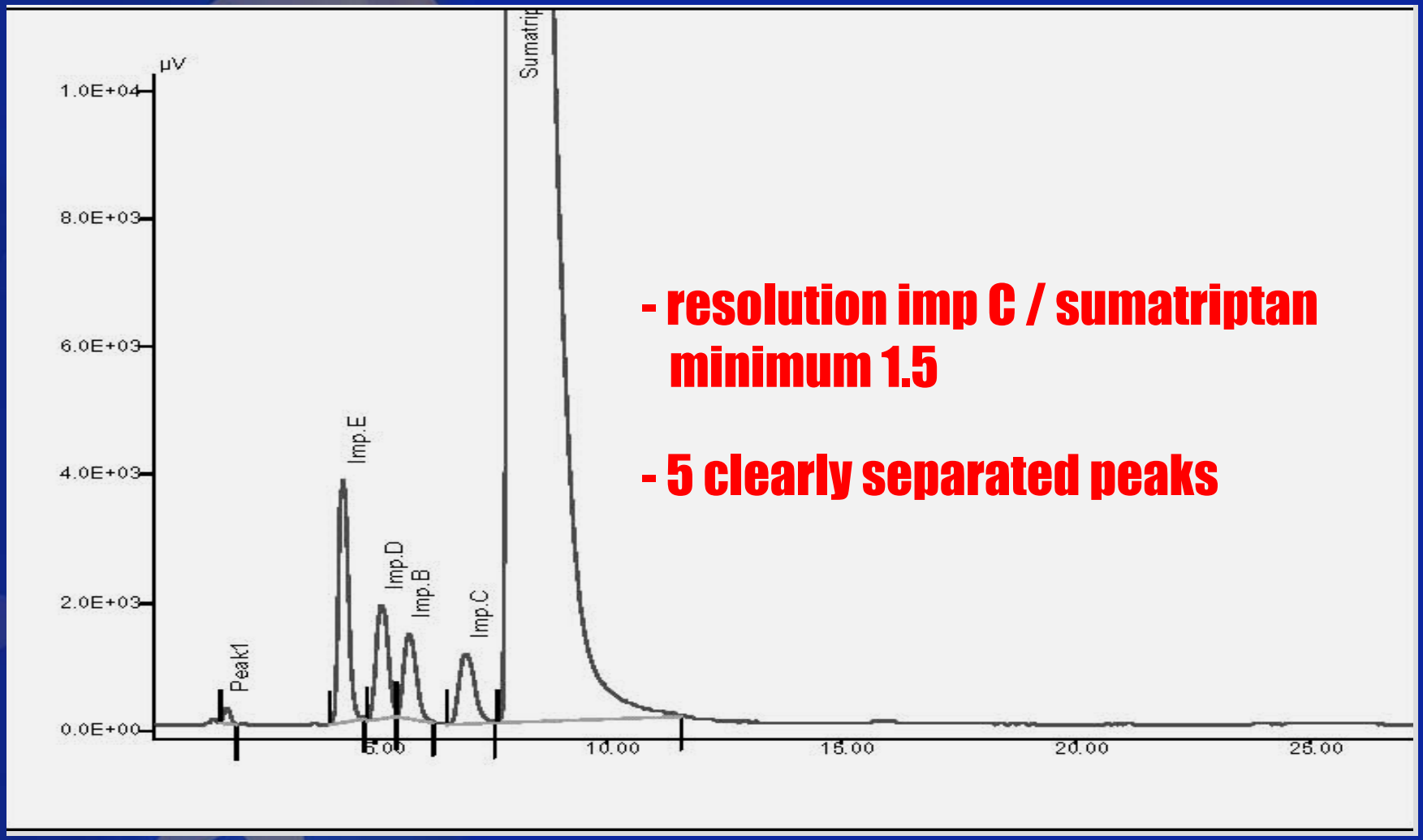
are limits applied to various tests designed to ensure the adequate performance of analytical procedure.

Compliance with the system suitability criteria is required throughout the chromatographic procedure.

