THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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Impurity Control in the European Pharmacopoeia

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Agenda

- Which impurities are controlled?
- General texts/monographs/ICH guidelines
- Analytical techniques
- Control of organic impurities
- Specification setting
- Validation
- Elemental impurities
- DNA reactive impurities
- Summary

Control of impurities in Ph. Eur.

Organic impurities

Inorganic impurities

Volatile impurities,
Water and residual solvents

Special groups, e. g. genotoxic (DNA reactive) imps, inorganics subjected to Q3D

General monographs and texts (1)

General monograph 2034 « Substances for pharmaceutical use »

- A general monograph describes requirements that have to be fulfilled, not only for substances or preparations covered by an individual monograph but for all substances or preparations within the scope of the Definition section.

- General and individual monographs are complementary. If a provision of a general monograph does not apply to a particular product, this is expressly stated in the individual monograph.

General texts and monographs (2)

- General monograph 2034 « Substances for pharmaceutical use »:
  describes general requirements for control of organic and inorganic impurities, volatiles, DNA reactive impurities
- General text 5.10: Control of impurities in substances for pharmaceutical use:
  helps to interprete the test for related substances, provides definitions, explanations, recommendations
- General text 5.4: Residual solvents: refers to ICH Q3C
- General text 5.20: Elemental impurities: refers to ICH Q3D
- Several general chapters

QUIZ

- **Organic impurities:**

1. What is the difference between « disregard limit » and « reporting threshold »?
2. What would you consider a suitable resolution criterion?
3. What is the meaning of a « correction factor » in the quantitative determination of an organic impurity?
4. How would you identify an impurity in a chromatographic system?

Related substances: some important statements

- Unless otherwise prescribed, organic impurities in active substances are to be reported, identified wherever possible, and qualified as indicated in Table 2034.-1. (general) or in table 2034.-2 (for peptides obtained by chemical synthesis) – implementation of ICH Q3 A which becomes legally binding

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

- If the individual monograph ***does not provide suitable control*** for a new impurity, a suitable test for control must be developed and included in the specification for the substance (Directive 2001/83/EC, as amended)

Requirements for active substances except synthetic peptides, Table 2034.1

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 lower)	>0.15 per cent or daily intake >1.0 mg (whichever lower)
Human or human and veterinary	> 2 g/day	>0.03 per cent	>0.05 per cent	> 0.05 per cent
Veterinary only	Not applicable	>0.10 per cent	>0.20 per cent	>0.50 per cent

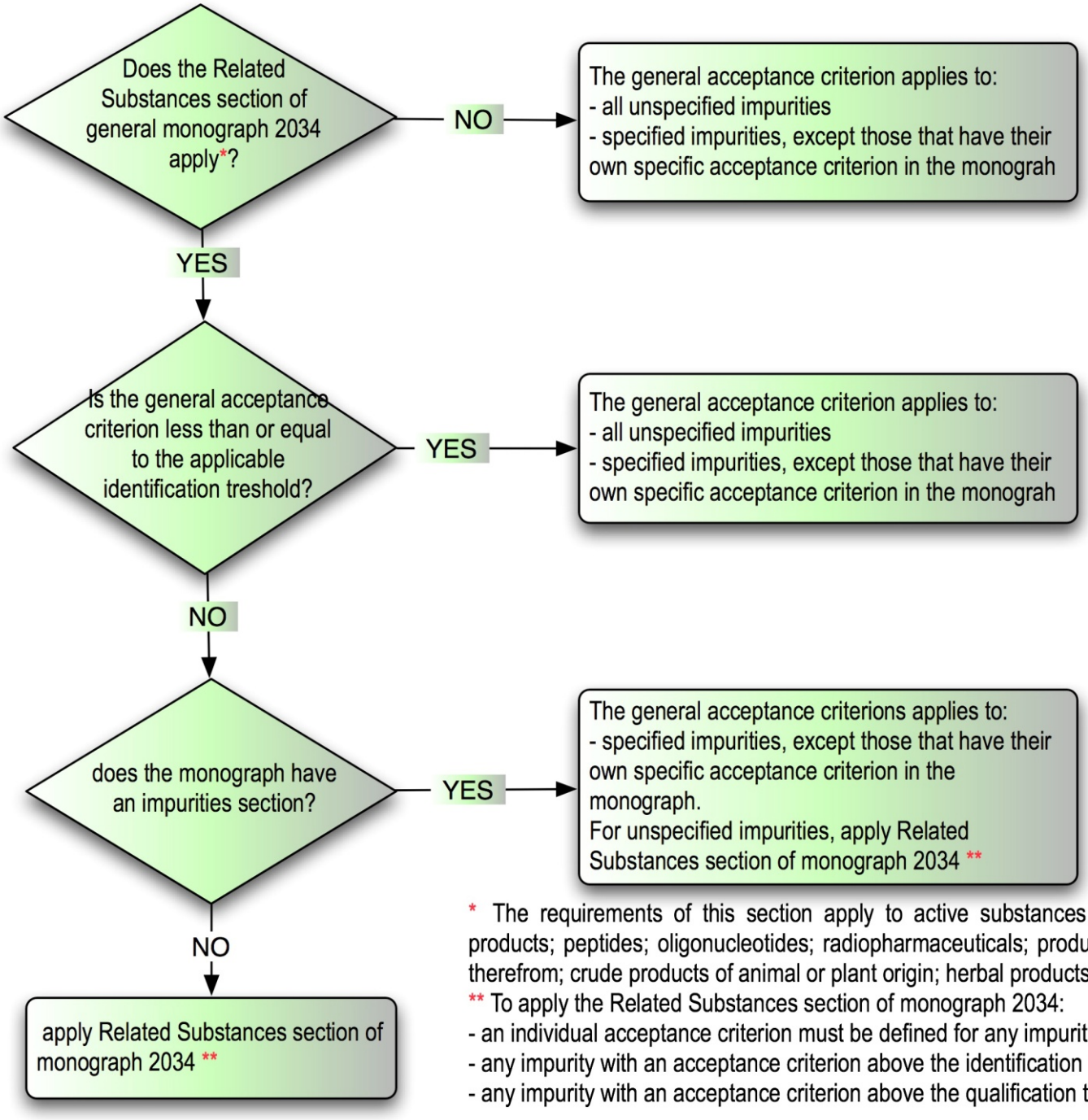
Chapter 5.10: Control of impurities in substances for pharmaceutical use (1)

