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

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Module 3:
Impurity Control in the European Pharmacopoeia

Ph. Eur. Training Webinar

5 December 2024, Strasbourg, France

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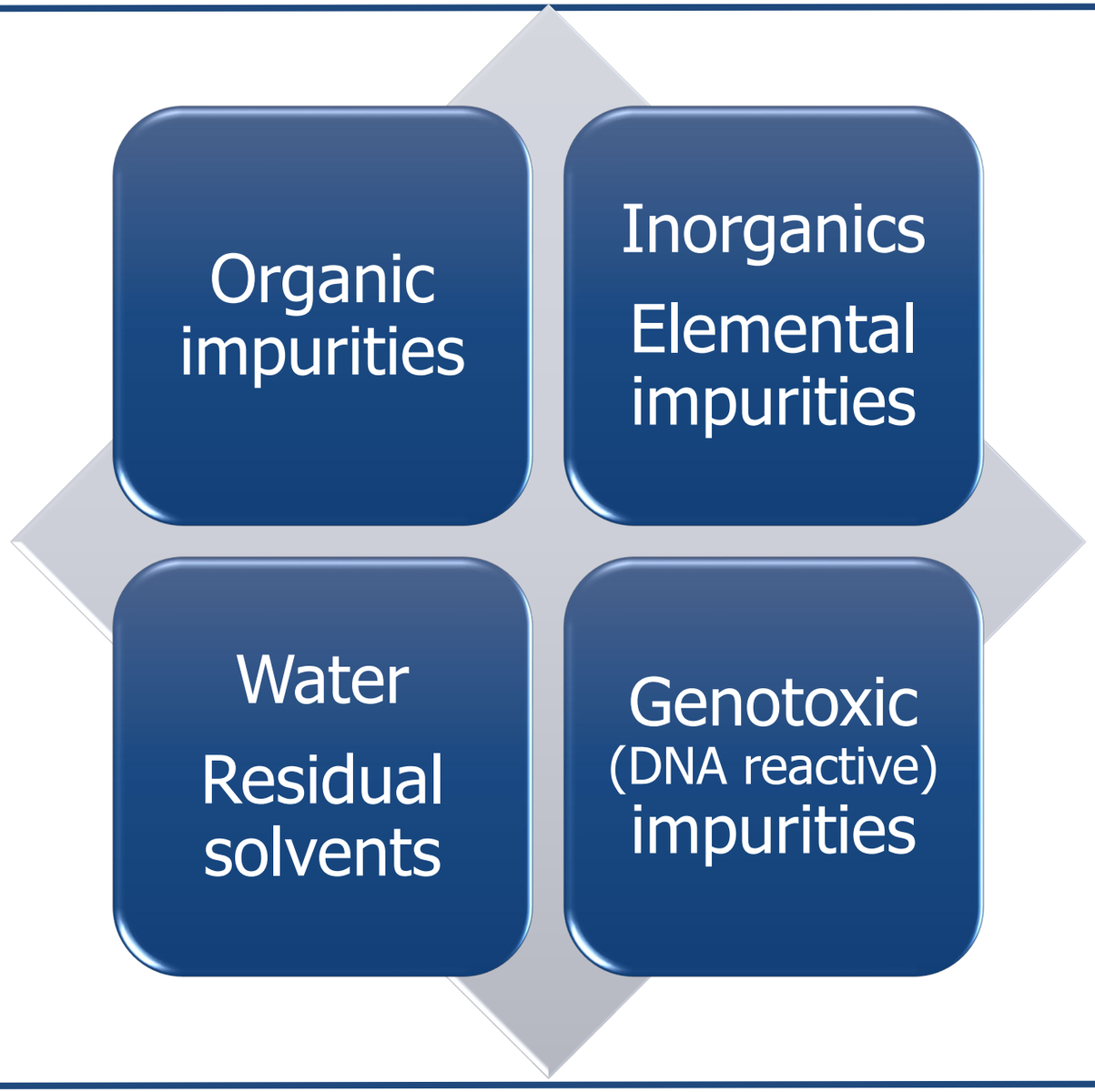
European Pharmacopoeia Department

Outline

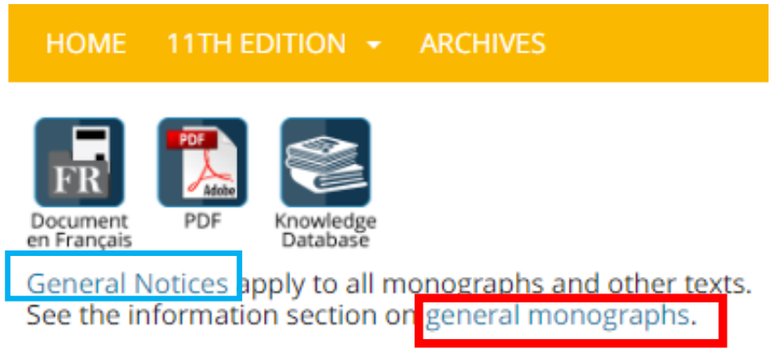
- ✓ Which impurities are controlled?
- ✓ General monographs and texts
- ✓ Control of organic impurities
  - General texts
  - Impurity identification
  - System suitability test
  - Response/Correction factors
- ✓ Specification setting
- ✓ Validation/Implementation
- ✓ Water/Residual solvents
- ✓ Inorganics/Elemental impurities
- ✓ Genotoxic impurities

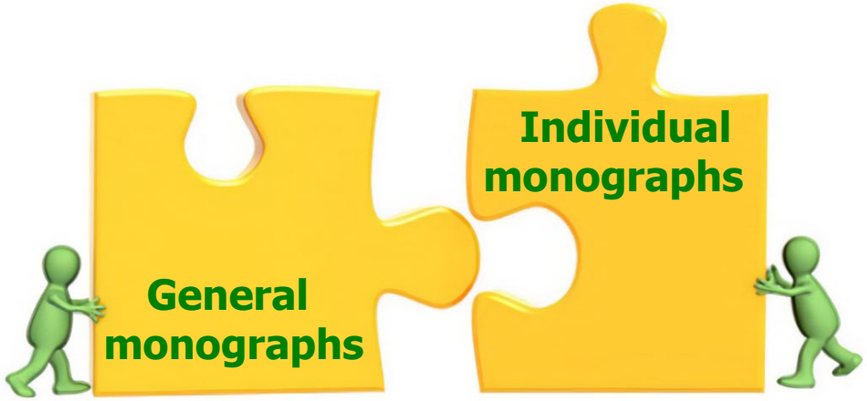
Control of impurities in Ph. Eur.



General monographs and texts

✓ **General monographs** 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.





✓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 monographs and texts

General monograph 2034

Substances for pharmaceutical use

Describes general requirements for control of residual solvents, organic, elemental and DNA reactive impurities

General text 5.10

Control of impurities in substances for pharmaceutical use

Helps to interpret the test for related substances, provides definitions, explanations, recommendations

General monograph 2619

Pharmaceutical preparations

Describes general requirements for control of degradation products, residual solvents, elemental impurities…