Suitability in terms of selectivity:

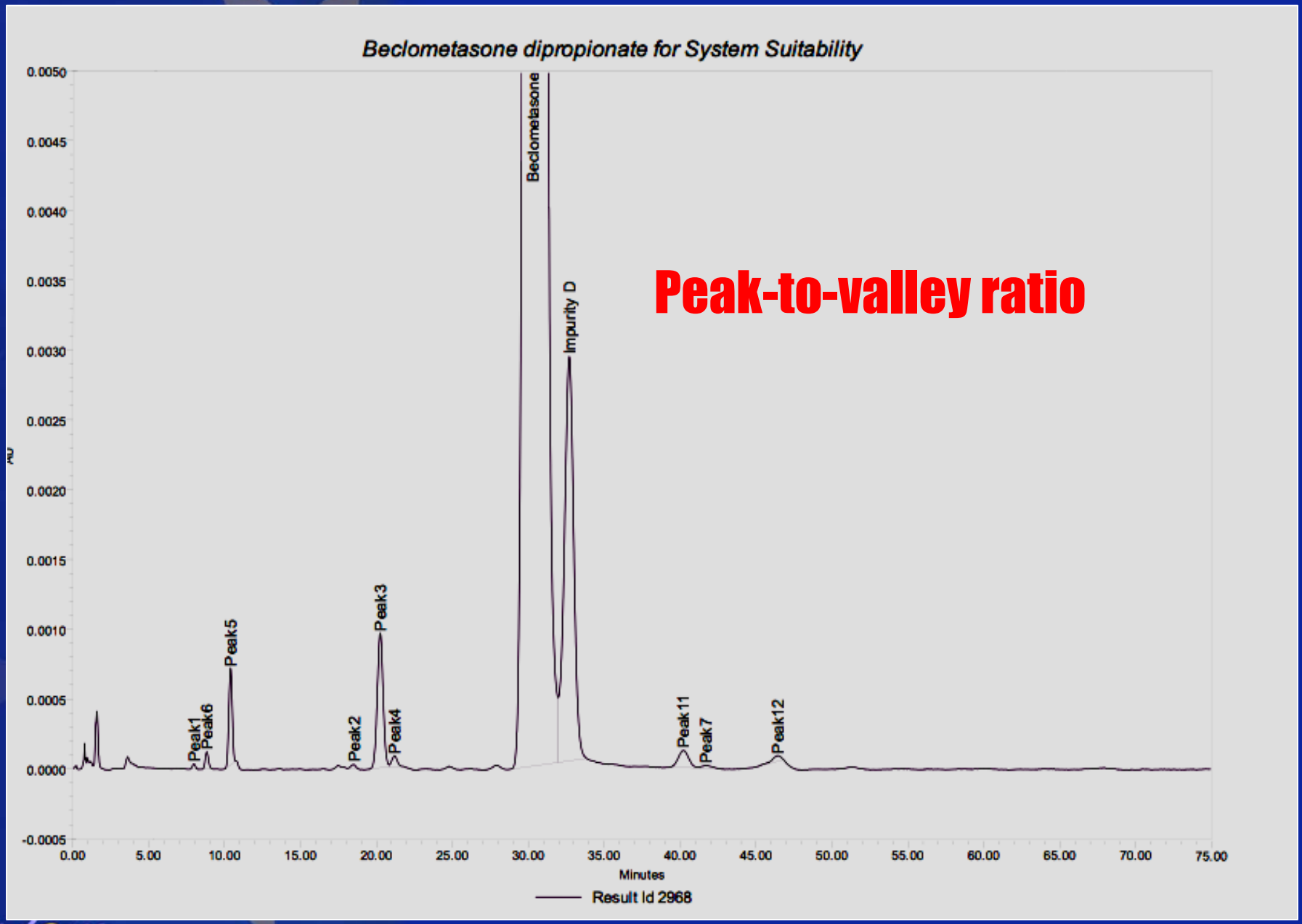
- **resolution** of two closely eluting peaks (critical pair): preferably peaks of similar size or at least not saturating)
- **peak-to-valley ratio** (incomplete separation, peaks of very different size)
- **"similarity" or "concordance"** with a chromatogram supplied

Sumatriptan impurity mixture CRS (spiked samples)