- Provides:
  - Basis for monographs and impurities control
  - Terminology
  - Interpretation of related substances tests
  - Other aspects of impurities control

Chapter 5.10: Control of impurities in substances for pharmaceutical use (2)

- How to interpret general acceptance criteria in relation with the Impurities section of the monograph
- In “older” monographs general acceptance criterion may be expressed in various ways in the monographs: “any other impurity”, “other impurities”, “any impurity”, “any spot”, “any band”, etc.
- Decision tree to help the users

Chapter 5.10 control of impurities in substances for pharmaceutical use



* The requirements of this section apply to active substances, with the exception of: biological and biotechnological products; peptides; oligonucleotides; radiopharmaceuticals; products of fermentation and semi-synthetic products derived therefrom; crude products of animal or plant origin; herbal products.

** To apply the Related Substances section of monograph 2034:
- an individual acceptance criterion must be defined for any impurity that may be present above the identification threshold;
- any impurity with an acceptance criterion above the identification threshold must wherever possible be identified
- any impurity with an acceptance criterion above the qualification threshold must be qualified.

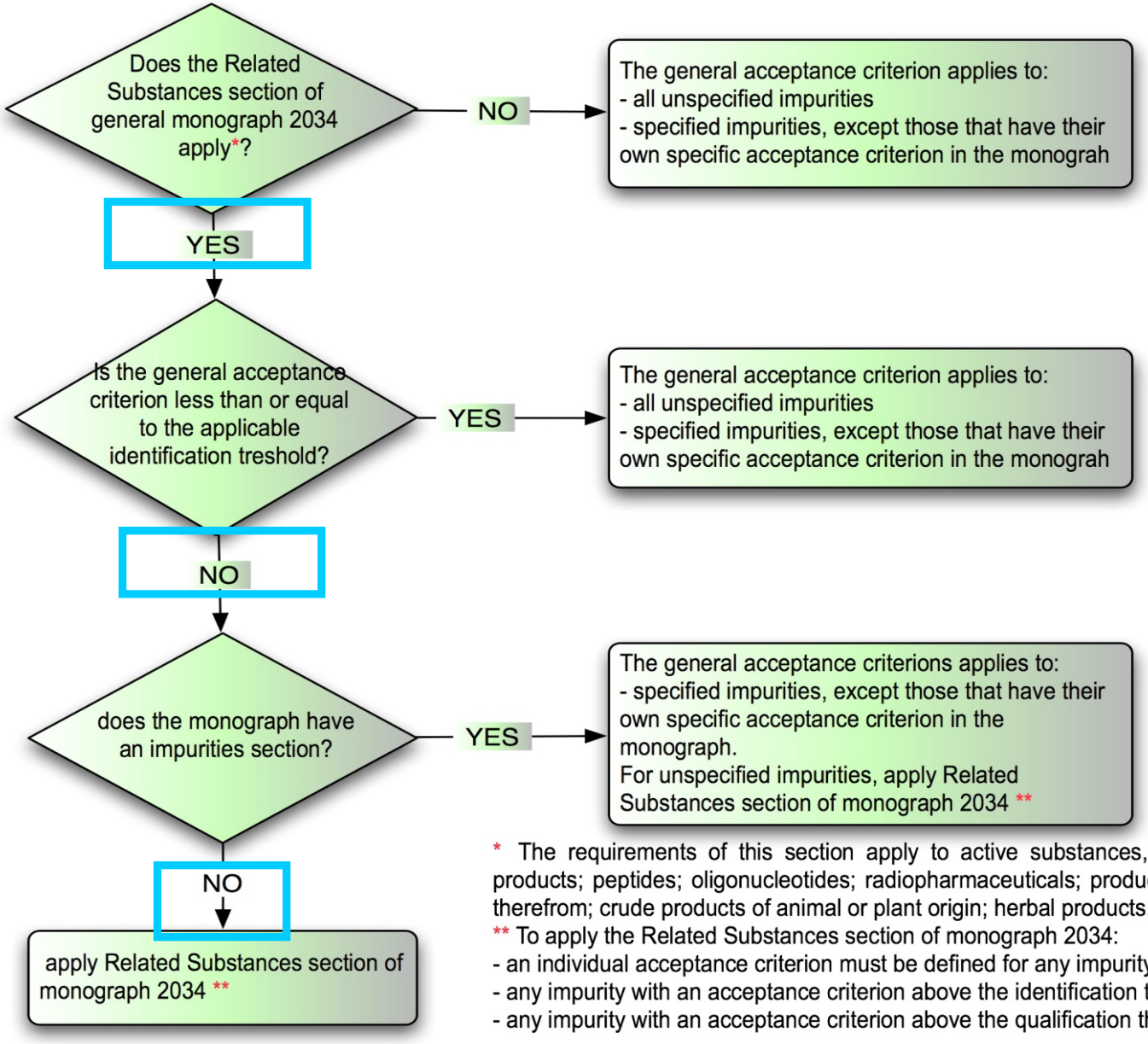
Example: Fludrocortisone acetate

Substance is an active substance for human use with maximum daily dose ≤ 2 g

Monograph describes under related substances:

- Any impurity ≤ 1.0 per cent
- Total ≤ 1.5 per cent
- No Impurities section (transparency list)

Chapter 5.10 control of impurities in substances for pharmaceutical use



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- any impurity with an acceptance criterion above the identification threshold must wherever possible be identified
- any impurity with an acceptance criterion above the qualification threshold must be qualified.