General text 5.4

Residual solvents

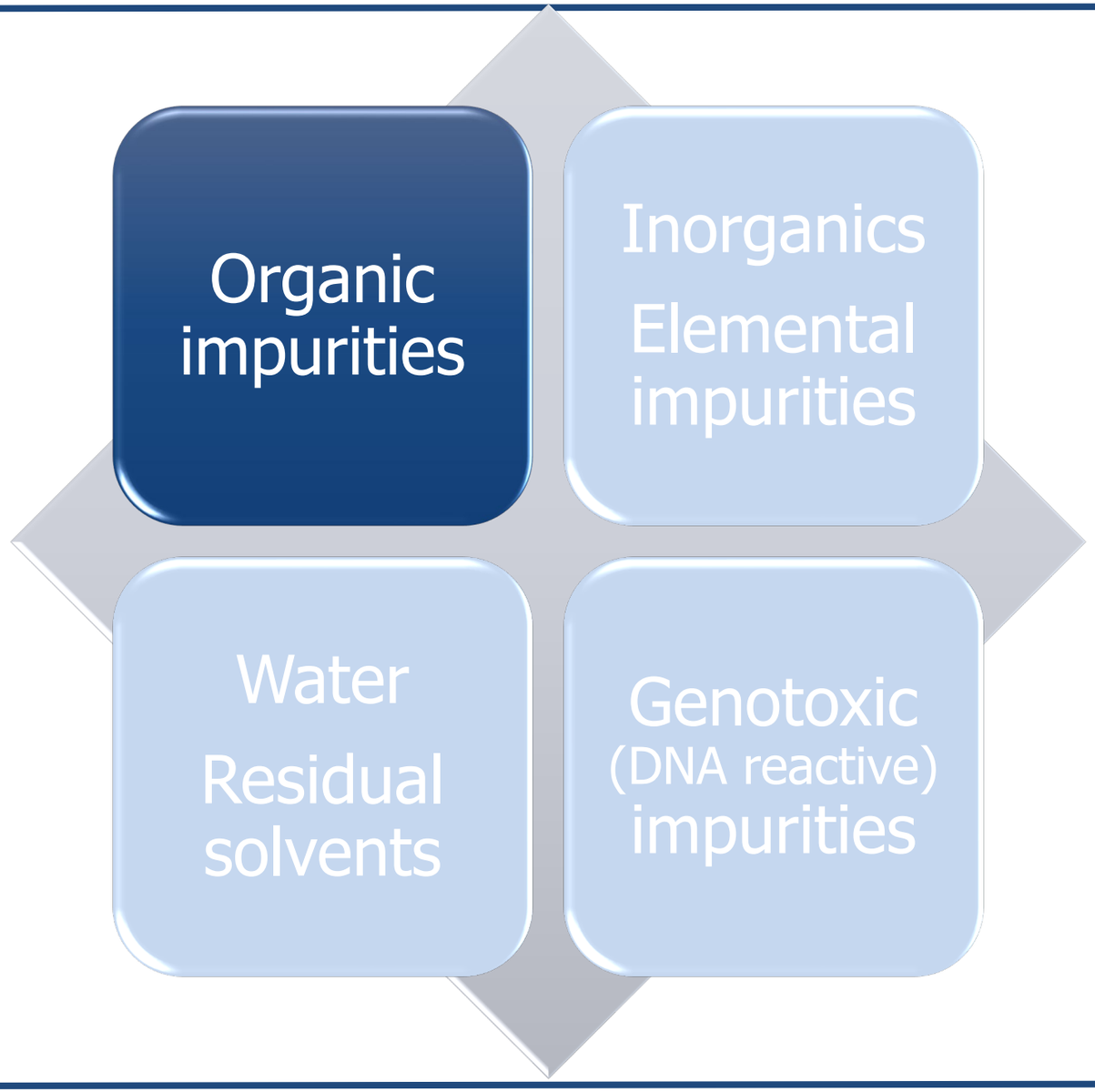
Refers to ICH Q3C

General text 5.20

Elemental impurities

Refers to ICH Q3D

Control of impurities in Ph. Eur.



Analytical techniques for organic impurities

HPLC, UHPLC

with different detection techniques e.g. UV/VIS, RI, MS, Fluorescence, ELSD, MALS, CAD

UV

e.g. absorbance ratios in riboflavin

Chemical reactions

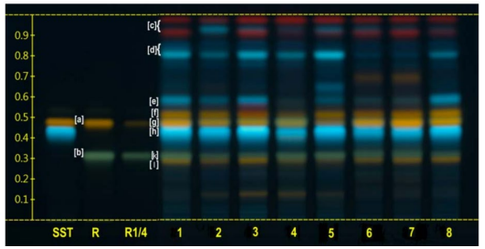
e.g. test for free acids in testosterone esters

TLC, HPTLC

mainly in the field of herbals

GC

with different detection techniques e.g. flame ionisation, MS



SST: reference solution (c)

R: reference solution (a)

R1/4: reference solution (b)

1-5: test solutions from different batches of *C. laevigata*

6-8: test solutions from different batches of *C. azarolus*

Figure 1432.-4 – *HPTLC chromatogram for identification test C of hawthorn leaf and flower (C. laevigata and C. azarolus)*

Example: *Raltegravir potassium (2887)*

Reference to general chapters: *2.2.29.*
↳ Reference to *2.2.46.*

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile R*, *water R* (25:75 *V/V*).

Test solution. Dissolve 25.0 mg of the substance to be examined in 100 mL of the solvent mixture using sonication for 5 min. Add about 140 mL of the solvent mixture then dilute to 250.0 mL with the solvent mixture.

Reference solution (a). Dissolve 25.0 mg of *raltegravir potassium CRS* in 100 mL of the solvent mixture using sonication for 5 min. Add about 140 mL of the solvent mixture then dilute to 250.0 mL with the solvent mixture.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c). Dissolve 2 mg of *raltegravir impurity E CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with reference solution (a).

Reference solution (d). In order to prepare impurity C *in situ*, dissolve 20 mg of the substance to be examined in a 40 g/L solution of *sodium hydroxide R* and dilute to 10 mL with the same solvent. Stir the solution for 30 min. To 5 mL of the solution add 5 mL of a 103 g/L solution of *hydrochloric acid R* and dilute to 50 mL with the solvent mixture.

Reference solution (e). Dissolve 5 mg of *raltegravir for peak identification CRS* (containing impurities F and G) in 20 mL of the solvent mixture using sonication for 5 min. Add about 25 mL of the solvent mixture then dilute to 50 mL with the solvent mixture.

System suitability test

Identification of impurities: use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E; use the chromatogram supplied with *raltegravir for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities F and G.

Relative retention with reference to raltegravir (retention time = about 10 min): impurity C = about 0.7; impurity E = about 0.95; impurity G = about 1.1; impurity F = about 1.15.

System suitability: reference solution (c):
- *resolution*: minimum 1.5 between the peaks due to impurity E and raltegravir.

Calculation of percentage contents:
- *correction factor*: multiply the peak area of impurity C by 1.6;
- for each impurity, use the concentration of raltegravir potassium in reference solution (b).

Limits:
- *impurity C*: maximum 0.3 per cent;
- *impurities E, F, G*: for each impurity, maximum 0.15 per cent;
- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 0.5 per cent;
- *reporting threshold*: 0.05 per cent.

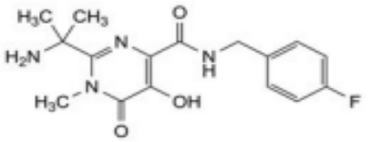
Acceptance criteria

Transparency list

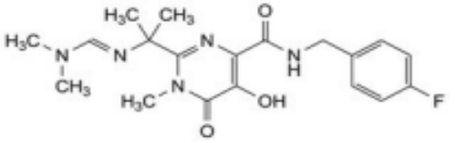
IMPURITIES

Specified impurities: *C, E, F, G.*

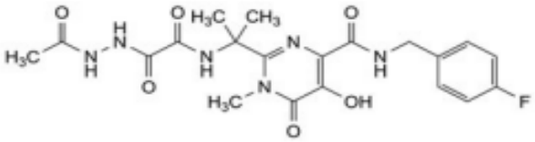
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



A. 2-(2-aminopropan-2-yl)-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



B. 2-[2-[(*E*)-[(dimethylamino)methylidene]amino]propan-2-yl]-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



General monographs and texts

2034

Substances for pharmaceutical use

- Implementation of **ICH Q3A** which becomes **legally binding**.

"Unless otherwise prescribed, organic impurities in active substances are to be reported, identified wherever possible, and qualified as indicated in Table 2034.-1. or in Table 2034.-2 for peptides obtained by chemical synthesis."

Table 2034.-1. – *Reporting, identification and qualification of organic impurities in active substances*

Use	Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
Human use or human and veterinary use	≤ 2 g/day	> 0.05 per cent	> 0.10 per cent or a daily intake of > 1.0 mg (whichever is the lower)	> 0.15 per cent or a daily intake of > 1.0 mg (whichever is the lower)
Human use or human and veterinary use	> 2 g/day	> 0.03 per cent	> 0.05 per cent	> 0.05 per cent
Veterinary use only	Not applicable	> 0.10 per cent	> 0.20 per cent	> 0.50 per cent

Table 2034.-2. – *Reporting, identification and qualification of organic impurities in peptides obtained by chemical synthesis*

Reporting threshold	Identification threshold	Qualification threshold
> 0.1 per cent	> 0.5 per cent	> 1.0 per cent

5.10

Control of impurities in substances for pharmaceutical use

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

Decision tree to help the users

How to interpret general acceptance criteria for *Impurities* in the monographs.

In "older" monographs: "any other impurity", "other impurities", "any impurity", "any spot", "any band", etc.

ICH Q3A R2 "Impurities in new drug substances"

Organic impurities in Ph. Eur.

Specified impurity

Defined in *5.10:* "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."

Other detectable impurities

Defined in *5.10:* "Potential impurities with a defined structure that are known to be detected by the tests in a monograph but not known to be normally present above the identification threshold in substances used in medicinal products that have been authorised by the competent authorities of Parties to the Convention. They are unspecified impurities and are thus limited by a general acceptance criterion."

Unspecified impurity

Defined in *5.10:* "An impurity that is limited by a general acceptance criterion and not individually listed with its own acceptance criterion."

Limits:

- *impurity C*: maximum 0.3 per cent;
- *impurities E, F, G*: for each impurity, maximum 0.15 per cent;
- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 0.5 per cent;
- *reporting threshold*: 0.05 per cent.

IMPURITIES

Specified impurities: C, E, F, G.