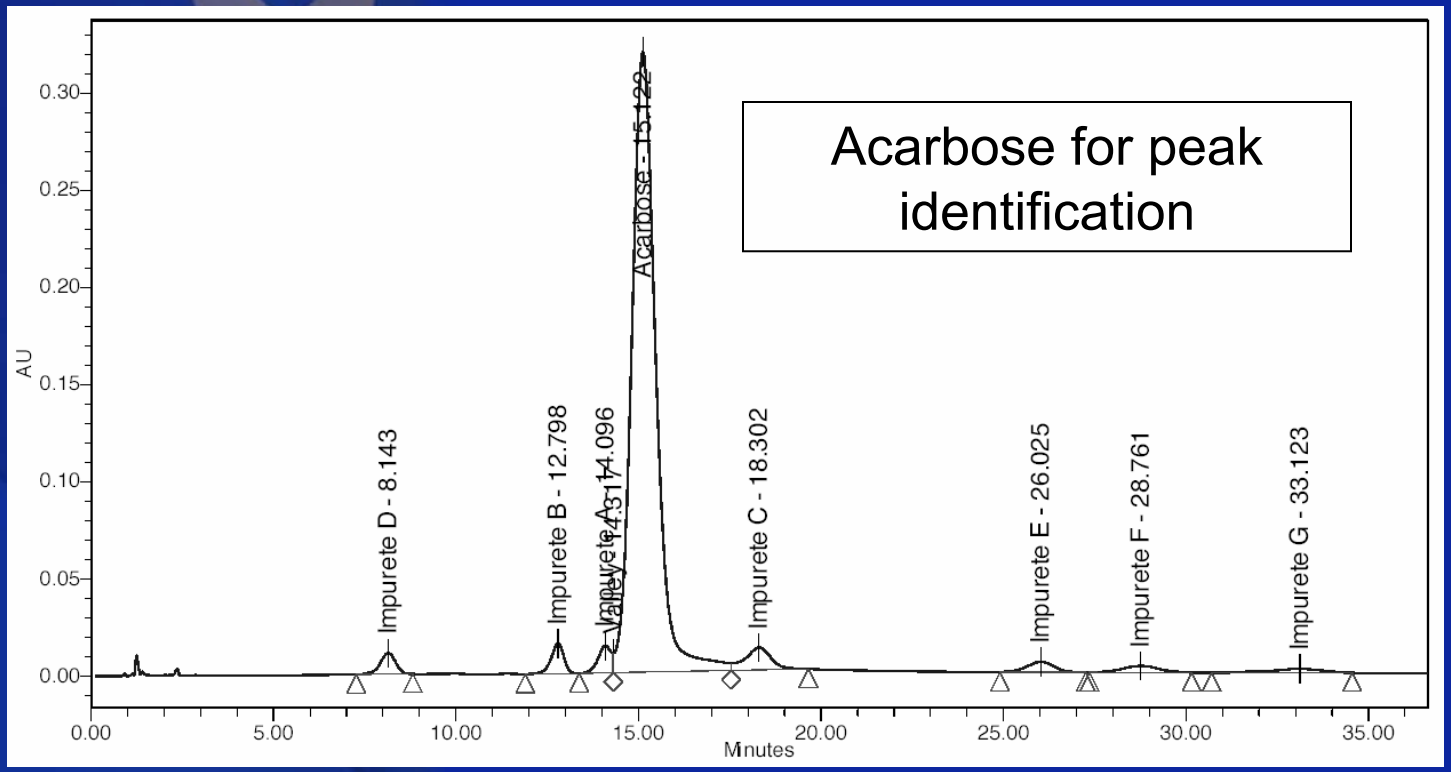


- resolution imp C / sumatriptan minimum 1.5

- 5 clearly separated peaks



Peak-to-valley ratio



SYSTEM SUITABILITY

Peak-to-valley ratio imp. A: 1.2

The chromatogram obtained is similar to the chromatogram supplied with acarbose for peak identification CRS

Suitability in terms of sensitivity:

Anhydrous paroxetine
Impurity H and I (Liquid chromatography)