Example (*continued*)

- Apply related substances section of General monograph 2034
- Reporting threshold > 0.05 %
- Identification threshold > 0.10 %
- Qualification threshold > 0.15 %

Monograph is currently under revision

Organic impurities in Ph. Eur (1)

- **Analytical Techniques:**

➢ Most often chromatographic methods

- HPLC with different detection techniques –
  e. g. UV/VIS, RI, MS, Fluorescence, ELSD, MALS, CAD
- UHPLC
- GC
- TLC, HPTLC, mainly in the field of herbals

➢ Rarely UV (e. g. absorbance ratios in riboflavin) or chemical reactions (e. g. test for free acids in testosterone esters)

Organic impurities in Ph. Eur. (2)

- General Text 5.10 defines:
- **Specified impurity:** *an impurity that is individually listed and limited with a specific acceptance criterion in a monograph. A specified impurity can be either identified or unidentified.*

- **Unspecified impurity:** *an impurity that is limited by a general acceptance criterion and not individually listed with its own acceptance criterion*

Plate: *TLC silica gel GF_{254} plate R.*

Mobile phase: *concentrated ammonia R, methanol R, ethyl acetate R* (10:10:80 *V/V/V*).

Application: 5 µL.

Development: over 1/2 of the plate.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

System suitability: reference solution (b):

- the chromatogram shows 2 clearly separated spots.

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

C. Dissolve about 10 mg in 10 mL of *ethanol (96 per cent) R*. To 1 mL of this solution add 0.2 mL of a mixture, prepared immediately before use, of equal volumes of a 6 g/L solution of *potassium ferricyanide R* and a 9 g/L solution of *ferric chloride R*. Allow to stand protected from light for 5 min. Add 3 mL of a 10 g/L solution of *hydrochloric acid R*. Allow to stand, protected from light, for 15 min. A blue colour develops and a precipitate is formed.

D. Dissolve 60 mg in 0.5 mL of *methanol R* and add 0.5 mL of *water R*. The solution gives reaction (b) of sodium (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and its absorbance (*2.2.25*) at 440 nm is not greater than 0.05.

Dissolve 1.25 g in *methanol R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a). Dilute 2.0 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 the contents of a vial of *diclofenac for system suitability CRS* (containing impurities A and F) in 1.0 mL of the mobile phase.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 34 volumes of a solution containing 0.5 g/L of *phosphoric acid R* and 0.8 g/L of *sodium dihydrogen phosphate R*, previously adjusted to pH 2.5 with *phosphoric acid R*, and 66 volumes of *methanol R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL.

Run time: 1.6 times the retention time of diclofenac.

Identification of impurities: use the chromatogram supplied with *diclofenac for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and F.

Relative retention with reference to diclofenac (retention time = about 25 min): impurity A = about 0.4; impurity F = about 0.8.

System suitability: reference solution (b):

- *resolution*: minimum 4.0 between the peaks due to impurity F and diclofenac.

Calculation of percentage contents:

- *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity F = 0.3;
- for each impurity, use the concentration of diclofenac in reference solution (a).

Limits:

- *impurity A*: maximum 0.2 per cent;
- *impurity F*: maximum 0.15 per cent;
- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 0.4 per cent;
- *reporting threshold*: 0.05 per cent.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

ASSAY

Dissolve 0.250 g in 60 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 31.81 mg of $C_{14}H_{10}Cl_2NNaO_2$.

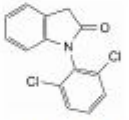
STORAGE

In an airtight container, protected from light.

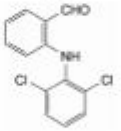
IMPURITIES

Specified impurities: *A, F.*

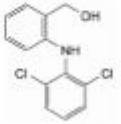
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical 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*): *B, C, D, E.*



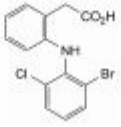
A. 1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one,



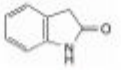
B. 2-[(2,6-dichlorophenyl)amino]benzaldehyde,