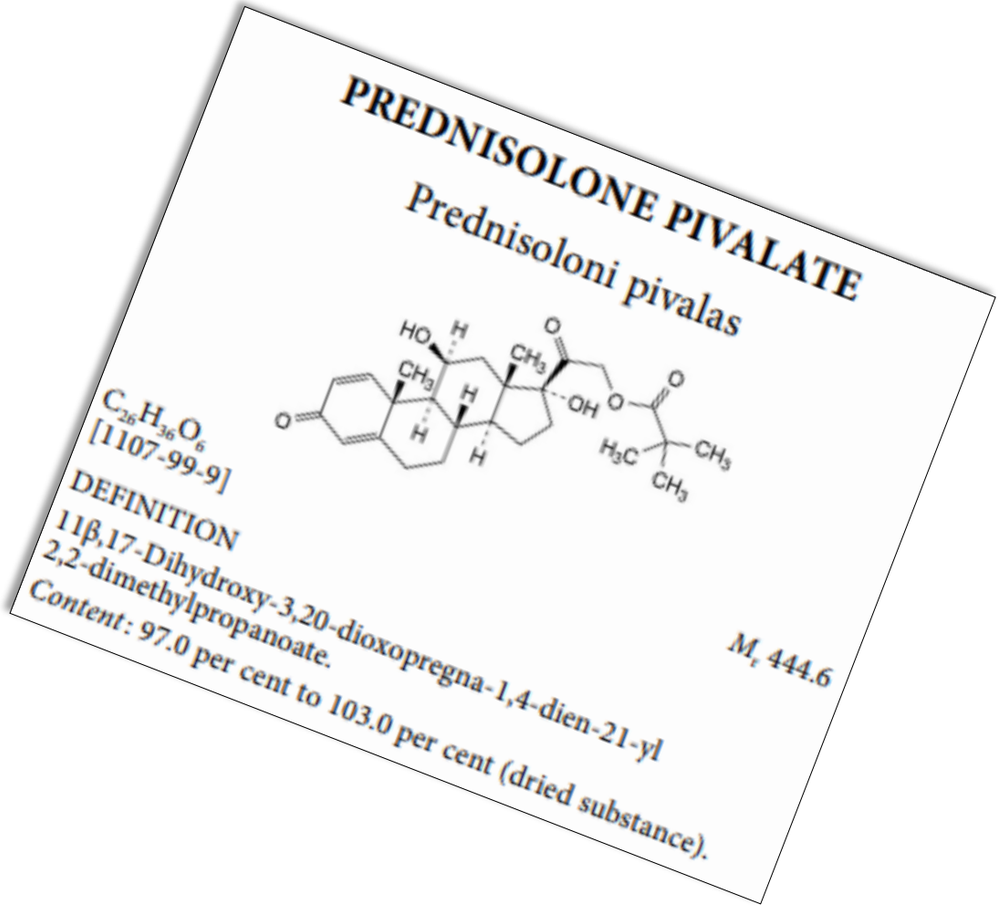
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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

Example: *Prednisolone pivalate (0736)*

Active substance for human use with a maximum daily dose ≤ 2 g

Monograph describes under related substances:

- ✓ Any impurity
  - for each impurity ≤ 2.0 %,
  - not more than one such peak ≥ 1.0 %
- ✓ Total ≤ 2.5 %
- ✓ Disregard limit 0.05%
- ✓ No Impurities section (transparency list)



PREDNISOLONE PIVALATE

Prednisoloni pivalas

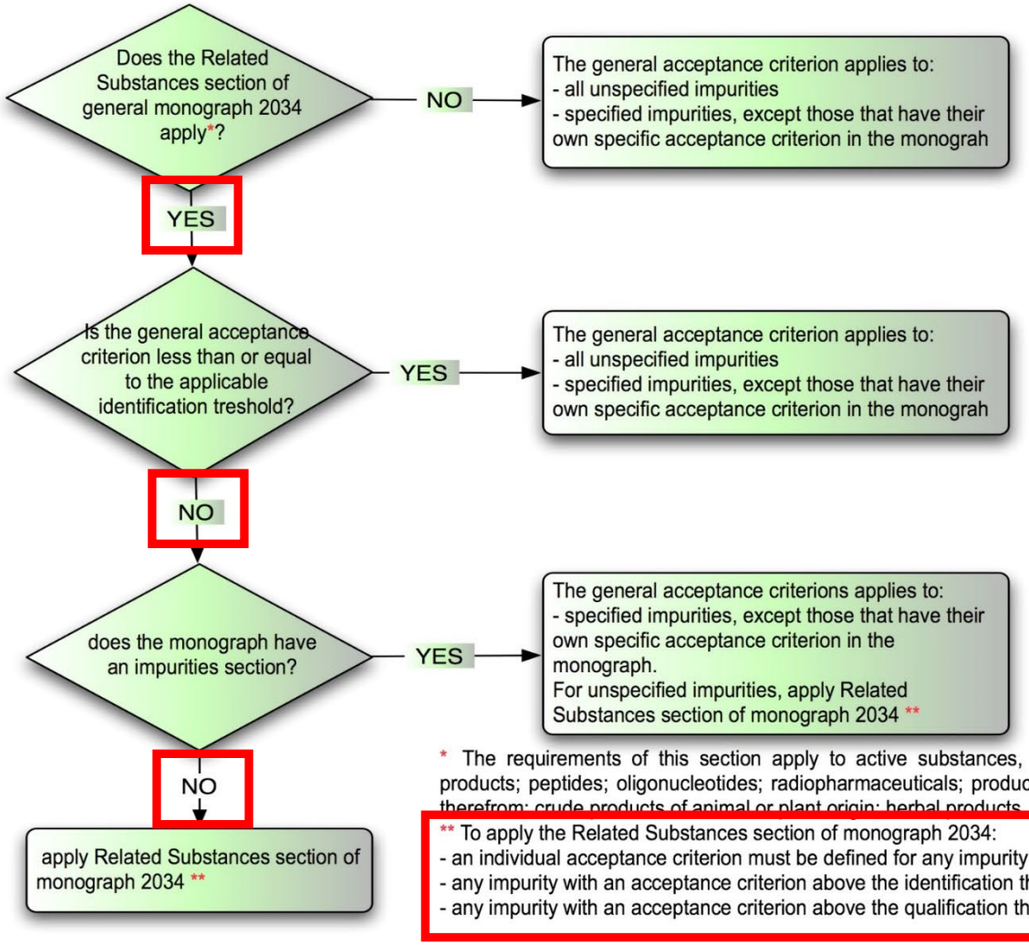
$C_{26}H_{36}O_6$
[1107-99-9]

DEFINITION

11β,17-Dihydroxy-3,20-dioxopregna-1,4-dien-21-yl 2,2-dimethylpropanoate.

M_r 444.6

Content: 97.0 per cent to 103.0 per cent (dried substance).



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.

Prednisolone pivalate (0736):

Any impurity:
- for each impurity ≤ 2.0 %,
- not more than one such peak ≥ 1.0 %

Total ≤ 1.5 %

Disregard limit 0.05%

No Impurities section (transparency list)

Identification threshold > 0.10 %

↳ Apply Related Substances section of general monograph *2034*

Table 2034.-1. – *Reporting, identification and qualification of organic impurities in active substances*

Use	Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
Human use or human and veterinary use	≤ 2 g/day	> 0.05 per cent	> 0.10 per cent or a daily intake of > 1.0 mg (whichever is the lower)	> 0.15 per cent or a daily intake of > 1.0 mg (whichever is the lower)
Human use or human and veterinary use	> 2 g/day	> 0.03 per cent	> 0.05 per cent	> 0.05 per cent
Veterinary use only	Not applicable	> 0.10 per cent	> 0.20 per cent	> 0.50 per cent

2034 Substances for pharmaceutical use

Related substances: some important statements

- ✓ 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)

Extract of the General Notices: **1.1.2.3 Demonstration of suitability of monographs**

"The manufacturer must evaluate the suitability of the monograph for the quality control of their substance or medicinal product, since the choice of analytical procedures may be influenced by the manufacturing process and/or the composition of the medicinal product. In cases where the **specification described in a monograph is considered to be insufficient** to ensure the quality of the product or substance by a competent authority, the latter may request **more-appropriate specifications from the manufacturer** in line with national or regional regulations. In such cases, the competent authority informs the Ph. Eur. Commission through either the national pharmacopoeia authority or the Secretariat of the Ph. Eur. Commission (EDQM). **The manufacturer is requested to provide the national pharmacopoeia authority or the EDQM with the details of the alleged insufficiency and the additional specifications applied**, so that the Ph. Eur. Commission can decide on the need to revise the monograph in question."

Identification of impurities (qualitative use)

Specified impurities and impurities used for the system suitability test (SST) must be identified in the chromatographic system, using:

- ✓ Reference standard (CRS)
  - Impurity CRS
  - Peak identification CRS
  - System suitability CRS
- ✓ Reagent (R)
- ✓ Alternative approach: in situ degradation
  - Hydrolysis
  - Oxidation
  - Ring-closure
  - Z-E Isomerisation
  - Epimerisation

Reference solution (c). Dissolve 2 mg of *raltegravir impurity E CRS* in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with reference solution (a).

Reference solution (d). In order to prepare impurity C *in situ*, dissolve 20 mg of the substance to be examined in a 40 g/L solution of *sodium hydroxide R* and dilute to 10 mL with the same solvent. Stir the solution for 30 min. To 5 mL of the solution add 5 mL of a 103 g/L solution of *hydrochloric acid R* and dilute to 50 mL with the solvent mixture.

Reference solution (e). Dissolve 5 mg of *raltegravir for peak identification CRS* (containing impurities F and G) in 20 mL of the solvent mixture using sonication for 5 min. Add about 25 mL of the solvent mixture then dilute to 50 mL with the solvent mixture.

