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

**29 June 2023, Strasbourg, France**

Aurélie BARTH

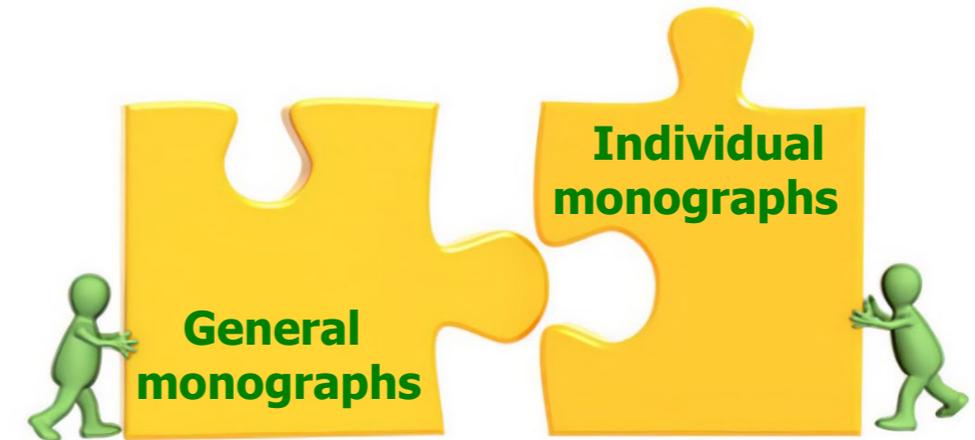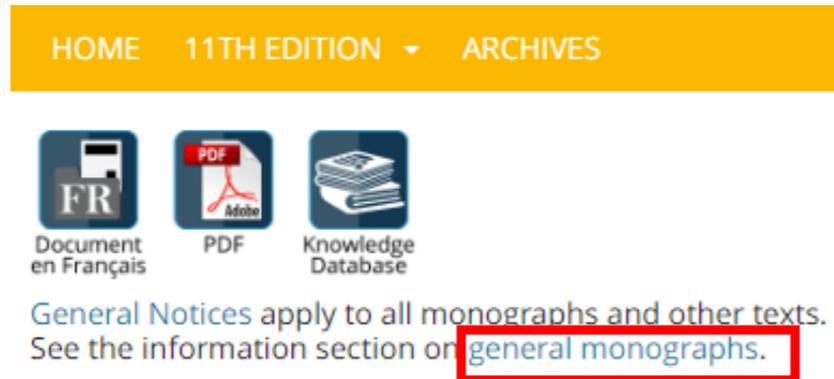**European Pharmacopoeia Department**

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

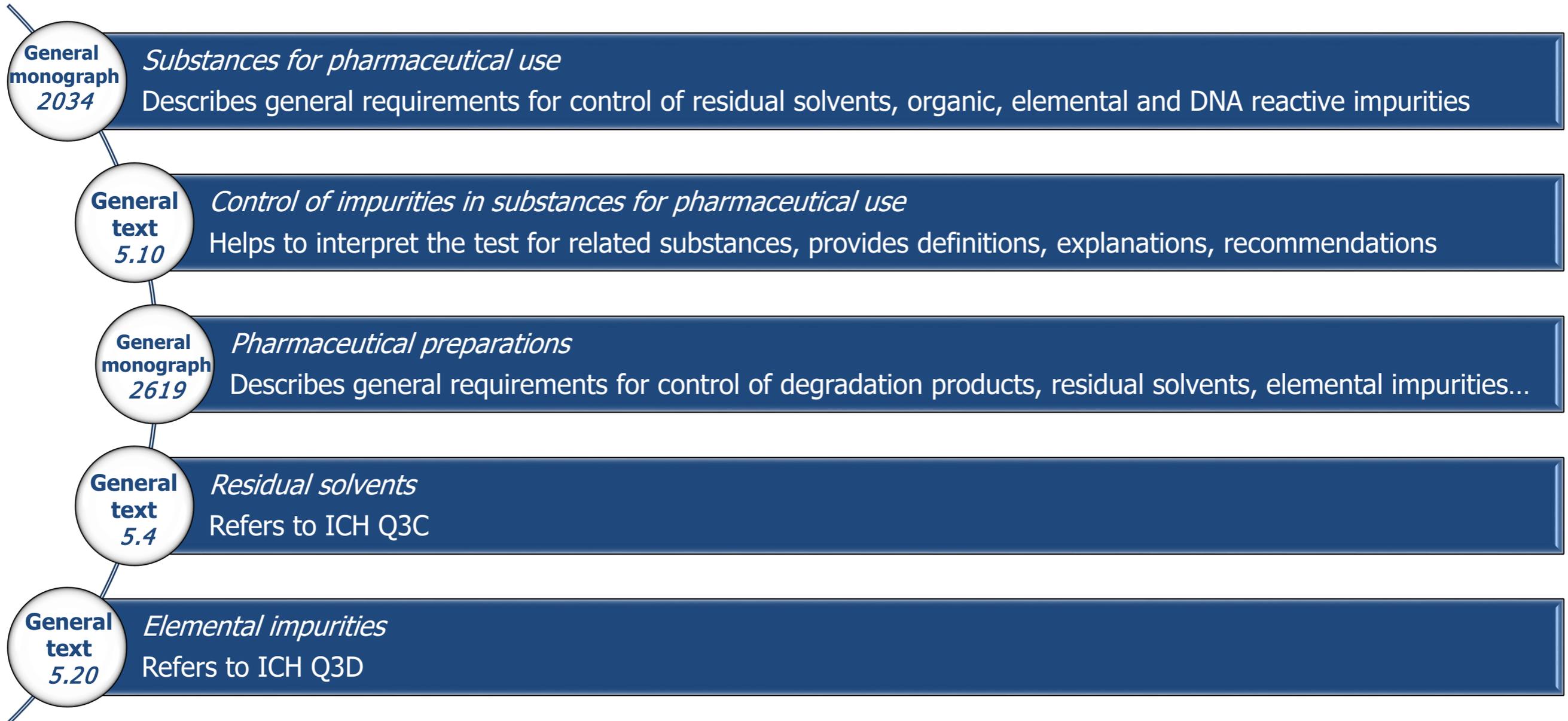# Control of impurities in Ph. Eur.