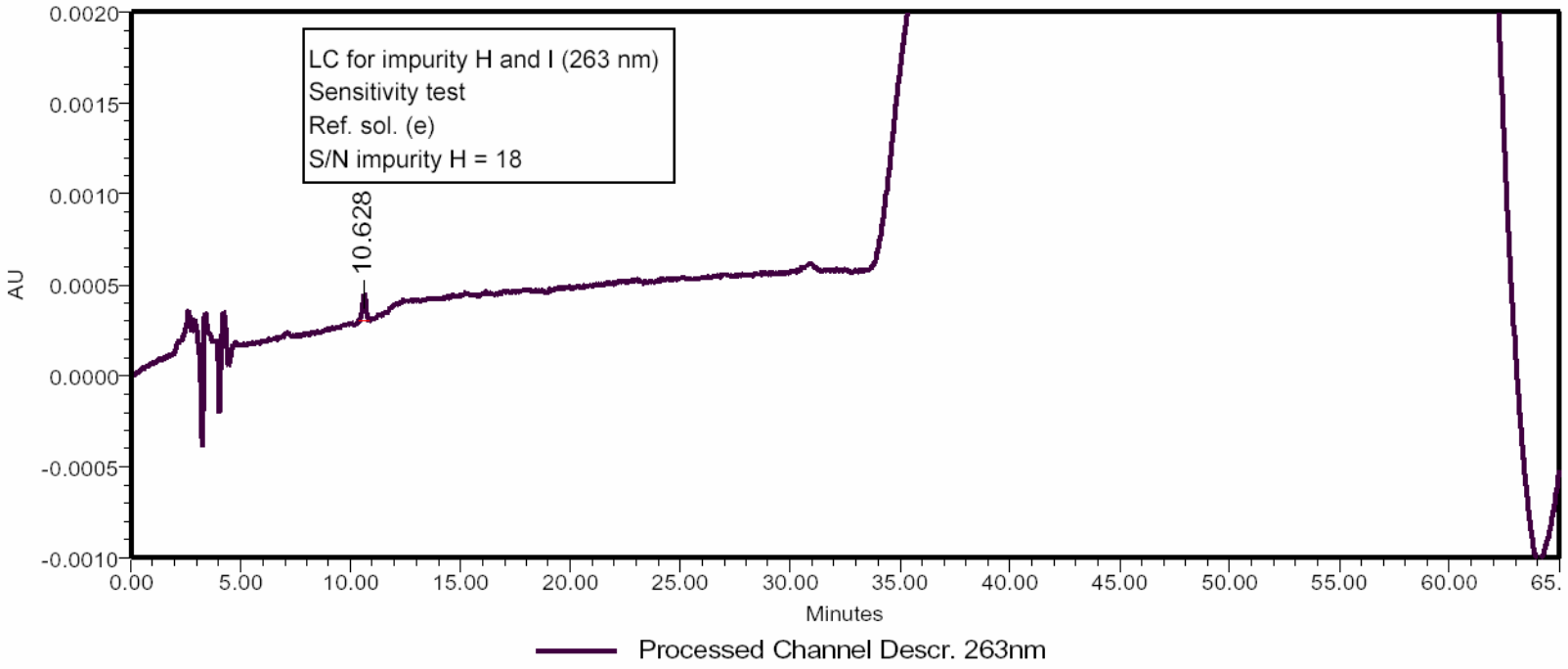
LC as for related substances but detection at 263 nm

Limit:

Impurity H, I: each impurity 0.1%

System suitability

Signal-to noise ratio: minimum 3 for the peak due impurity H in reference solution (e). = 0.05%