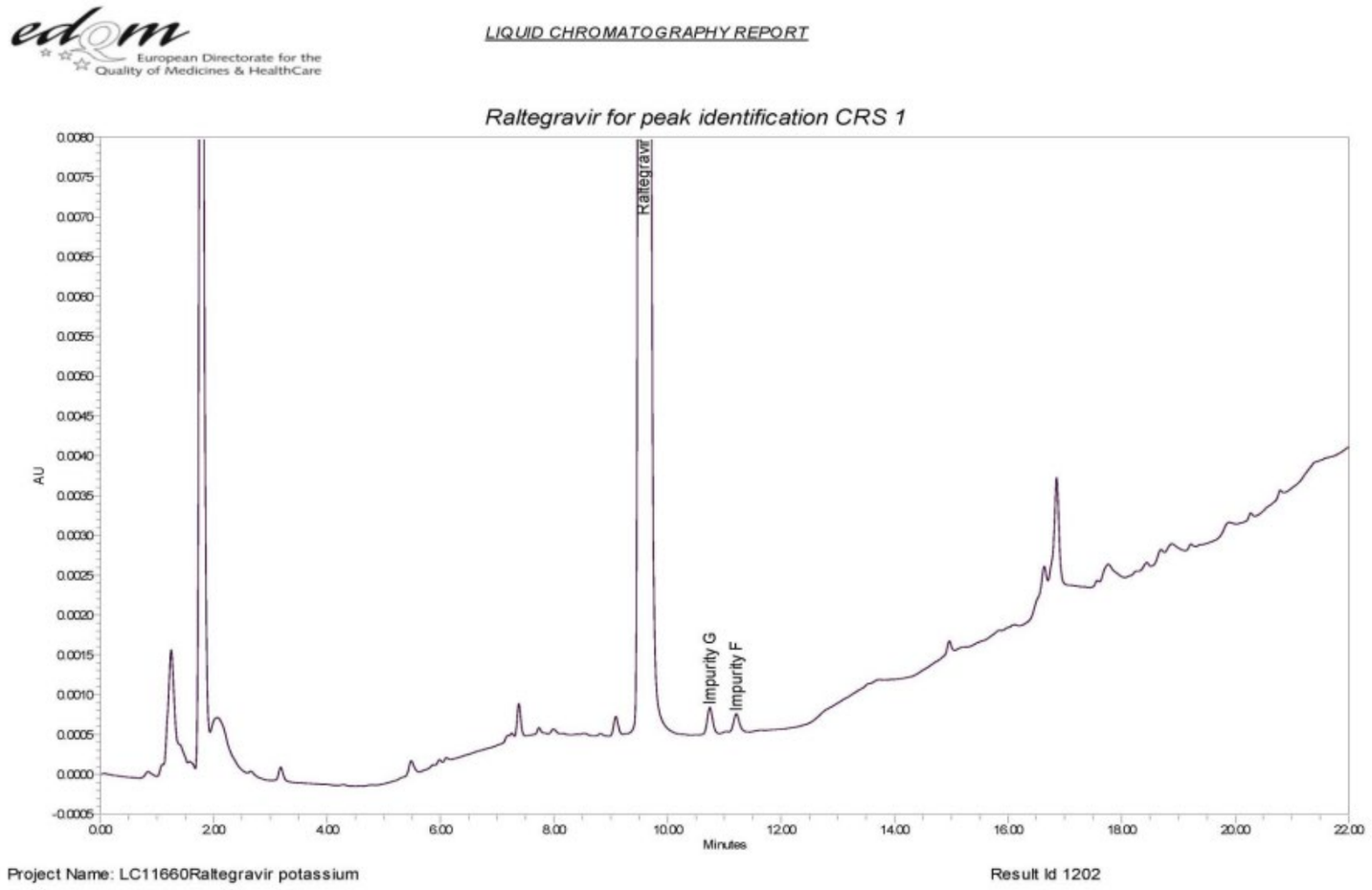
Identification of impurities (qualitative use)

Chromatograms might be provided in CRS leaflets

Identification of impurities: use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E; use the chromatogram supplied with *raltegravir for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities F and G.

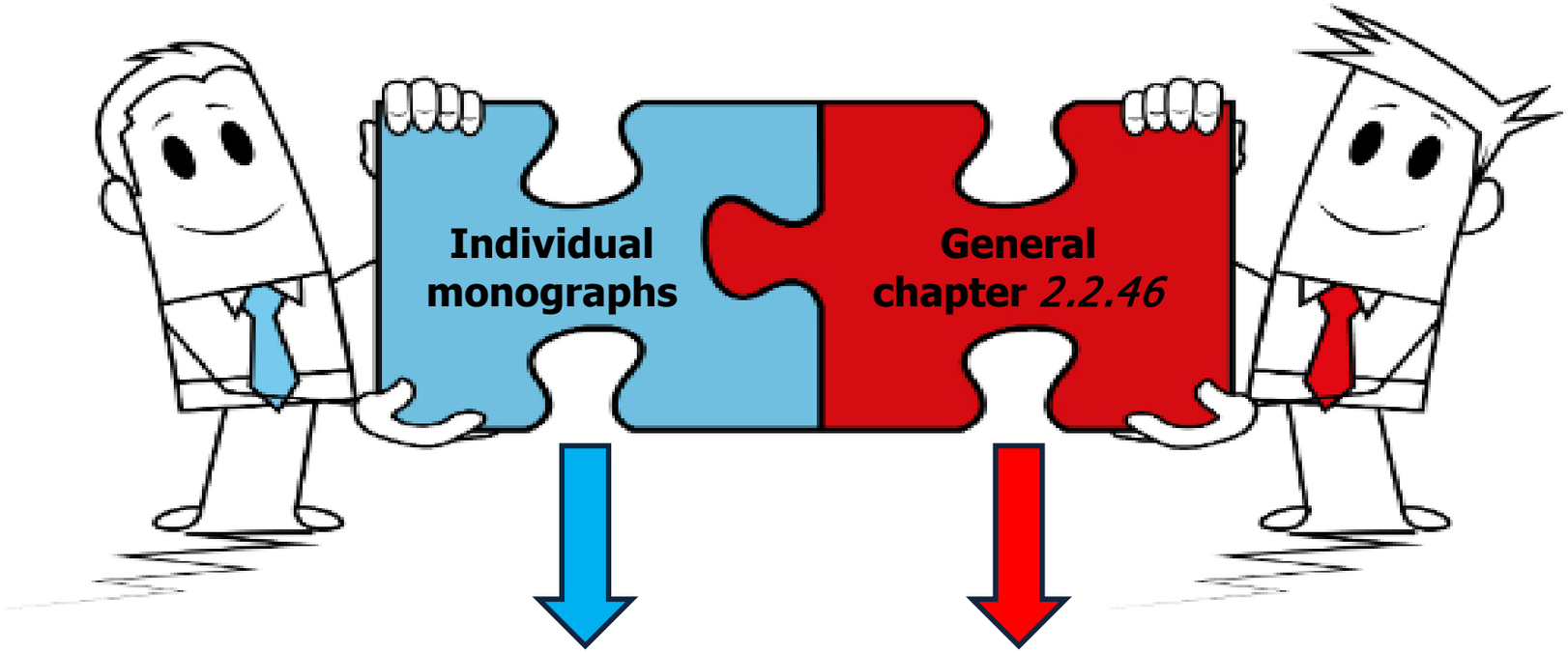
Retention times and relative retention values are given <u>for information only</u>

Relative retention with reference to raltegravir (retention time = about 10 min): impurity C = about 0.7; impurity E = about 0.95; impurity G = about 1.1; impurity F = about 1.15.



System suitability tests

Revised chapter *2.2.46* published in 11th Edition



Resolution
Peak-to-valley ratio

Symmetry factor 0.8 to 1.8
Minimum S/N 10 at reporting threshold*

* Calculation on a window of at least 5 times the peak width at half height.

System suitability test - Separation capacity (Selectivity)

Defined to verify the separation or partial separation of a critical pair

- ✓ **Resolution**:
  - generally below 5, but may be above if no other critical pair
  - minimum resolution requirement should be ≥ 1.5
- ✓ **Peak-to-valley ratio:**
  - when complete separation between 2 adjacent peaks cannot be achieved (i.e. Rs < 1.5)
  - minimum p/v ratio requirement should be ≥ 1.5

What to do when the monograph describes a p/v ratio and baseline separation is achieved?

The peak-to-valley ratio cannot be calculated; however the requirement is fulfilled since the separation is even better than that prescribed by the monograph

Calculation of percentage contents

✓ **Option 1:**
- using an external standard
- dilution of the test solution
- impurity itself

↳ Preferred methods in Ph. Eur.

Calculation of percentage contents:
- *correction factor*: multiply the peak area of impurity C by 1.6;
- for each impurity, use the concentration of raltegravir potassium in reference solution (b).

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Dilution of test solution consider response factor of impurities!