- Organic impurities
- Inorganics Elemental impurities
- Water Residual solvents
- Genotoxic (DNA reactive) impurities
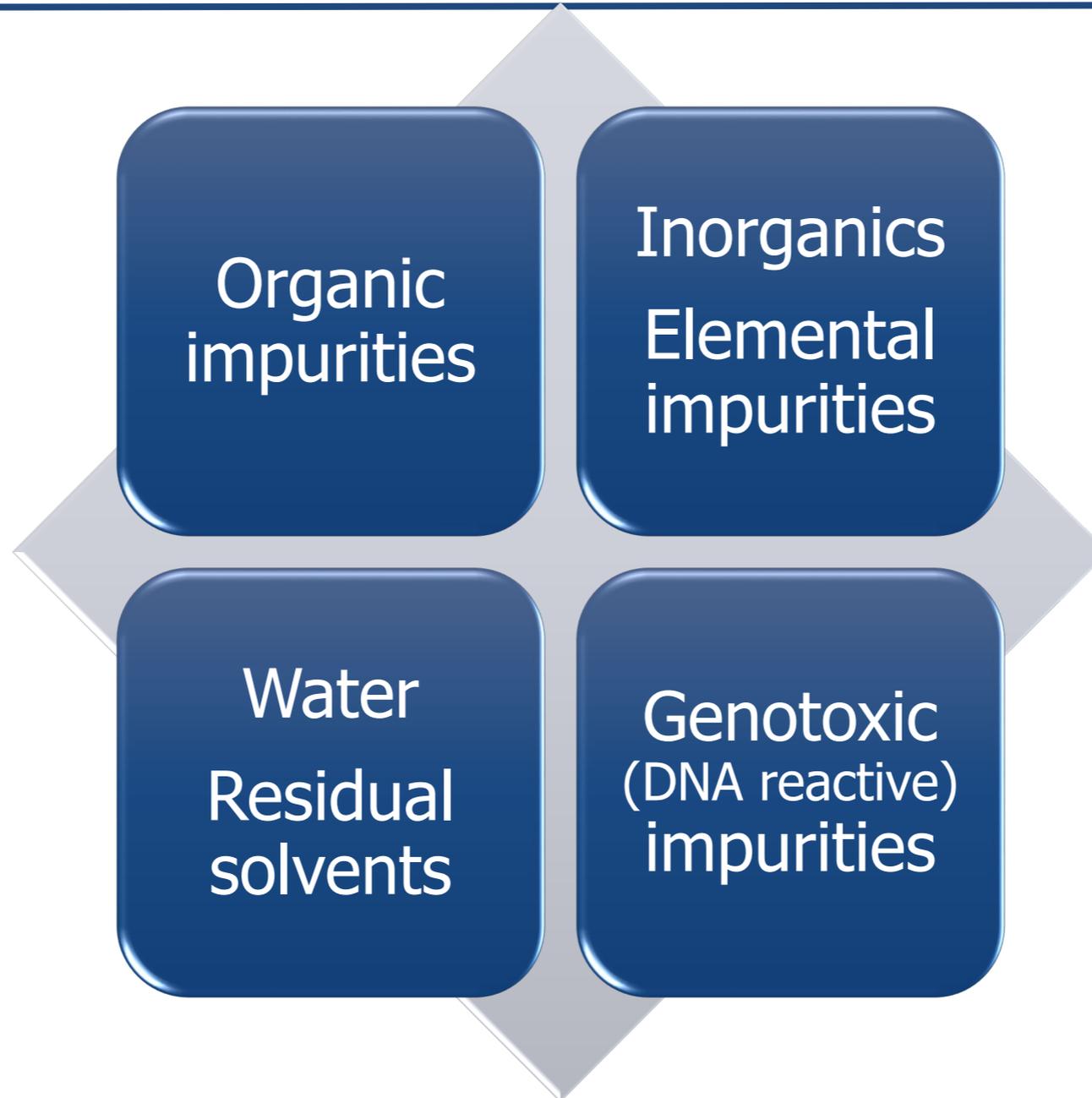
General monographs and texts

✓ **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.
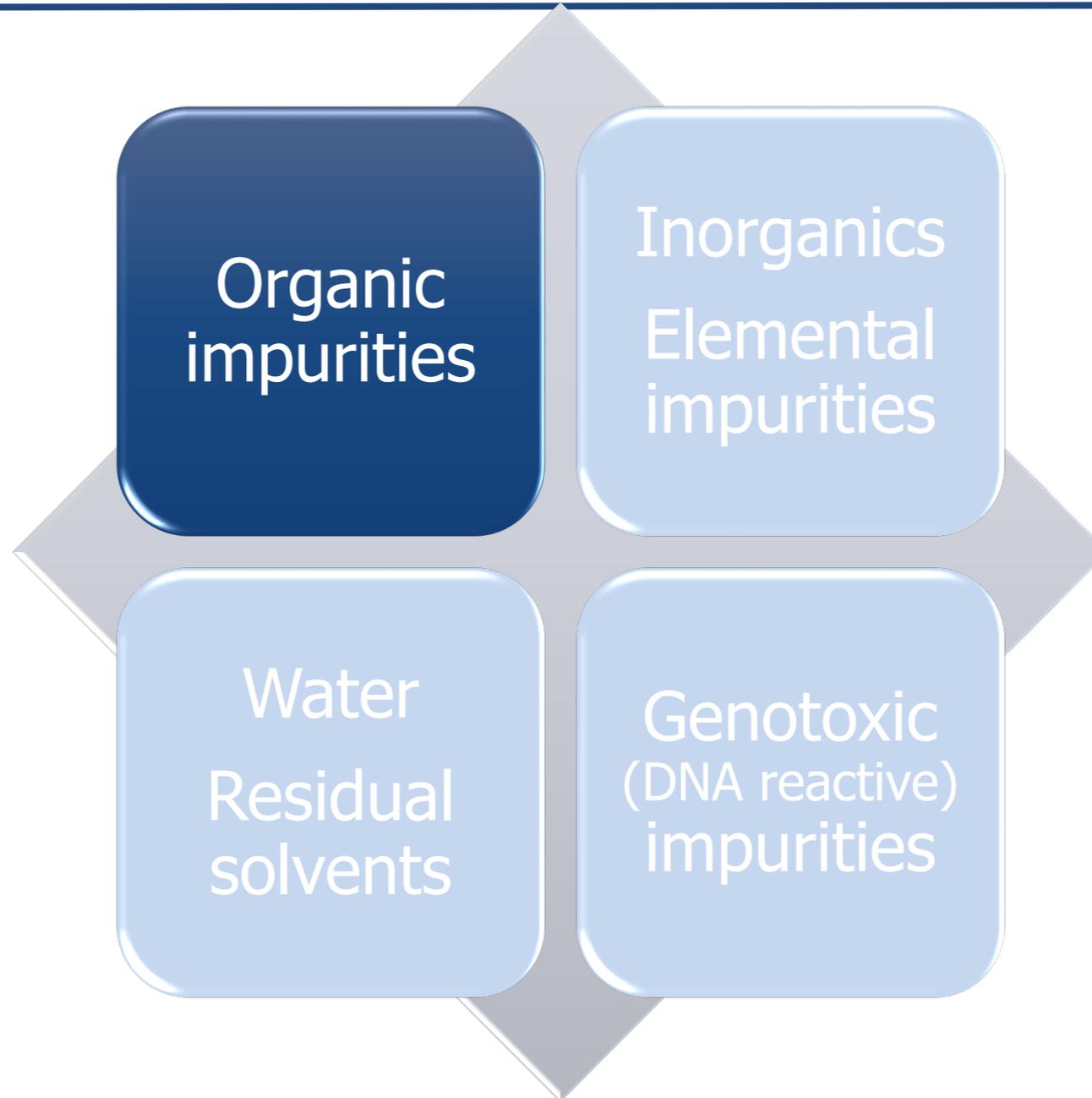

HOME   11TH EDITION ▾   ARCHIVES

Document en Français   PDF   Knowledge Database

General Notices apply to all monographs and other texts. See the information section on general monographs.