C. [2-[(2,6-dichlorophenyl)amino]phenyl]methanol,



D. [2-[(2-bromo-6-chlorophenyl)amino]phenyl]acetic acid,



E. 1,3-dihydro-2*H*-indol-2-one,

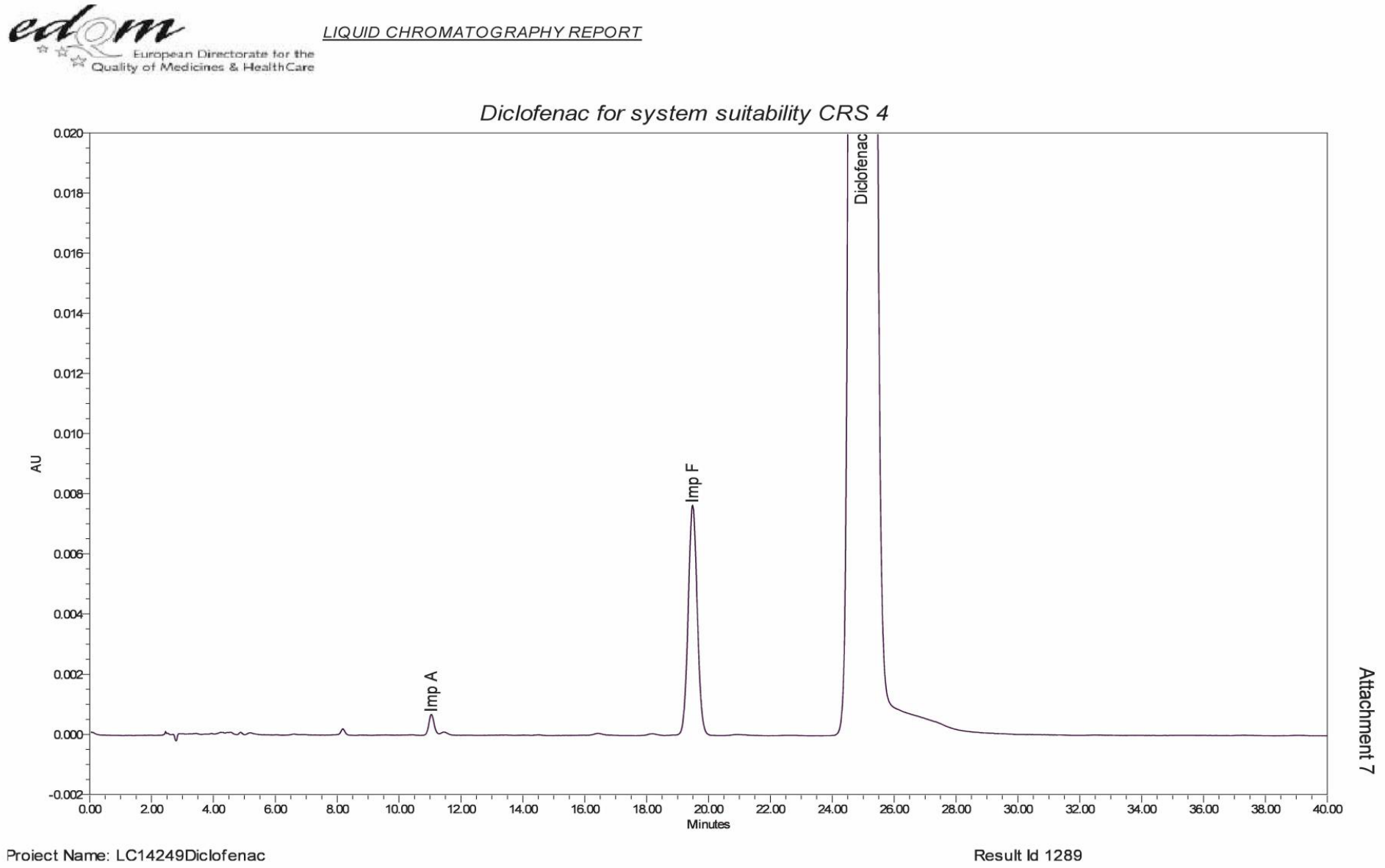
Reference to general Chapters: 2.2.29

←Transparency list

Organic impurities in Ph. Eur. (3)

- **Monograph Diclofenac sodium**
- *Identification of impurities* : use the chromatogram supplied with **diclofenac for system suitability CRS** and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A and F.
- *Relative retention* with reference to diclofenac (retention time = about 25 min): impurity A = about 0.4; impurity F = about 0.8.
- *System suitability*: reference solution (b):
- – *resolution*: minimum 4.0 between the peaks due to impurity F and diclofenac.
- *Calculation of percentage contents:*
- – *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity F = 0.3;
- – for each impurity, use the concentration of diclofenac sodium in reference solution (a).
- *Limits*:
- – *impurity A*: maximum 0.2 per cent;
- – *impurity F*: maximum 0.15 per cent;
- – *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- – *total*: maximum 0.4 per cent;
- – *reporting threshold*: 0.05 per cent.

Organic impurities in Ph. Eur. (4)



Qualitative: Identification and system suitability test

➢ *Identification:* Specified impurities must be identified in the chromatographic system

- Use of CRS – System suitability CRS or Peak identification CRS
- Retention times and relative retention values:

  only given for information

Identification and system suitability test

- Alternative approach

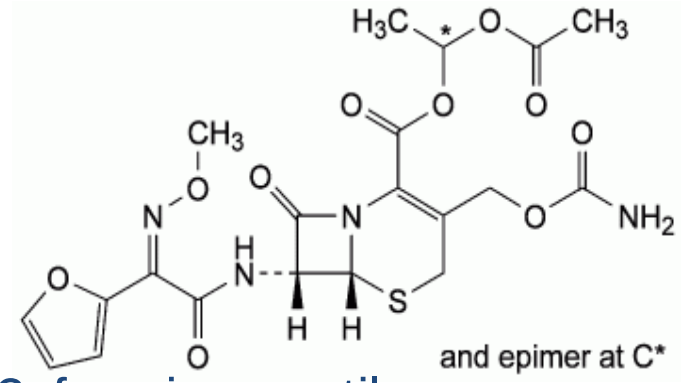
  In situ degradation to form specified impurities

- ✓ Hydrolysis
- ✓ Oxidation
- ✓ Ring-closure
- ✓ Z-E Isomerisation
- ✓ Epimerisation