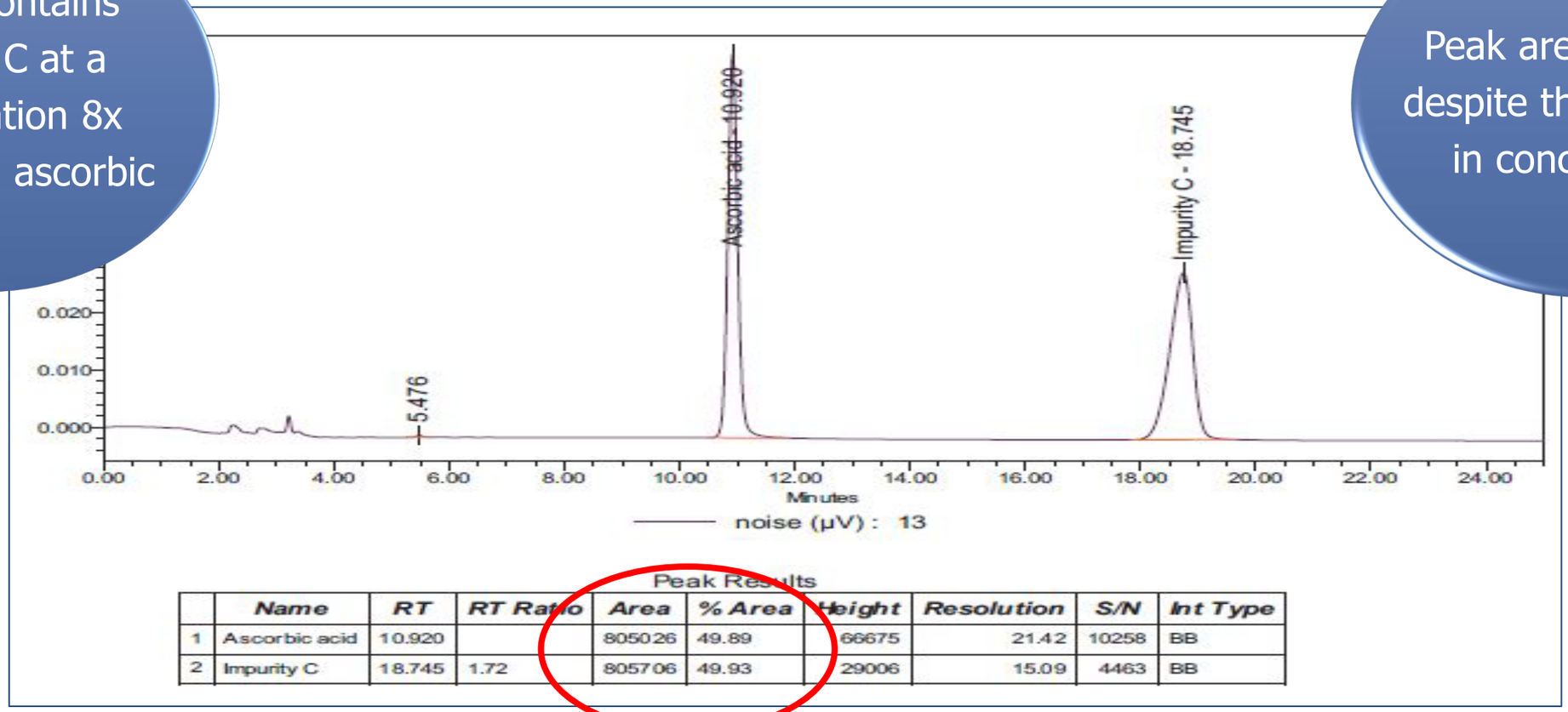
✓ **Option 2:** peak area normalisation

↳ To be avoided, whenever possible

Importance of correction factors

Example of different response factors: Ascorbic acid and impurity C

Sample contains impurity C at a concentration 8x higher than ascorbic



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

Peak area is similar despite the difference in concentration

Response and correction factors

✓Response factors between 0.8 and 1.2 are considered negligible

↳ No correction factors between 0.8 and 1.25 in monographs

Importance of impurity sample!

✓ When correction factors are > 5

↳ Quantification should be performed using impurities as external standards

✓ Calculation by comparing the response of the reference peak (used for quantitation) and the impurity peak by using either:

- the mean of the area ratios over the whole range of linearity, or
- the ratio of the slopes of the respective linearity regression equations

More information: Technical Guide or Pharmeuropa online (Useful information)

Calculation of 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.

Correction factor (CF): reciprocal value of response factor

Calculation of response and correction factors

Important points to consider:

✓ **Purity** of the impurity and the test substance

Purity calculation:

$$\text{Content (\%)} = [100 - (\text{water} + \text{solvents})] \times \frac{\text{chromatographic purity (\%)}}{100}$$

✓ **Form** (base/acid or salt) of the impurity and the test substance

↳ If different, need for an additional correction factor for molecular mass ratio

✓ Perform the chromatography at the wavelength and flow rate defined in the monograph

Reporting threshold (previously disregard limit)

✓ Limit above which an impurity should be reported (ICH Q3A)

✓ **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 reporting threshold

  (LOQ ≤ reporting threshold)

Limits:

- *impurity C*: maximum 0.3 per cent;
- *impurities E, F, G*: for each impurity, maximum 0.15 per cent;
- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 0.5 per cent;
- *reporting threshold*: 0.05 per cent.

ICH Q3A R2 "Impurities in new drug substances"

System suitability test - Sensitivity

✓ Sensitivity must be verified for controlling impurities not only at their acceptance criterion, but down to the reporting threshold

↳ Addition of a sensitivity test for low responding impurities (RRF < 0.8)

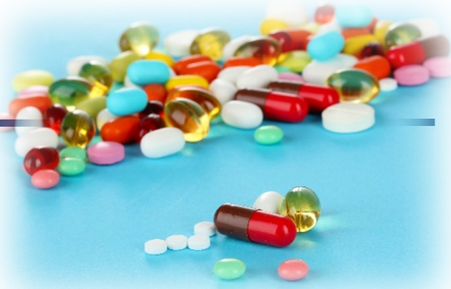
Example: Impurity X: Response factor 0.5 (i.e. CF of 2.0 stated in monograph)

In case of limited sensitivity observed during validation, introduction of a sensitivity criterion:

- **Option 1:** dilution of test solution used: S/N ratio minimum 20 at reporting threshold (S/N ≥ 10 x CF of 2 ⇨ S/N ≥ 20)

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

Impurities in medicinal product monographs



Degradation products

- Controlled
- Arising during the manufacturing process and throughout shelf-life, including impurities of synthesis that are also degradation products
- Individual limit (for specified) or general acceptance criterion (for unspecified)

Impurities of synthesis

- Not controlled
- If detected by the procedure, they are included in the transparency list
- If present at a level greater than the reporting threshold, they are:
  - identified (e.g. using a reference standard or reagent) and
  - disregarded

ICH Q3B R2 "Impurities in new drug products"
ICH Q6A "Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical Substances"

Impurities in medicinal product monographs

Thresholds

- In line with ICH Q3B - "Impurities in new drug products"
- Reporting, identification and qualification thresholds are higher than for API

Ticagrelor (3087)

- Identification threshold: 0.10%
- Reporting threshold: 0.05%

Limits:
- *impurity D*: maximum 0.3 percent;
- *impurities A, B*: for each impurity, maximum 0.2 per cent;
- *impurity C*: maximum 0.1 per cent;
- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 1.0 per cent;
- *reporting threshold*: 0.05 per cent.

Max daily dose ≤ 1g

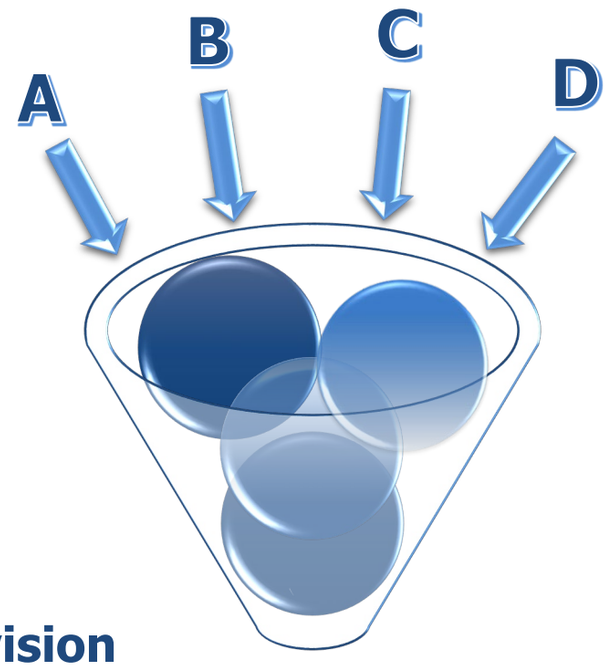
Ticagrelor tablets (3097)

- Identification threshold: 0.2%
- Reporting threshold: 0.1%

Limits:
- *unspecified impurities*: for each impurity, maximum 0.2 per cent;
- *total*: maximum 0.5 per cent;
- *reporting threshold*: 0.1 per cent; disregard the peaks due to impurities A, B and D.

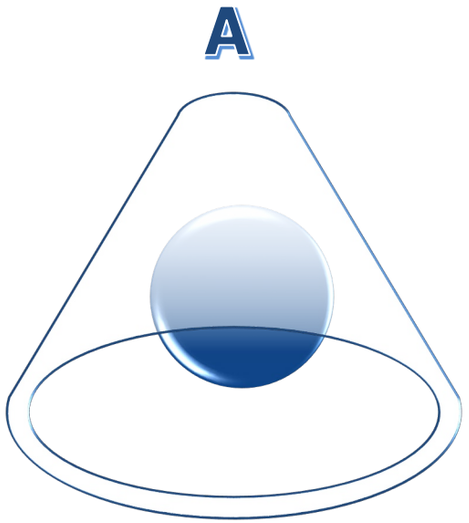
Specifications in monographs

PROCEDURE 1 (P1)
Multi-source products



Revision

MONOGRAPH
valid for A, B, C & D
Monograph covers **all impurities** observed in the different synthetic pathways



MONOGRAPH

To be applicable to B, C, D ….