Individual monographs

General monographs

✓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

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Control of impurities in Ph. Eur.

Organic impurities

Inorganics
Elemental impurities

Water
Residual solvents

Genotoxic
(DNA reactive)
impurities

2034 Substances for pharmaceutical use

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. or in Table 2034.-2 for peptides obtained by chemical synthesis."

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

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

ICH Q3A R2 "Impurities in new drug substances"

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."

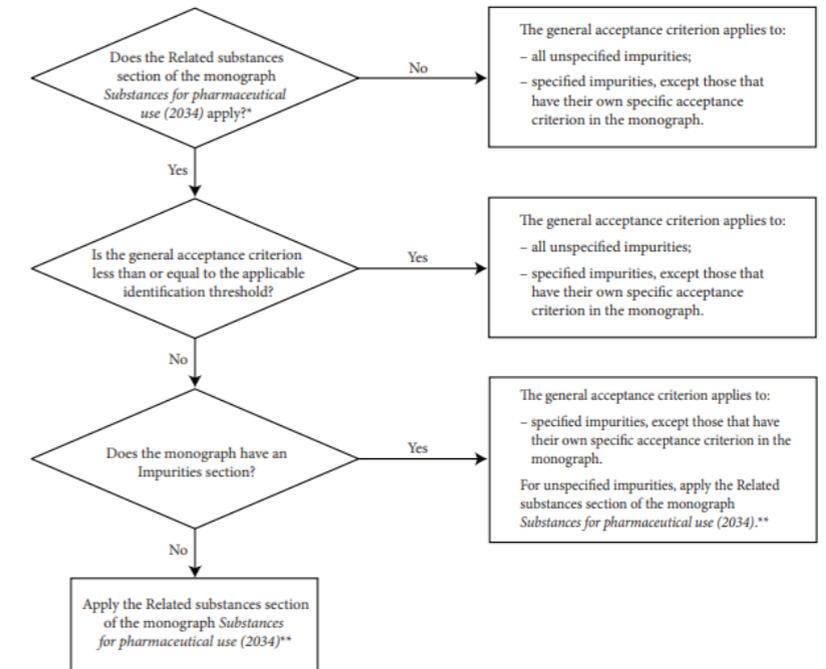# 5.10. Control of impurities in substances for pharmaceutical use

Provides:

✓ 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 in relation to the *Impurities* section of the monograph.

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

Does the Related substances section of the monograph *Substances for pharmaceutical use (2034)* apply?*

No → The general acceptance criterion applies to:
– all unspecified impurities;
– specified impurities, except those that have their own specific acceptance criterion in the monograph.

Yes ↓

Is the general acceptance criterion less than or equal to the applicable identification threshold?

Yes → The general acceptance criterion applies to:
– all unspecified impurities;
– specified impurities, except those that have their own specific acceptance criterion in the monograph.

No ↓

Does the monograph have an Impurities section?

Yes → The general acceptance criterion applies to:
– specified impurities, except those that have their own specific acceptance criterion in the monograph.
For unspecified impurities, apply the Related substances section of the monograph *Substances for pharmaceutical use (2034).***

No ↓

Apply the Related substances section of the monograph *Substances for pharmaceutical use (2034)***