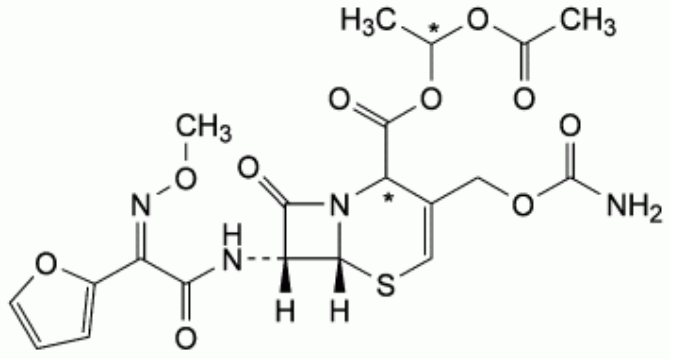
Identification and system suitability test

- Alternative approach

In situ degradation

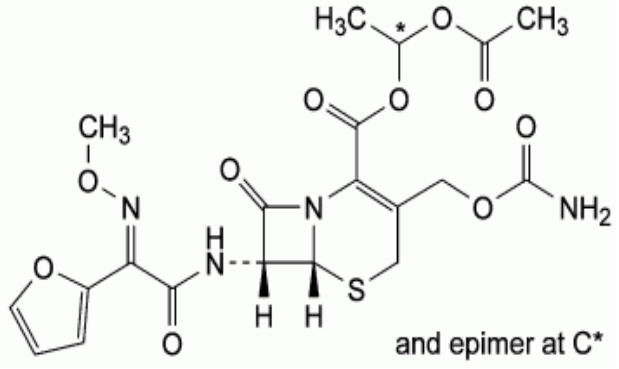


Cefuroxime axetil



Impurity A heat the test solution at 60 °C for 1h

Impurity B



expose the test solution to uv-light at 254 nm for 24 h

Identification and system suitability test

System suitability test

Individual monograph

Resolution test

Peak-to-valley ratio

General chapter 2.2.46

Chromatographic separation techniques

Symmetry factor 0.8 to 1.5

Minimum S/N 10 at reporting threshold

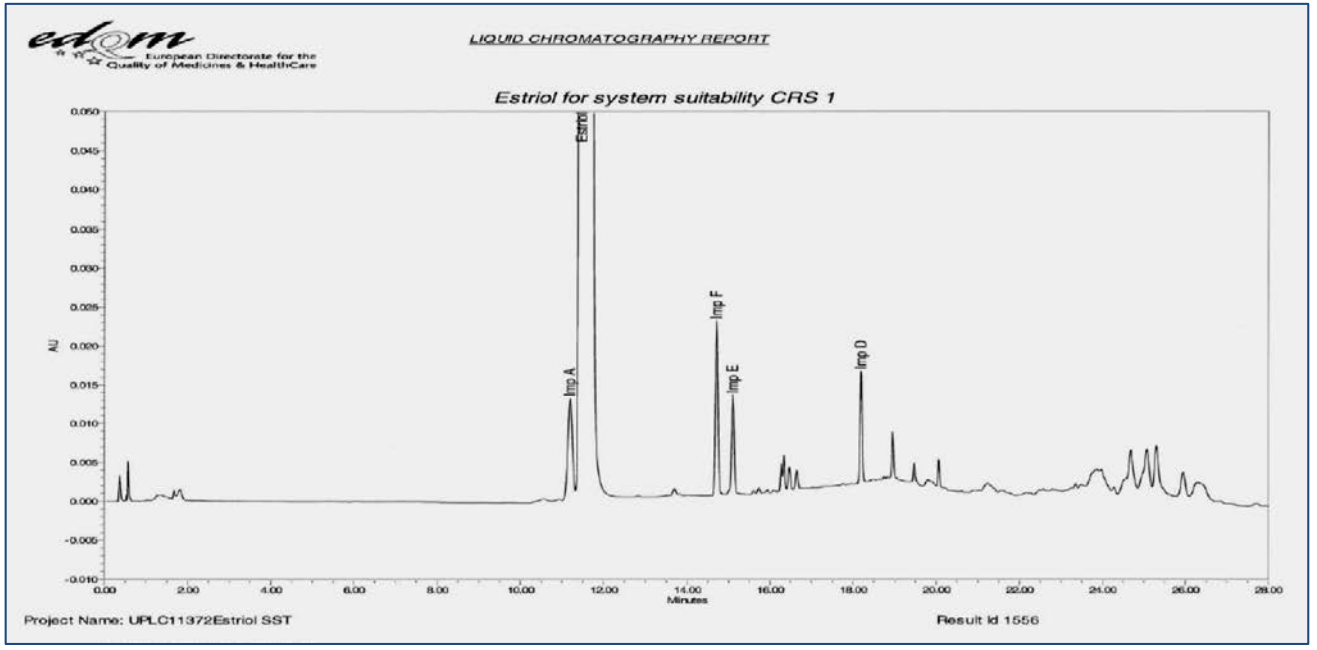
Repeatability requirement for assays

Identification and system suitability test

System suitability test: e. g. peak-to-valley ratio

- Often used for closely eluting peaks when Rs is not possible
- Imitates « real life » situation: example Estriol

Requirement: p/v imp. A - estriol minimum 5.0



Calculation of percentage contents (1)

- Option 1: using an external standard – dilution of the test solution or impurity itself: preferred method in Ph. Eur.

  Attention: dilution of test solution

  → consider response factor!