Revision P1

PROCEDURE 4 (P4)
Single-source products

Specifications in monographs

✓ Based on limits approved by competent authorities

✓ Based on representative batch and stability data

<u>Example</u>: Need for arbitration:

Request for revision to include impurity X in an API monograph

- Approved limit: 0.2%
- Batch data (15x): 2x not detected / 3x 0.01% / 3x 0.02% / 1x 0.03% / 2x 0.04% / 1x 0.05% / 3x 0.06%
- Mean + 3sigma = 0.029% + 0.063 = 0.092%

→ Limit proposed at 0.10% (unspecified)
Avoid the need for a CRS for peak identification

Validation & Implementation

Extract of the General Notices:

1.1.2.4 Validation and implementation of Ph. Eur. analytical procedures

"The **analytical procedures** given in an individual monograph have been **validated** in accordance with accepted scientific practice and recommendations on analytical validation. **Unless otherwise stated** in the individual monograph or in the corresponding general chapter, **validation of these procedures by the user is not required**. [….]
When **implementing a Ph. Eur. analytical procedure**, **the user must assess whether and to what extent its suitability** under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.."

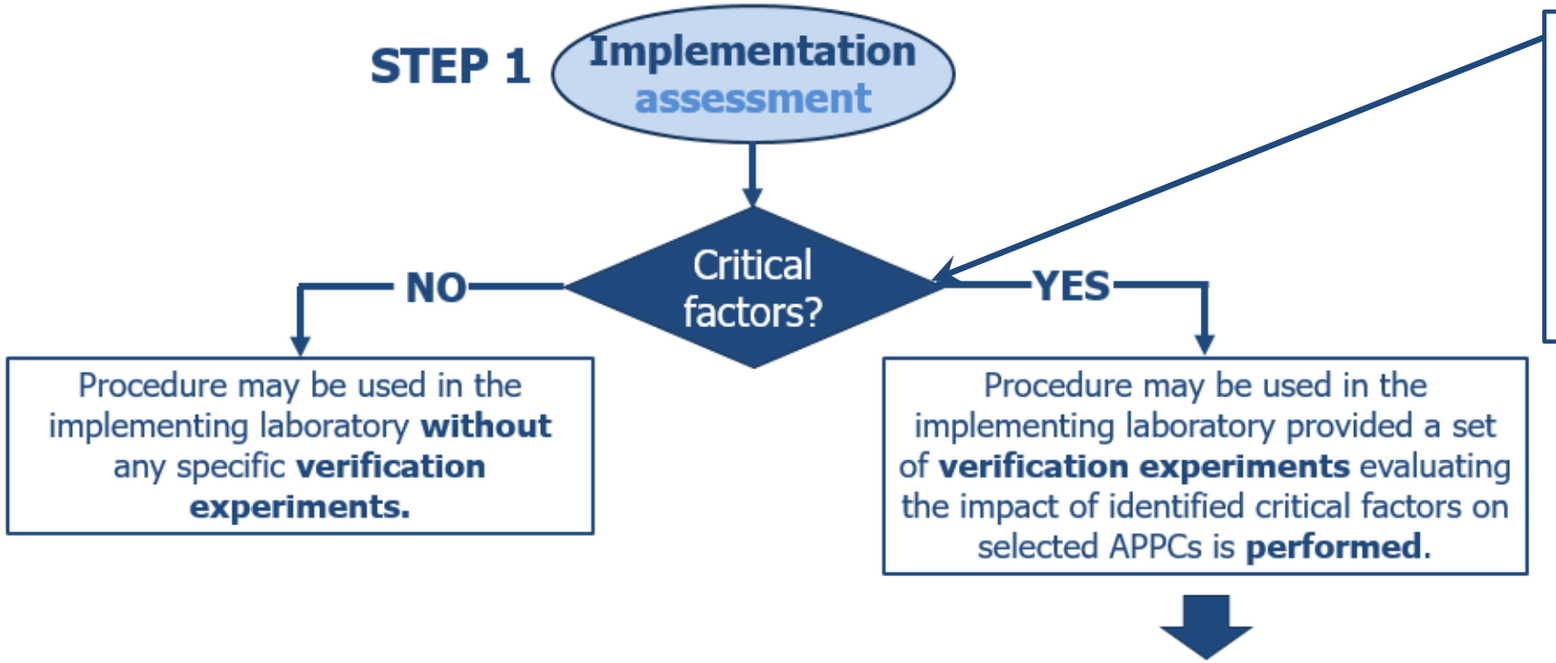
Chapter *5.26 Implementation of pharmacopoeial procedures*

Implementation of a pharmacopoeial procedure is the **process of demonstrating its suitability** and applying it under the actual conditions of use in the implementing laboratory

Examples of implementation of pharmacopoeial procedures

Implementation of pharmacopoeial procedures *5.26*

- **Aim**: to provide guidance on setting up an approach for implementation
- « **For information** » chapter; other approaches may be appropriate



- composition of the article under test ;
- complexity of the sample preparation ;
- reagents required to run the procedure ;
- laboratory equipment required to run the procedure ;
- laboratory environment.

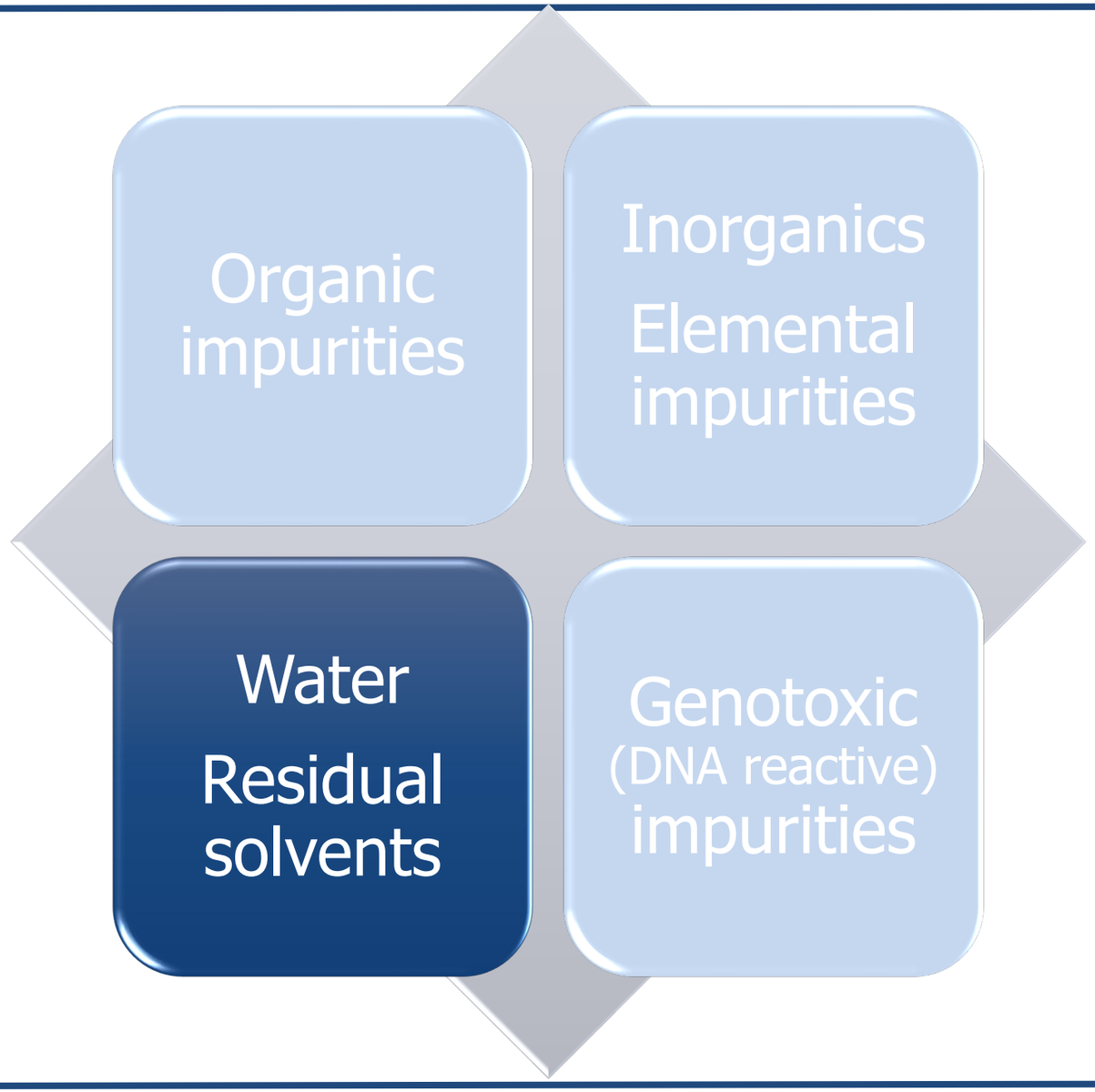
STEP 2 VERIFICATION

= experiments to verify **relevant APPCs*** depending on **intended use** with respect to defined **acceptance criteria**

Intended use / APPCs	Identification	Testing for impurities		Assay - content/potency - dissolution (measurement only)	Other quantitative tests
		limit	quant.		
Accuracy	○	○	○	◗	◗
Precision					
Repeatability	○	○	●	●	●
Interm. prec.	○	○	◗	◗	◗
Specificity/ Selectivity	◗	●	●	●	◗
Sensitivity	○	●	●	○	◗
Linearity	○	○	○	◗	◗
Range	○	○	○	◗	◗
Robustness	○	○	◗	◗	◗

* APPC: analytical procedure performance characteristics

Control of impurities in Ph. Eur.