* The requirements of this section apply to active substances with the exception of: biological and biotechnological products; oligonucleotides; radiopharmaceuticals; products of fermentation and semi-synthetic products derived therefrom; crude products of animal or plant origin; herbal products.
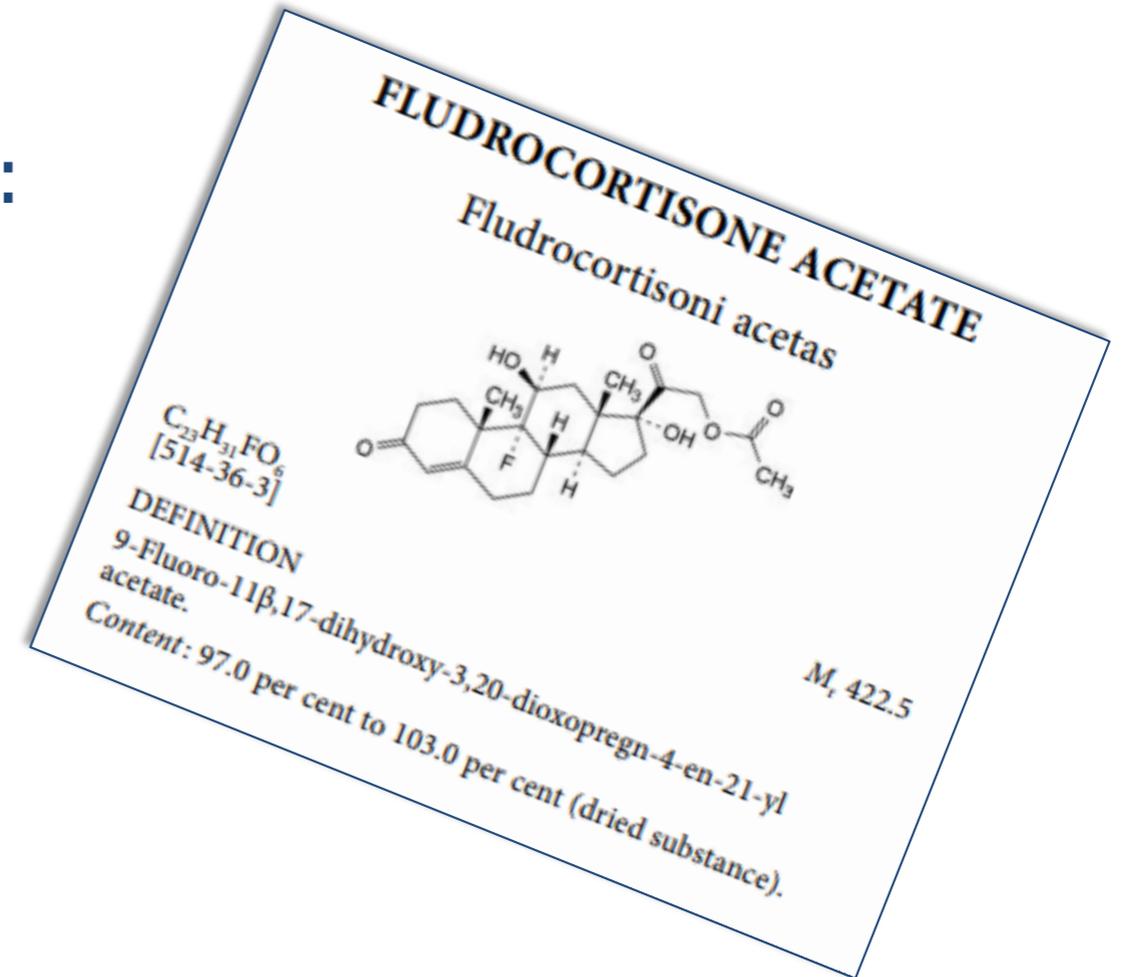** To apply the Related substances section of the monograph *Substances for pharmaceutical use (2034)*:
– an individual acceptance criterion must be defined for any impurity that may be present above the identification threshold;
– any impurity with an acceptance criterion above the identification threshold must wherever possible be identified;
– any impurity with an acceptance criterion above the qualification threshold must be qualified.
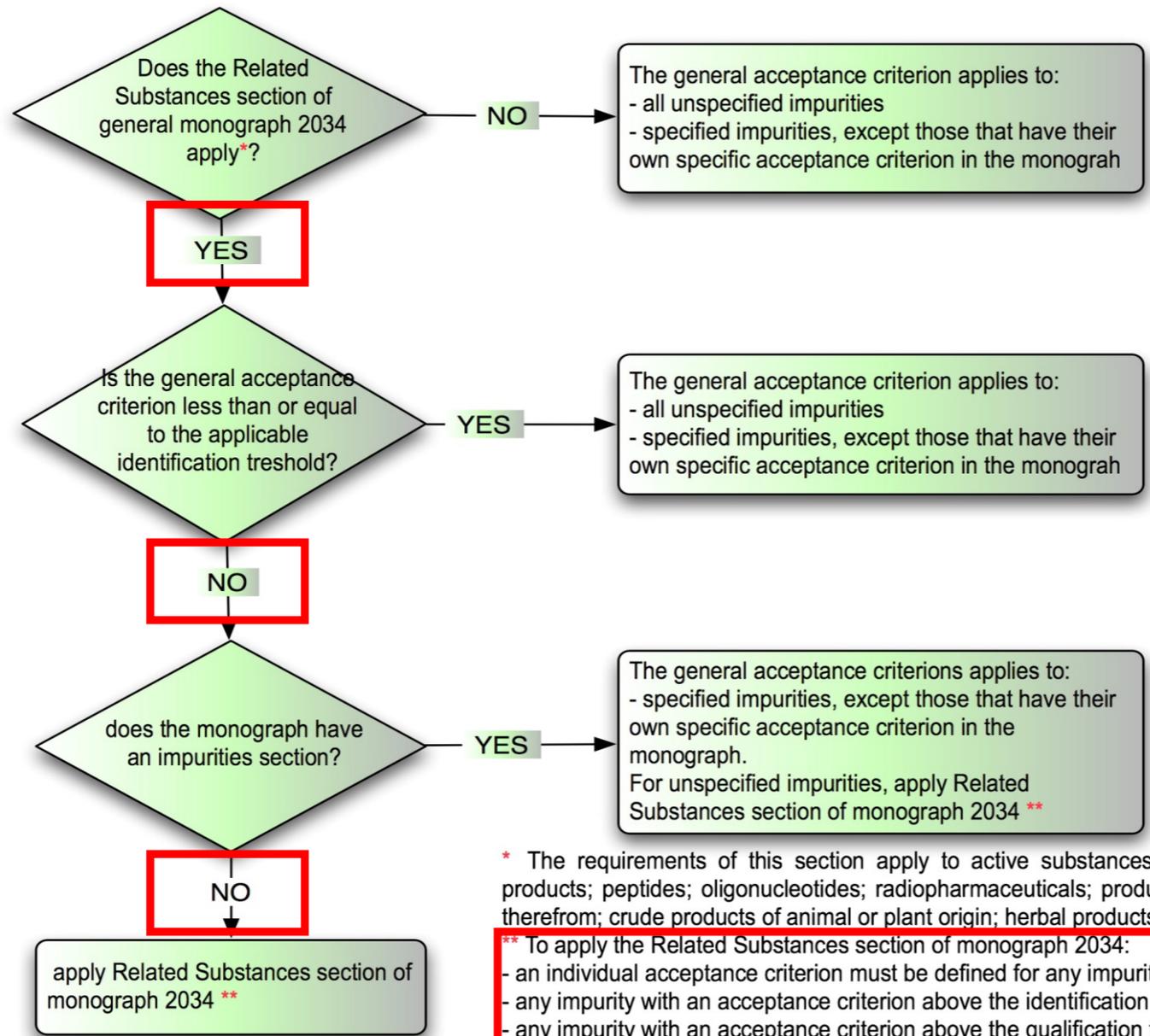
Example: *Fludrocortisone acetate (0767)*

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

Monograph describes under related substances:
- ✓ Any impurity ≤ 1.0 per cent
- ✓ Total ≤ 1.5 per cent
- ✓ Disregard limit 0.05 per cent
- ✓ No Impurities section (transparency list)

FLUDROCORTISONE ACETATE

Fludrocortisoni acetas

$C_{23}H_{31}FO_6$
[514-36-3]

M_r 422.5

DEFINITION

9-Fluoro-11β,17-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate.

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

Chapter 5.10 control of impurities in substances for pharmaceutical use

Does the Related Substances section of general monograph 2034 apply*? — **NO** → The general acceptance criterion applies to:
- all unspecified impurities
- specified impurities, except those that have their own specific acceptance criterion in the monograh

YES

Is the general acceptance criterion less than or equal to the applicable identification treshold? — **YES** → The general acceptance criterion applies to:
- all unspecified impurities
- specified impurities, except those that have their own specific acceptance criterion in the monograh

NO

does the monograph have an impurities section? — **YES** → The general acceptance criterions applies to:
- specified impurities, except those that have their own specific acceptance criterion in the monograph.
For unspecified impurities, apply Related Substances section of monograph 2034 **

NO

apply Related Substances section of monograph 2034 **

Fludrocortisone acetate (0767):

Any impurity ≤ 1.0 per cent

Total ≤ 1.5 per cent

Disregard limit 0.05 per cent

No Impurities section (transparency list)

* 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.