Peak Results

	Name	RT	Area	Height	Int Type	SN
1	impurete H	10.628	1700	146	bb	18

Anhydrous paroxetine HCl

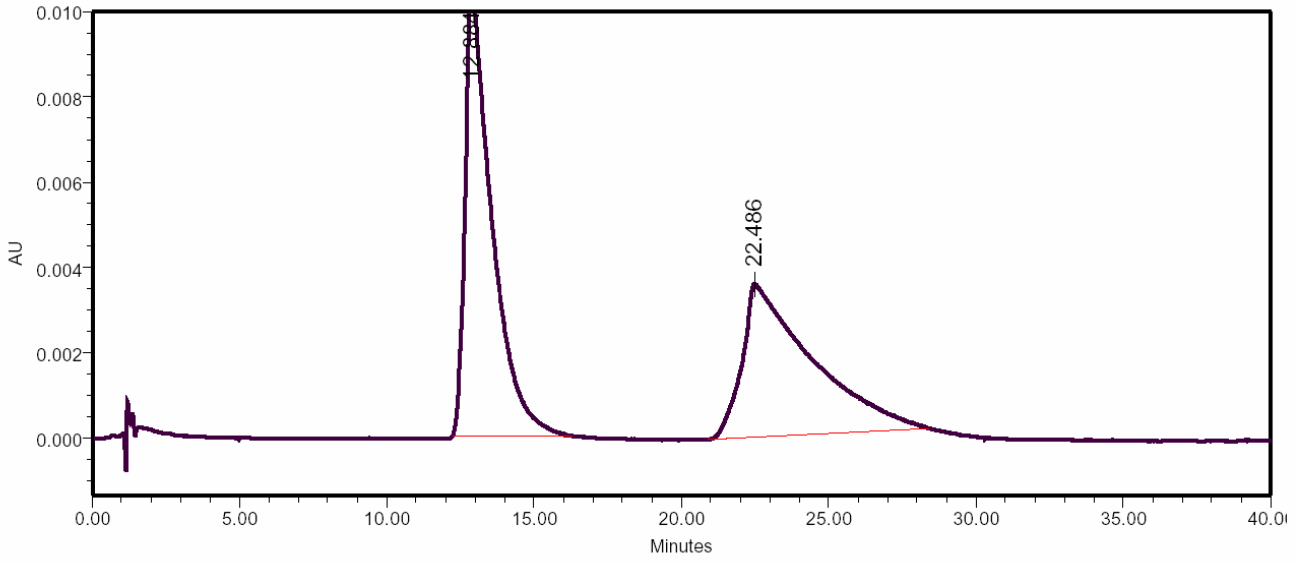
Impurity D (Liquid chromatography): (Chiral chromatography, column: Chiral AGP, Detection: UV 295 nm)

System suitability:

- *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 paroxetine in the chromatogram obtained with reference solution (b);
- *signal-to-noise ratio*: minimum 3 for the principal peak in the chromatogram obtained with reference solution (c);
- *symmetry factor*: the requirements stated in chapter *2.2.46* are not applicable.

Anhydrous paroxetine HCl

Impurity D - Chiral chromatography,



Peak Results

	Name	RT	Area	Height	Int Type	SN	Resolution
1	impurete D	12.884	660989	10606	Bb	2651	
2	Paroxetine HCl anhydre	22.486	586842	3586	bB	897	3.61

Adjustment of chromatographic conditions

The extent to which the various parameters of a defined chromatographic test may be adjusted to satisfy the system suitability criteria without fundamentally modifying the methods are given in

<2.2.46> Chromatographic separation techniques

revision proposal Pharmeuropa 18.3

Which chromatographic adjustements are allowed ?

LIQUID CHROMATOGRAPHY
isocratic

Composition of the mobile phase: minor solvent component ± 30% relative (or ± 2% absolute).

pH of aqueous part of mobile phase: ± 0.2 pH units (± 1.0 pH with neutral substances).

Concentration of salts in the buffer component of mobile phase: ± 10%

Detector wavelength: no adjustment is permitted.

Stationary phase:

column length: ± 70%,
column int. diameter: ± 25%,
particle size: max - 50%, no increase permitted.

Flow rate correction required

Flow rate:

± 50%.

proposed change: add adjustment formula

Temperature:

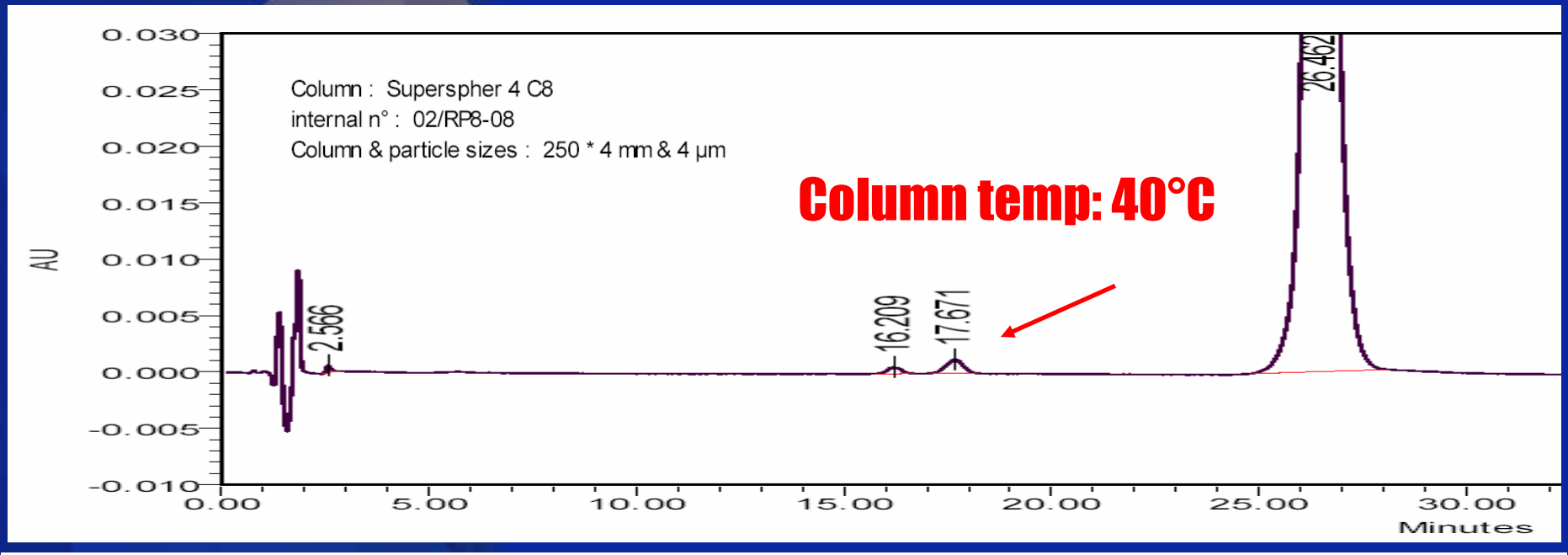
± 10% to a maximum of 60 °C.

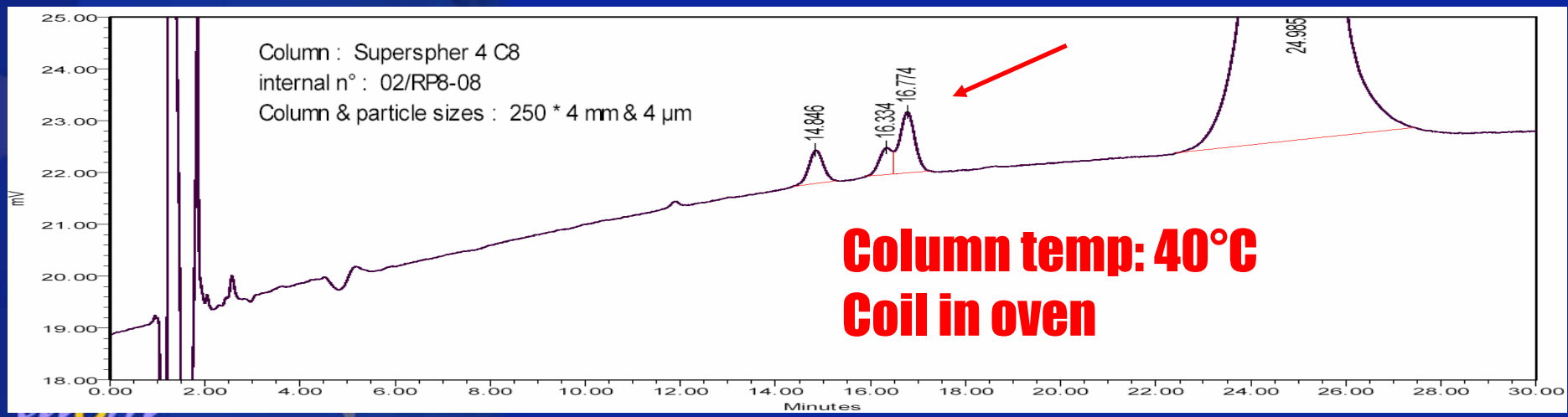
proposed change to ± 5 °C, where specified

Injection volume:

may be decreased provided detection & repeatability are satisfactory.

Yohimbine hydrochloride





LIQUID CHROMATOGRAPHY:
(proposed changes):

Gradient elution

Change of composition of mobile phase not recommended

Dwell volume : fomula for correction of gradient times

Flow rate: Adjustment formula for other column dimensions

Vielen Dank für Ihre Aufmerksamkeit