- Option 2: peak area normalisation

Calculation of percentage contents (2)

•Response and correction factors:

Response factor: Sensitivity of a detector for a given substance relative to a standard substance

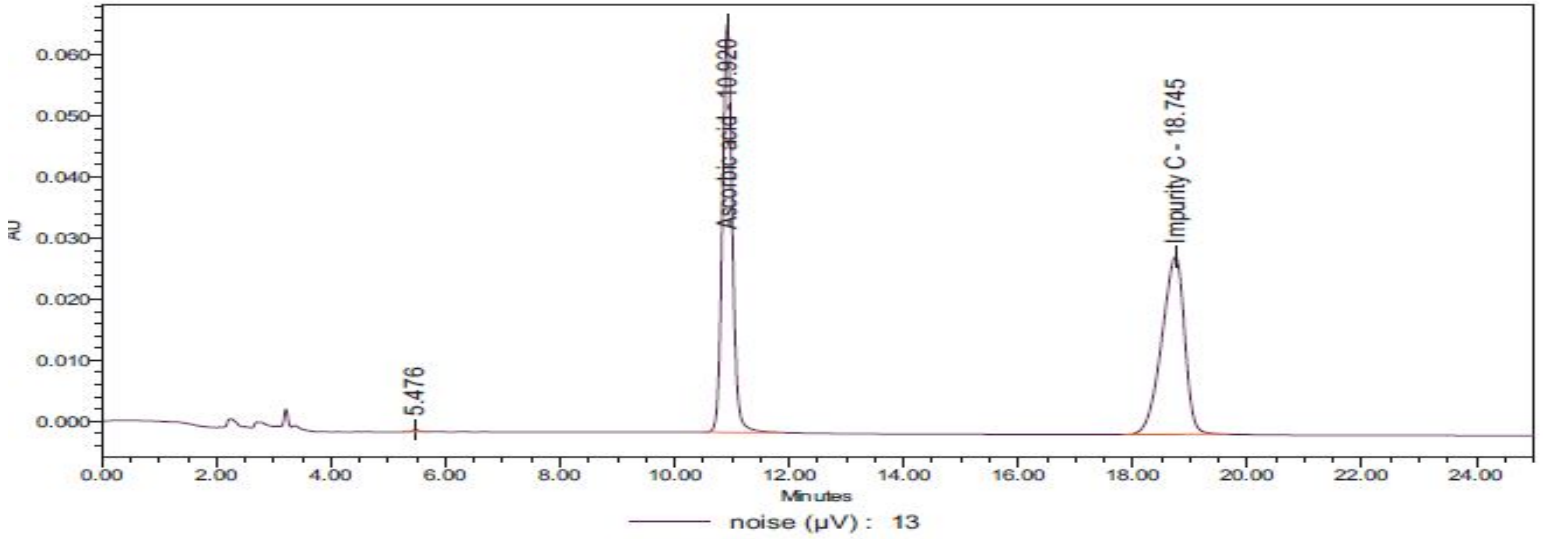
- $$RRF = Ai/As \times Cs/Ci$$
- RRF = response factor
- Ai = area of the peak due to the impurity
- As = area of the peak due to the test substance
- Cs = concentration of the test substance in milligrams per millilitre
- Ci = concentration of the impurity in milligrams per millilitre.

- According to Ph. Eur. is negligible when between 0.8 and 1.2

- Correction factor: reciprocal value of response factor

Calculation of percentage contents (3)

- Ascorbic acid and impurity C: example for different response factors (Imp. C is 8 x more concentrated that ascorbic acid)



Peak Results

	Name	RT	RT Ratio	Area	% Area	Height	Resolution	S/N	Int Type
1	Ascorbic acid	10.920		805026	49.89	66675	21.42	10258	BB
2	Impurity C	18.745	1.72	805706	49.93	29006	15.09	4463	BB

Calculation of percentage contents (4)

- Response/correction factors:

- Note: when correction factors are > 5, the quantification should be performed using impurities as external standards (Ph. Eur. Technical Guide)
- **Calculation of response factors:**
- using the mean of the area ratios over the whole range of linearity or the ratio of the slopes of the respective linearity regression equations

Calculation of percentage contents (5)

- Response factor - important points to consider:

➢ Take into account the purity of the impurity and of the test substance

➢ Purity calculation: Content (%) = [100 – (water + solvents)] x chromatographic purity (%)/100

➢ Take into account the form (base/acid or salt) of the impurity and the test substance, an additional correction factor for the molecular mass ratio may be introduced

➢ Perform the chromatography at defined wavelength and flow rate

➢ For more information see: Technical Guide or Pharmeuropa online/Useful information

Calculation of percentage contents (6)

Sensitivity:

- It must be assured that the system is sufficiently sensitive to control impurities not only at their acceptance criterion, but down to the reporting threshold: it may be necessary to add a sensitivity criterion in the case of low responding impurities (RRf < 0.8)

Example: sensitivity criterion

Impurity X: Response factor 0.5, correction factor 2.0

In case of insufficient sensitivity, demonstrated during validation, introduction of a sensitivity criterion:

Option 1: dilution of test solution used: S/N minimium 20 at reporting threshold

Option 2: Use of impurity X itself as external standard: S/N minimum 10 at reporting threshold

Calculation of percentage contents (7)

*Reporting threshold (**previously disregard limit**)*

- *Is the limit above which an impurity should be reported (ICH Q3A R2)*
- 2-fold purpose

- decision criterion for the user whether a peak area or a corrected peak area of an impurity is to be included in the total of impurities
- general criterion for the **user** to determine compliance of his actual chromatographic system with the requirement of general chapter 2.2.46  S/N ratio minimum 10 at the disregard limit/reporting threshold (LOQ should be equal or less than reporting threshold)

Specifications in monographs (1)

- Are based on specifications approved by competent authorities
- Are based on real batch and stability data
- Assays: depending on precision and accuracy of the method

Example: Request for revision to include impurity X in an API monograph

- Approved limit 0.2 %
- Batch data 0.04 – 0.02 – 0.06 – not detected – 0.01 %
- Mean + 3sd = 0.026 % + 0.065 = 0.091 %
- Limit fixed at 0.10 % (unspecified) 

no CRS for peak id needed !