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Example: *Fludrocortisone acetate (0767)*

✓ 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

✓ Reporting threshold > 0.05%

✓ Identification threshold > 0.10%

✓ Qualification threshold > 0.15%

Fludrocortisone acetate (0767):

Any impurity ≤ 1.0 per cent

Total ≤ 1.5 per cent

Disregard limit 0.05 per cent

No Impurities section (transparency list)

⇨ Monograph is currently under revision

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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
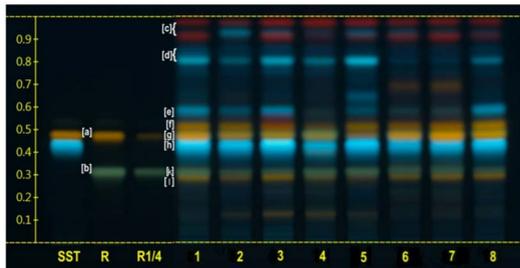
SST: reference solution (c)

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.*

System suitability test

Transparency list

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.

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

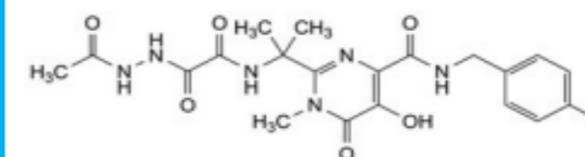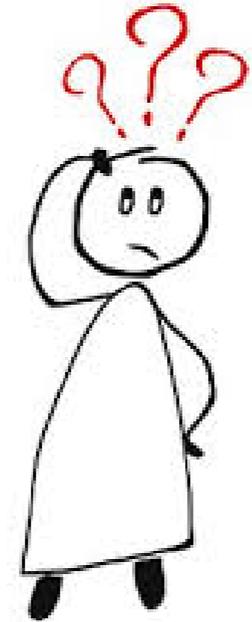**IMPURITIES**

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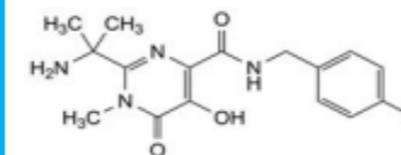
A. 2-(2-aminopropan-2-yl)-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,
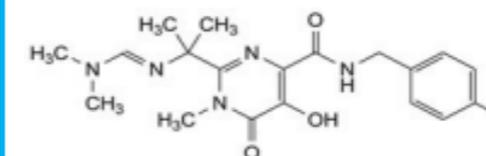
B. 2-[2-[(*E*)-[(dimethylamino)methylidene]amino]propan-2-yl]-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,

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.*

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Poll

How would you identify an impurity in a chromatographic system?

A) By retention time
B) By relative retention
C) Using a reference standard or a reagent
D) In-situ degradation reaction
E) No need to identify an impurity

(Multiple choice with multiple answers)

Poll - Answers

How would you identify an impurity in a chromatographic system?

A) By retention time

B) By relative retention

C) Using a reference standard or a reagent

D) In-situ degradation reaction

E) No need to identify an impurity

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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 for information only

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.