Water/Residual solvents

Water

In API monographs, most often controlled by:

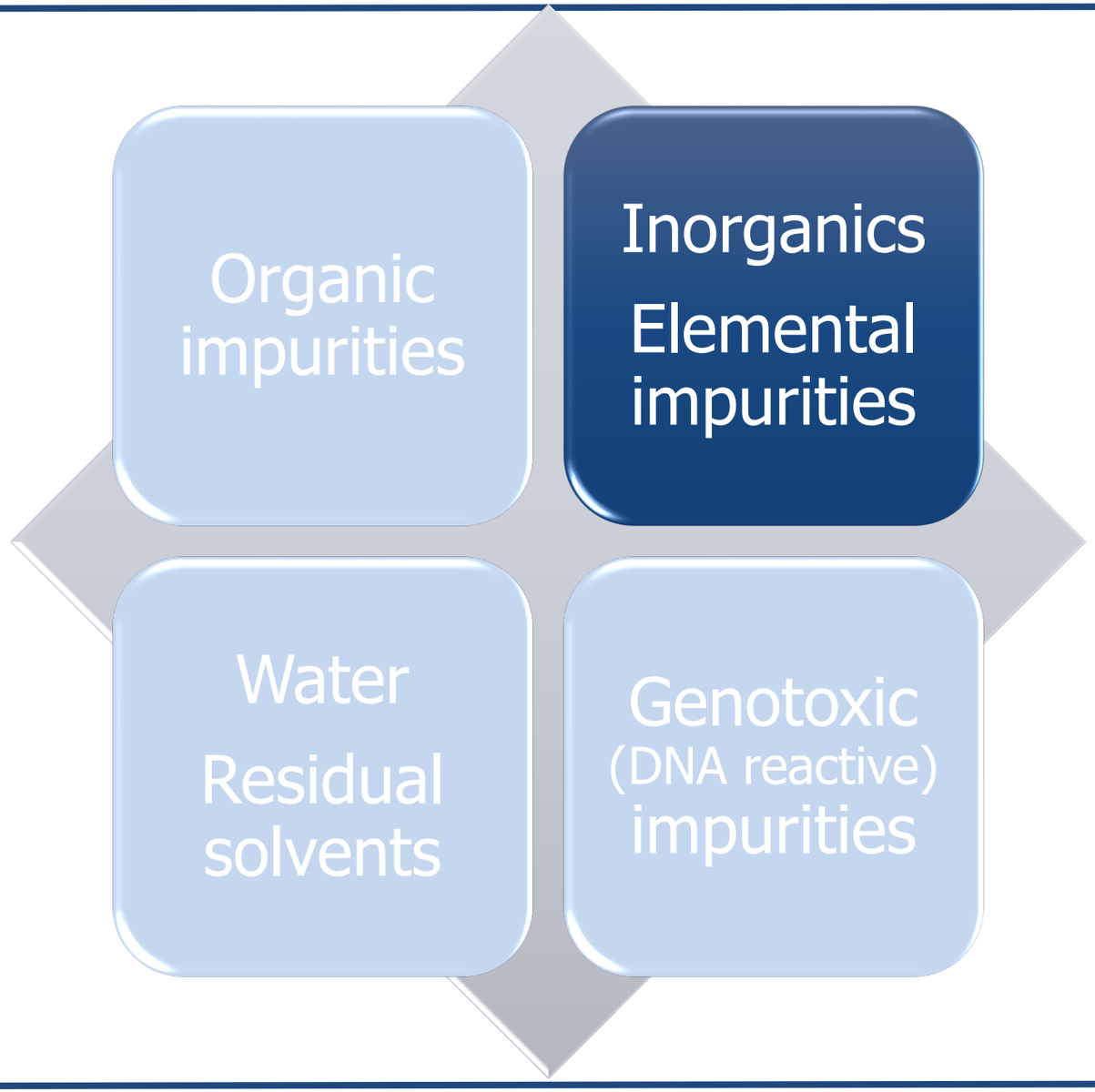
- Semi-micro determination (volumetric Karl Fischer - *2.5.12*)
- Micro determination (coulometry - *2.5.32*)
- Loss on drying (*2.2.32*)

In medicinal product monographs: usually no test

Residual solvents

- Controlled according to general text *5.4. Residual solvents* (reproduction of ICH Q3C) and general chapter *2.4.24. Identification and control of residual solvents*
- ICH Q3C becomes legally binding through *2034* & *2619*
- Test in individual API monographs:
  - Class 1 solvents are always named and limited
  - Class 2 solvents not included; limit set by option 2 (cf. *5.4*)
  - Class 3 solvents are only named and limited when they exceed 0.5%
- Class 3 solvents (volatile) may be controlled by LOD (up to 0.5%)

Control of impurities in Ph. Eur.



Inorganics/Elemental impurities

General texts

Inorganics: controlled by general tests like sulfated ash, specific tests like AAS, ICP-AES/MS or general chapter *2.4.20*

General text *5.20*

Implementation of ICH Q3D *Elemental impurities* in the Ph. Eur.

General text *2.4.20*

Determination of elemental impurities

↳ Now harmonised within PDG (Publication in 11.8 – January 2025)

Revised chapter

General monograph *2034*

Substances for pharmaceutical use: "Permitted daily exposures for elemental impurities (….) apply to the medicinal product. Individual monographs on substances for pharmaceutical use therefore do not contain specifications for elemental impurities unless otherwise prescribed."

General monograph *2619*

Pharmaceutical preparations: "General chapter *5.20. Elemental impurities* applies to pharmaceutical preparations..."

↳ ICH Q3D becomes legally binding

Elemental impurities

General monograph *2619 Pharmaceutical preparations:*

"Elemental impurities

General chapter *5.20. Elemental impurities* applies to pharmaceutical preparations except products for veterinary use, unlicensed preparations and other products that are excluded from the scope of this chapter. ↳ ICH Q3D becomes legally binding

For pharmaceutical preparations outside the scope of general chapter *5.20*, manufacturers of these products remain responsible for controlling the levels of elemental impurities using the principles of risk management.

If appropriate, testing is performed using suitable analytical procedures according to general chapter *2.4.20. Determination of elemental impurities."*

↳ Classical heavy metal tests (*2.4.8*) ⇨ deleted from individual monographs:

- Since the 9th Edition for substances for both human and veterinary use
- As of the 11th Edition for substances for veterinary use only

Elemental impurities

Specific elemental impurity tests ⇨ No systematic deletion from monographs

- ✓ Tests suppressed when elements have been "intentionally added", (i.e. reagents or catalysts used in synthesis)
- ✓ Tests remain when elements are of natural abundance which cannot be eliminated by purification (e.g. mined excipients)

Example:
Calcium phosphate (1052)

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

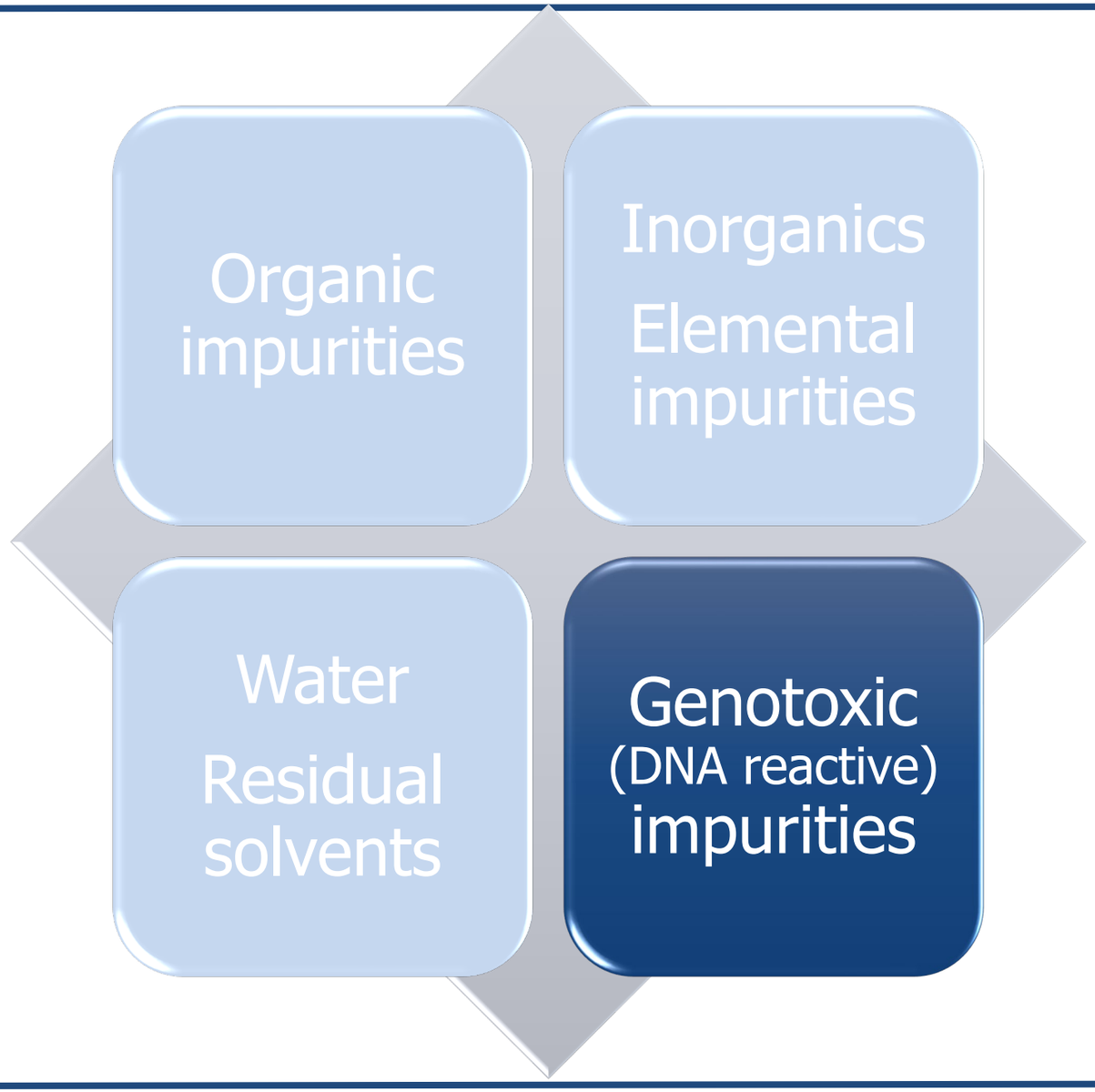
Element	Maximum content (ppm)
Arsenic	2
Lead	1