Specifications in monographs (2)

- **Single-source monographs:**

So-called P4 procedure: impurity profile of the originator is taken into account: analytical procedure in the monograph is based on the originator's method

- **Multi-source monographs:**

So-called P1 procedure: impurity profile of all known manufacturers with a marketing autorisation in Europe are taken into account: analytical procedure described in the monograph will cover **all** impurities that are observed in the different synthetic pathways

Validation of impurity tests (1)

- Follows ICH Q2 (R1)

- Different requirements for limit tests (area comparison) and quantitative tests

- Typical parameters:
  - Accuracy
  - Specificity (selectivity)
  - Precision
  - Linearity and range
  - Limit of detection (limit test)
  - Limit of quantitation (quantitative test)
  - Linearity and range (quantitative test)
  - Robustness

Validation of impurity tests (2)

In practice:

- A revision of a monograph from limit test to quantitative test requires additional validation.
- In case of revisions of related substances tests, partial validation of the relevant parameters may be sufficient.
- The user of a monograph is not requested to perform validation but implementation of a pharmacopoeial procedure which may require additional testing (see General Notices).

Impurities in finished products (1)

Ph. Eur. Policy:

- Follows ICH Q3 B:

➢ Thresholds for identification, reporting and qualification are higher than for APIs

➢ Only degradation impurities above the reporting threshold are reported and taken into account for the total of impurities

➢ Synthetic impurities identified in the chromatographic system (e. g. by CRS) are excluded

Impurities in finished products (2)

Example: *Rosuvastatin tablets, extract of the test for related substances:*

Identification of impurities: use the chromatogram supplied with *rosuvastatin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C; use the chromatogram supplied with *rosuvastatin impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D; use the chromatogram obtained with reference solution (d) to identify impurity FP-A.

Limits:

– *impurity C*: maximum1.5 per cent;

– *impurity D*: maximum1.5 per cent;

– *impurity FP-A*: maximum 0.5 per cent;

– *unspecified impurities*: for each impurity, maximum 0.2 per cent;

– *total*: maximum 2.5 per cent;

– *reporting threshold* : 0.1 per cent; disregard the peaks due to impurities A and B.

Synthetic impurities A and B not taken into account

Other impurities controlled

- **Inorganics:** are controlled by general tests like sulfated ash, heavy metals (2.4.8, now only for substances for veterinary use), specific tests like AAS, ICP or general chapter 2.4.20
- **Volatiles:** residual solvents are controlled according to general text 5.4 and general chapter 2.4.24. Class 3 solvents may be controlled by LOD (up to 0.5 %). Water is most often controlled by semi-micro determination, coulometry or loss on drying.
- **DNA-reactive (mutagenic) impurities:** as from 1st January 2016 subjected to ICH M7. Control tests in monographs are in the test or production section.

Elemental Impurities (1)

- ICH Q3D fully implemented in Ph. Eur. (via General Text 5.20)
- General monographs 2034 (Substances for pharmaceutical use) and 2619 (Pharmaceutical preparations) revised
- Classical heavy metal tests have been deleted from individual monographs (except for monographs on substances only for veterinary use)
- Monographs on substances « for veterinary use » under revision
- Chapter 2.4.20 « Determination of elemental impurities » under revision in PDG

Elemental Impurities (2)

➢ Chapter 2.4.20

- This chapter is currently being harmonised within PDG
- New concept: Example procedures are provided (ICP-MS/OES), validation criteria provided (e.g. accuracy, range, precision), user can choose own method, provided validation criteria are fulfilled

Public enquiry finalised

Elemental Impurities (3)

- Specific elemental impurity tests

- No systematic deletion from individual monographs

- Particular case: substances of natural origin, e. g. mined excipients:

- Some case-by-case decisions: e. g. Methylthioninium chloride

Example monograph: Calcium phosphate (revised)

Adopted in Nov 2020

Elemental impurities. Any method that fulfils the requirements of general chapter *2.4.20. Determination of elemental impurities* may be used.

Element	Maximum content (ppm)
Arsenic	2
Lead	1

~~**Arsenic** (*2.4.2, Method A*): maximum 4 ppm, determined on 5 mL of solution S.~~

Iron (*2.4.9*): maximum 400 ppm.

DNA reactive (mutagenic) impurities (1)

Ph. Eur. follows ICH M7:

Tests are described when there is proof for genotoxicity, not based on structural alerts

- General monograph 2034 Substances for pharmaceutical use:

« For DNA reactive impurities, the requirements of ICH Guideline M7 *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* must be complied with for active substances to be used in medicinal products for human use, in cases defined in the scope of the guideline. “

DNA reactive (mutagenic) impurities (2)

Ph. Eur. follows ICH M7:

- Individual monographs:

Two options

1. Production section: Either no suitable, selective or sensitive test is known or the test requires too sophisticated equipment. MAH has to ensure the compliance of production with defined requirements.
2. Test section: Test to be included when suitable method is available and limits are known.