LIQUID CHROMATOGRAPHY REPORT

Raltegravir for peak identification CRS 1

Project Name: LC11660Raltegravir potassium

Result Id 1202

System suitability tests

Individual monographs

General chapter *2.2.46*

Resolution
Peak-to-valley ratio

Symmetry factor 0.8 to 1.8
Minimum S/N 10 at reporting threshold*
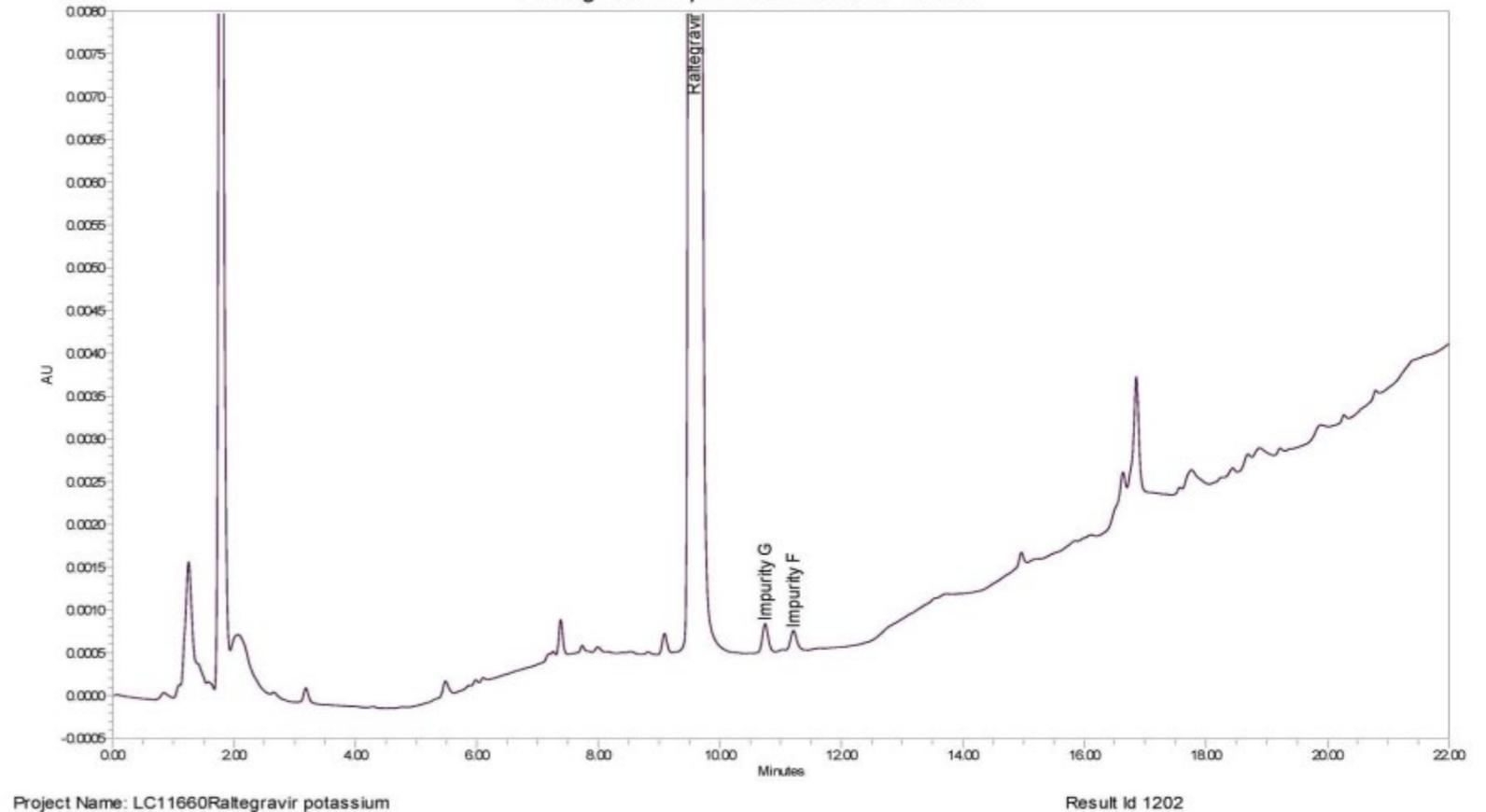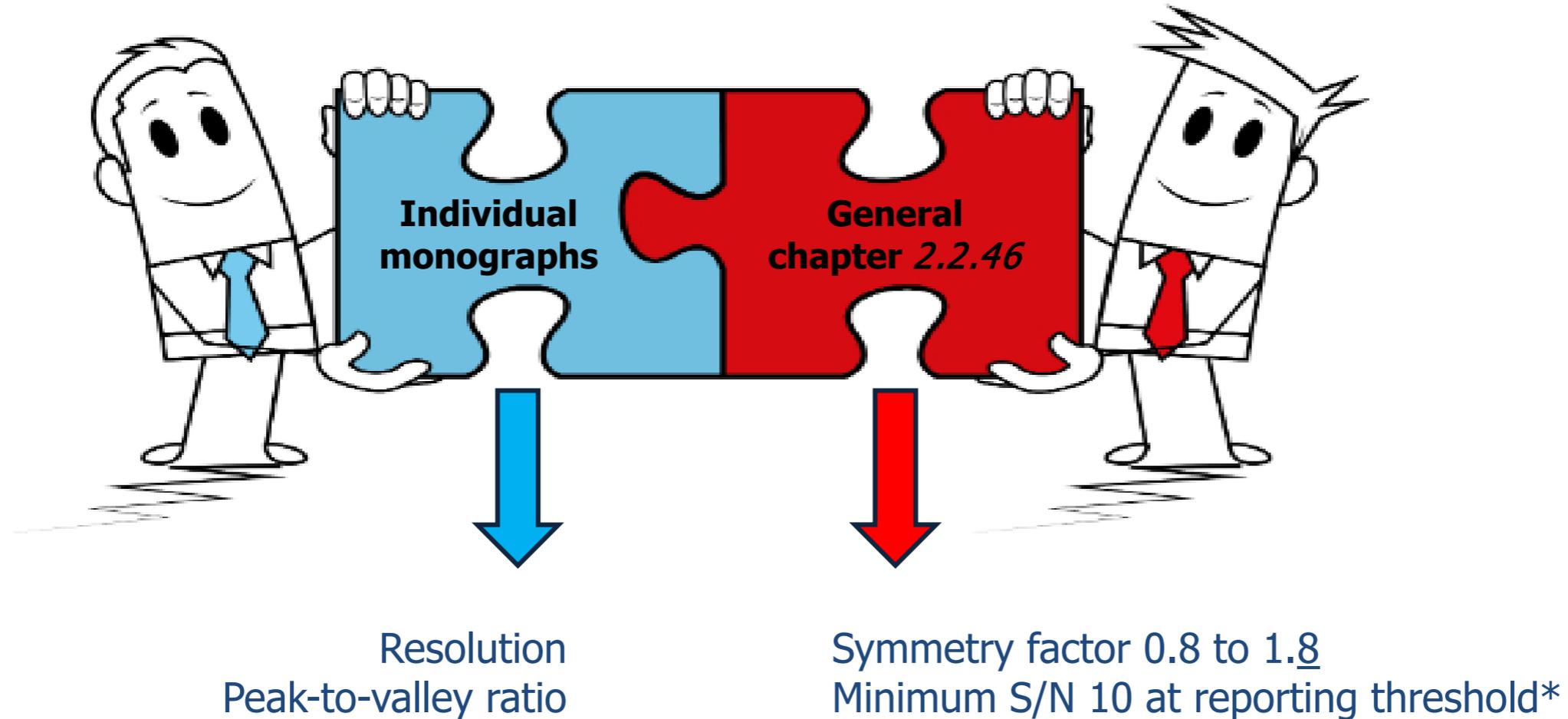
* Calculation on a window of at least 5 times the peak width at half height has been reinstated instead of 20 times (as prescribed in the 11th Edition). See News.

System suitability test - Separation capacity (Selectivity)

Defined to verify the separation or partial separation of a <u>critical pair</u>

✓ **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 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; <u>however</u> 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 area is similar despite the difference in concentration

noise (µV) : 13
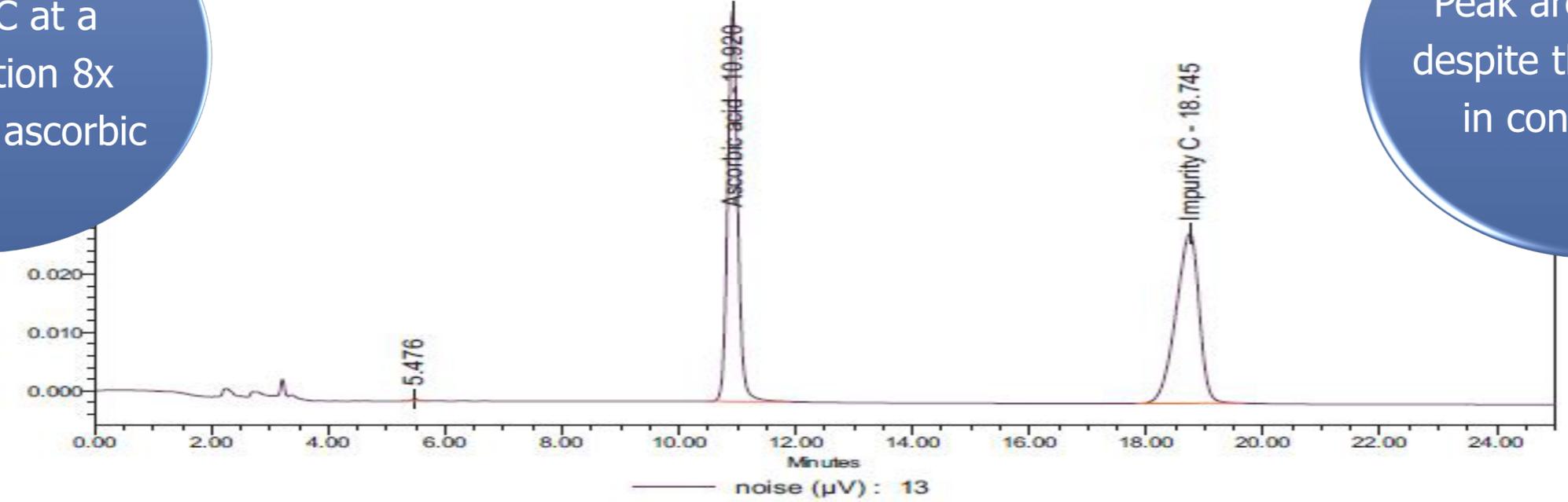
Peak Results

	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

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

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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