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

Iron (*2.4.9*): maximum 400 ppm.

- ✓ Tests may remain when important to ensure the quality
- ✓ Special cases: *Methylthioninium chloride hydrate (1132)* (methylene blue) - Elements may have an effect on therapeutic activity (API is a chelating agent)

Control of impurities in Ph. Eur.



DNA reactive (mutagenic) impurities

Ph. Eur. follows ICH M7:

- ✓ Reference to ICH M7 included in general monograph *2034 Substances for pharmaceutical use*
- ✓ Tests are described when **proof for genotoxicity** is provided (e.g. Ames test, toxicological studies), NOT based solely on structural alerts
- ✓ Control tests in individual monographs are in:
  - Production section: when the technique is special or no specific test/limit is known
  - Tests section: when suitable procedure is available and limits are known

ICH M7 "Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk"

Nitrosamines: general monographs *2034* & *2619*

- ✓ **Production:** addition of a paragraph explaining the Ph. Eur. approach

Revised 11.3

- ✓ Approach defined based on the feedback from Heads of Medicines Agencies & European Medicines Agency groups as well as from National Competent Authorities of non-EU Ph. Eur. Member states

2034 Substances for pharmaceutical use

"*N*-Nitrosamines. As many *N*-nitrosamines are classified as probable human carcinogens, **manufacturers of active substances for human use** are expected to **evaluate the potential risk of *N*-nitrosamine** formation and contamination occurring throughout **their manufacturing process and during storage**. If the risk is confirmed, manufacturers should mitigate as much as possible the presence of *N*-nitrosamines – for example by modifying the manufacturing process – and a **control strategy should be implemented** to detect and control these impurities. General chapter 2.5.42 *N-Nitrosamines in active substances* is available to assist manufacturers."

2619 Pharmaceutical preparations

"N-Nitrosamines. As many N-nitrosamines are classified as probable human carcinogens, **manufacturers of medicinal products,** except products for veterinary use only and unlicensed pharmaceutical preparations, are expected to **evaluate the potential risk of *N*-nitrosamine** formation and contamination occurring throughout their manufacturing process and throughout their shelf-life, according to the requirements of the relevant competent authorities. If the risk is confirmed, manufacturers should mitigate as much as possible the presence of *N*-nitrosamines – for example by modifying the manufacturing process – **and a control strategy must be implemented** to detect and control these impurities. General chapter 2.5.42. *N-Nitrosamines in active substances* is available to assist manufacturers."

Nitrosamines in Sartans: general chapter *2.5.42*

2.5.42.

N-Nitrosamines in active substances

- Detection of 7 nitrosamines in sartan active substances (NDMA, NDEA, NDBA, NMBA, NDIPA, NEIPA, NDPA)
- 7 nitrosamine reference standards available
- Adopted in November 2020, published on the EDQM website then in 10.6

Revised 12.1

2.5.42.

***N*-Nitrosamines in active substances and medicinal products**

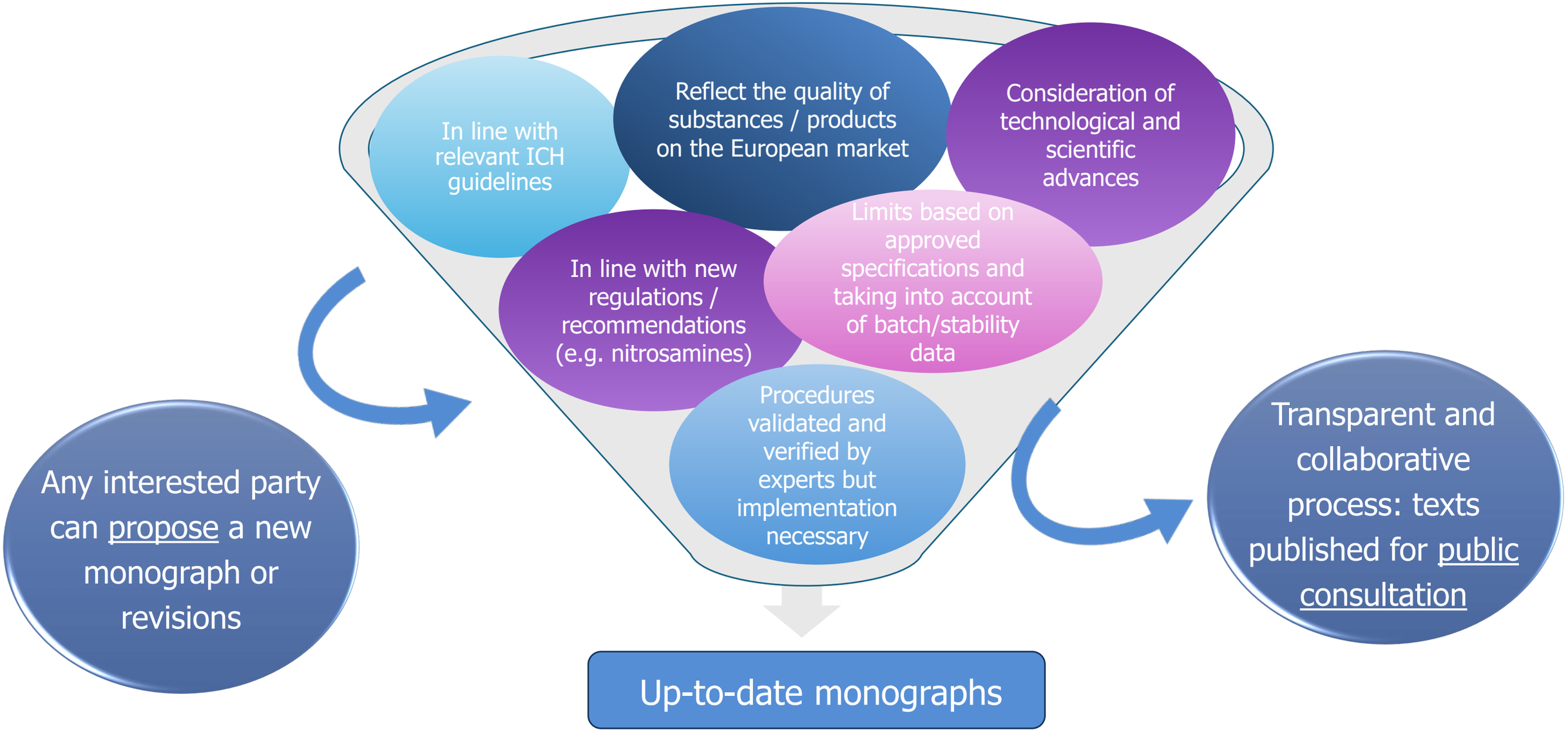
- Extension of the scope: inclusion of sartan-containing medicinal products in procedures A and C and both procedures can be applied as a quantitative test
- Adopted in November 2024, publication in 12.1 (July 2025)

Nitrosamines: tackling the risk in individual monographs

- ✓ In general, nitrosamines covered by the general monographs 2034 & 2619
  - ↳ No Production section, no test in Test section
  - ↳ Sartan monographs revised to delete the Production section (Publication in 11.6)

- ✓ <u>Other options:</u>
  - Keep/Introduce a test in Test section only if the presence of nitrosamines is confirmed, risk from the API manufacturing/stability
  - Use of an antioxidant
    - ↳ The statement "a suitable antioxidant may be added" introduced in the Definition

Conclusions - Impurity Control in the Ph. Eur.



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