DNA reactive (mutagenic) impurities (3)

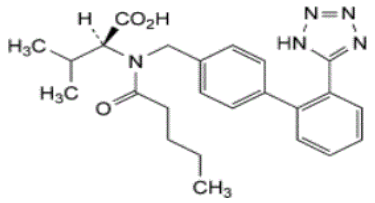
Nitrosamines in Sartans:

Following decision of EU Commission (EU referral (2019) 2698 of 2 April 2019):

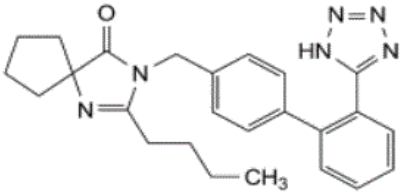
Production and Test section of 5 sartan monographs* containing a tetrazole ring revised and interim limits introduced

* Valsartan, Irbesartan, Losartan potassium, Candasartan cilexetil, Olmesartan modexomil

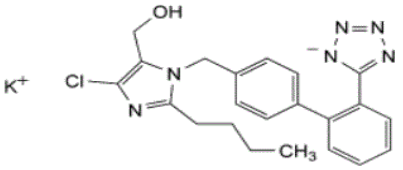
Sartans with a tetrazole ring structure in the Ph. Eur.



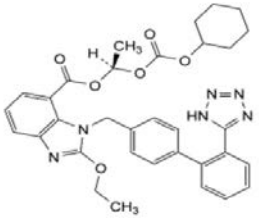
Valsartan



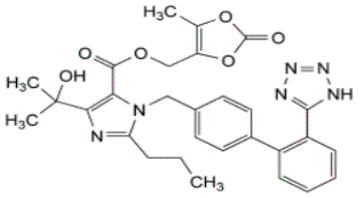
Irbesartan



Losartan potassium



Candesartan cilexetil



Olmesartan medoxomil

Revision of Sartan monographs

Following the most recent CHMP recommendations published on 9 July 2020 and the EMA press release published on 13 Nov. 2020:

=> Recommendations regarding the detection, management and prevention of presence of N-nitrosamines in medicinal products for human use. (recommendations of 9th of July 2020)

=> "*EMA's human medicines committee (CHMP) has aligned recommendations for limiting nitrosamine impurities in sartan medicines with recent recommendations it issued for other classes of medicines*." (press release of 13th of November 2020)

Latest revision of Sartan monographs (1)

Production Section

As *N*-nitrosamines are classified as probable human carcinogens, their presence in valsartan should be avoided or limited as much as possible. For this reason, manufacturers of valsartan for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in valsartan. The general chapter *2.5.42. N-Nitrosamines in active substances* is available to assist manufacturers.

Test Section

Interim limits for NDMA and NDEA deleted

Latest revision of Sartan monographs (2)

Implementation of these monographs:

- Revised monographs were adopted on 5th of February 2021
- To avoid a gap between regulatory recommendations and mandatory pharmacopoeial monographs, the procedure of « rapid implementation » has been chosen:

5 revised Sartan monographs will came into force on 1st April 2021

The new general chapter **2.5.42, N-Nitrosamines in active substances** has been adopted in November 2020 and is already published on the EDQM website. 7 new nitrosamine reference standards are available.

Revisions of general monographs

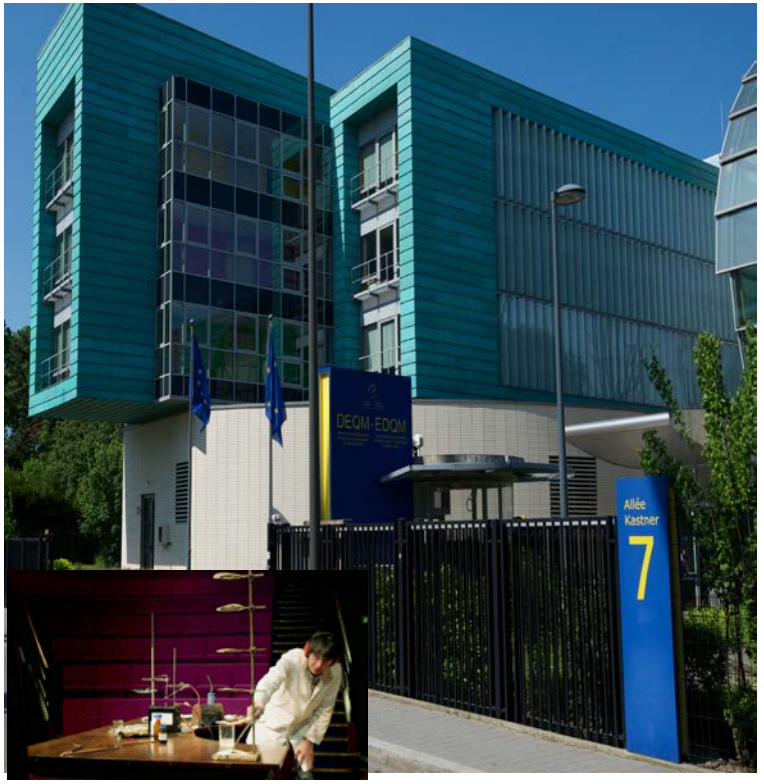
Revision of general monographs 2034 and 2619, published for comments in Pharmeuropa 33.2

- Production section proposed for revision
- Manufacturer shall perform risk assessment
- If a risk is identified, manufacturers are asked to minimise the nitrosamine presence, e. g. by modification of the manufacturing process, and a control strategy must be implemented

Conclusions

- Ph. Eur. impurity control strategy is in line with ICH guidelines
- Impurity tests are validated
- Monographs provide information on all known organic impurities controlled, specified or unspecified
- Limits based on specifications as approved by competent authorities and taking into account batch data. Limits provided for specified, unspecified and sum of impurities
- Nowadays quantitative tests preferred over comparative tests
- Peak identification and system suitability tests in chromatography performed using Ph. Eur. reference standards (or reagents)

Thank you for your attention



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