Thresholds

- In line with ICH Q3B

- Reporting, identification and qualification thresholds are higher than for API

Reporting Thresholds	
Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

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 method, 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"

Specifications in monographs

PROCEDURE 1 (P1)
Multi-source products

A B C D

Revision

**MONOGRAPH
valid for A, B, C & D**
Monograph covers **all impurities** observed in the different synthetic pathways
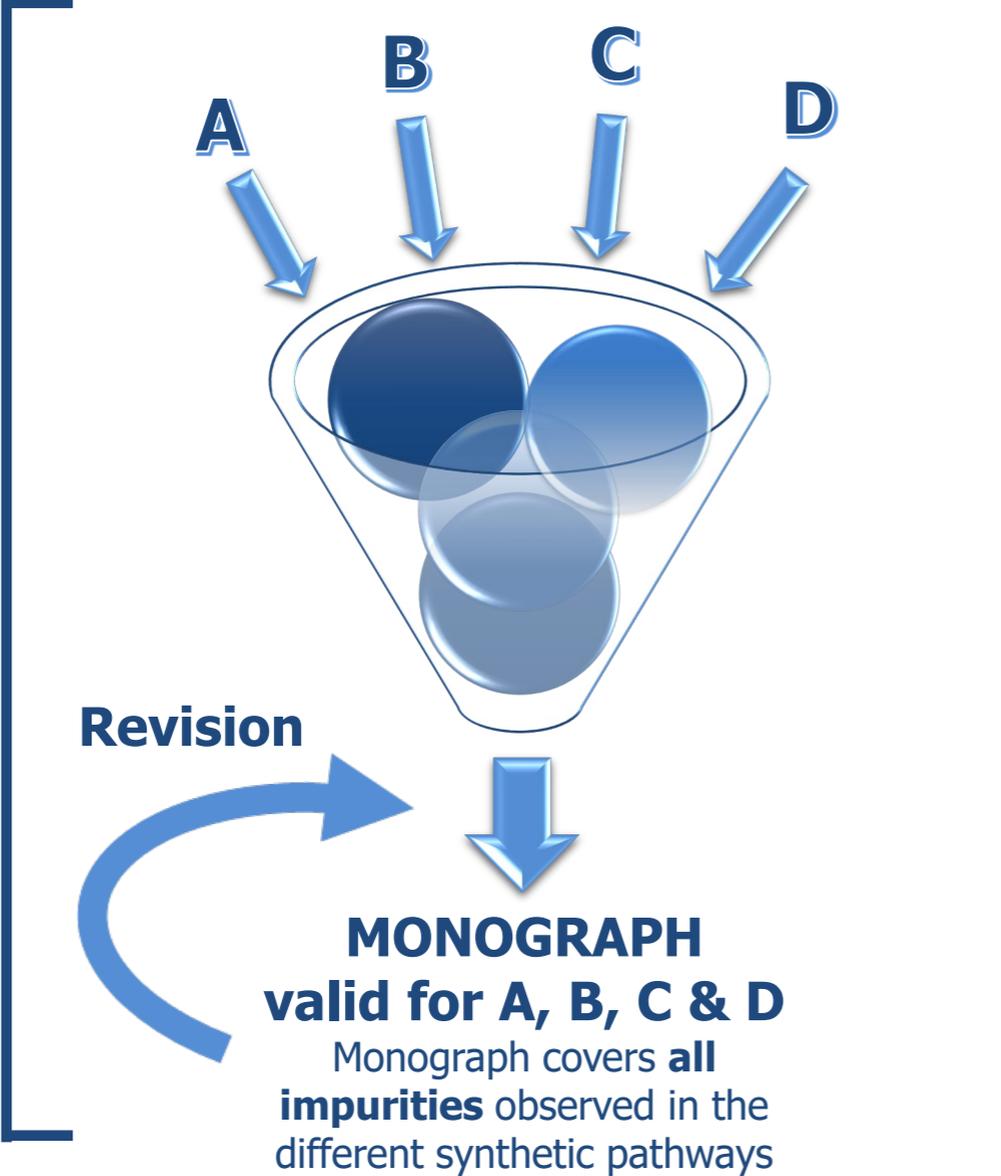
PROCEDURE 4 (P4)
Single-source products

A

MONOGRAPH

To be applicable to B, C, D ....
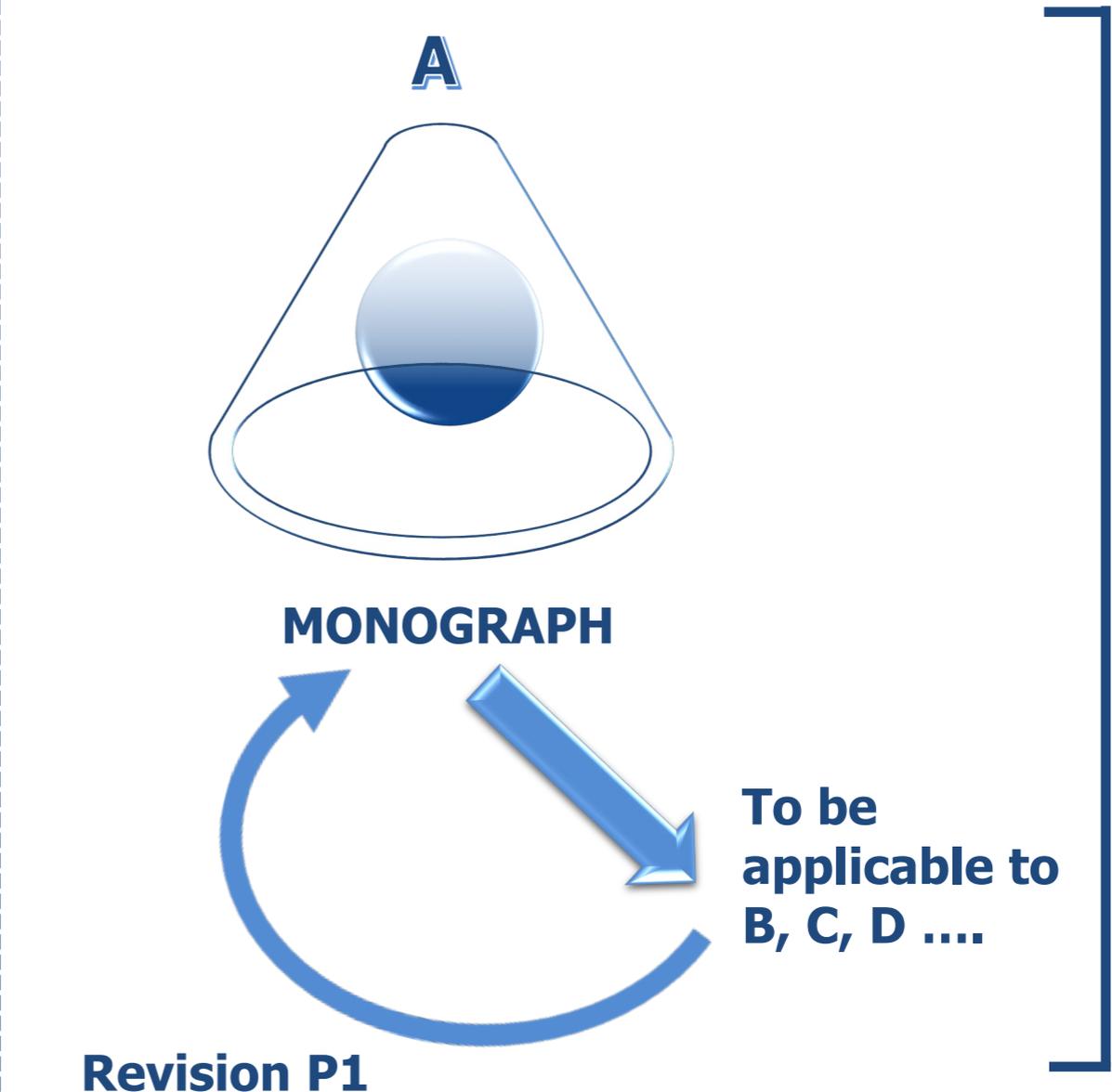
Revision P1

Specifications in monographs

✓ Based on limits approved by competent authorities
✓ Based on representative batch and stability data

Example: 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.."

Typical parameters (ICH Q2)	Testing for impurities	
	Quantitative	Limit
Accuracy	+	-
Repeatability	+	-
Intermediary Precision	+	-
Specificity (selectivity)	+	+
Linearity and range	+	-
Limit of detection	-	+
Limit of quantification	+	-

ICH Q2 R1 "Validation of analytical procedures"

Chapter *5.26. Implementation of pharmacopoeial procedures* (11th Edition)

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 according to chapter 5.26

Control of impurities in Ph. Eur.

Organic impurities

Inorganics Elemental impurities

Water Residual solvents

Genotoxic (DNA reactive) impurities
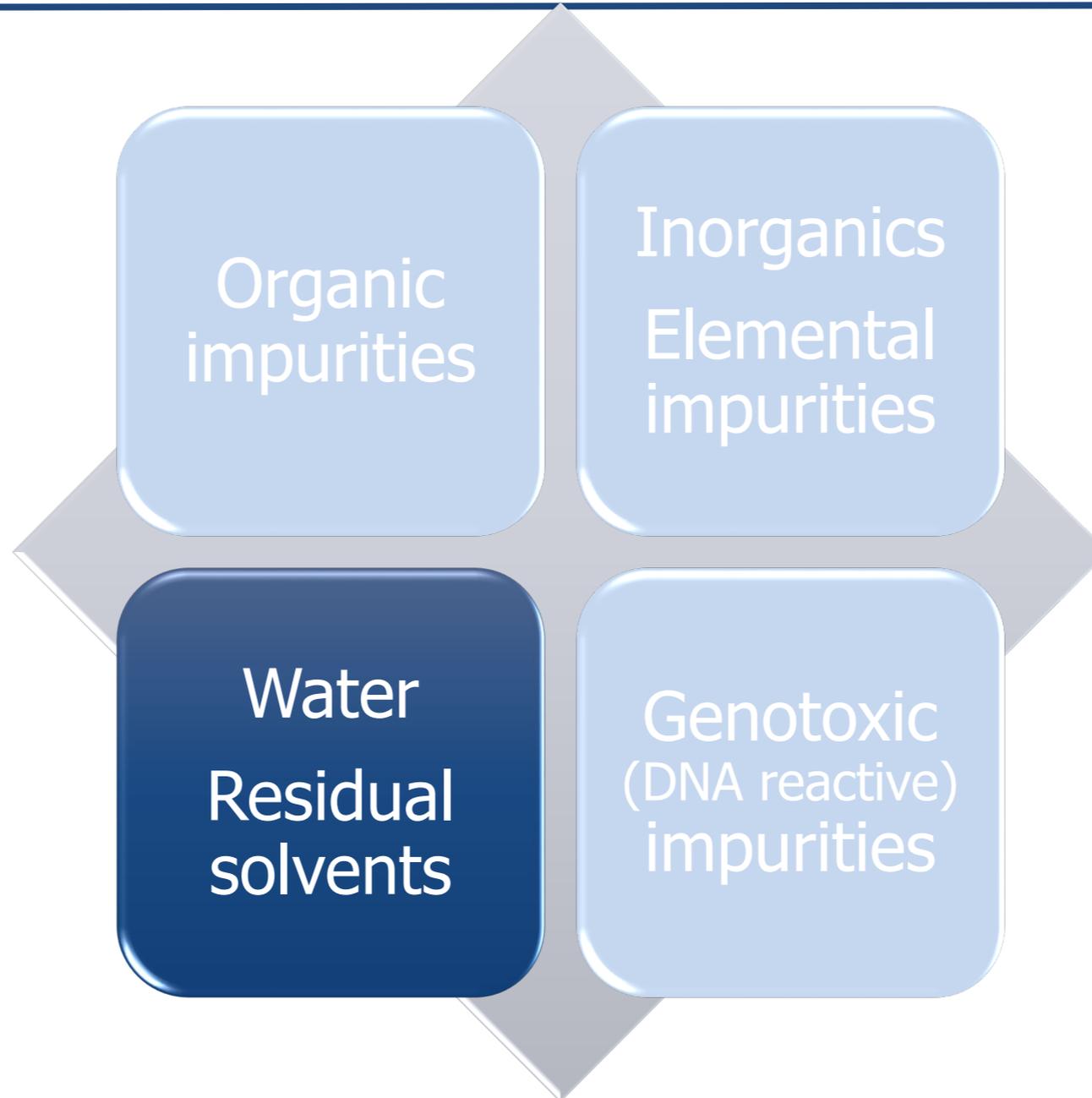
Water/Residual solvents

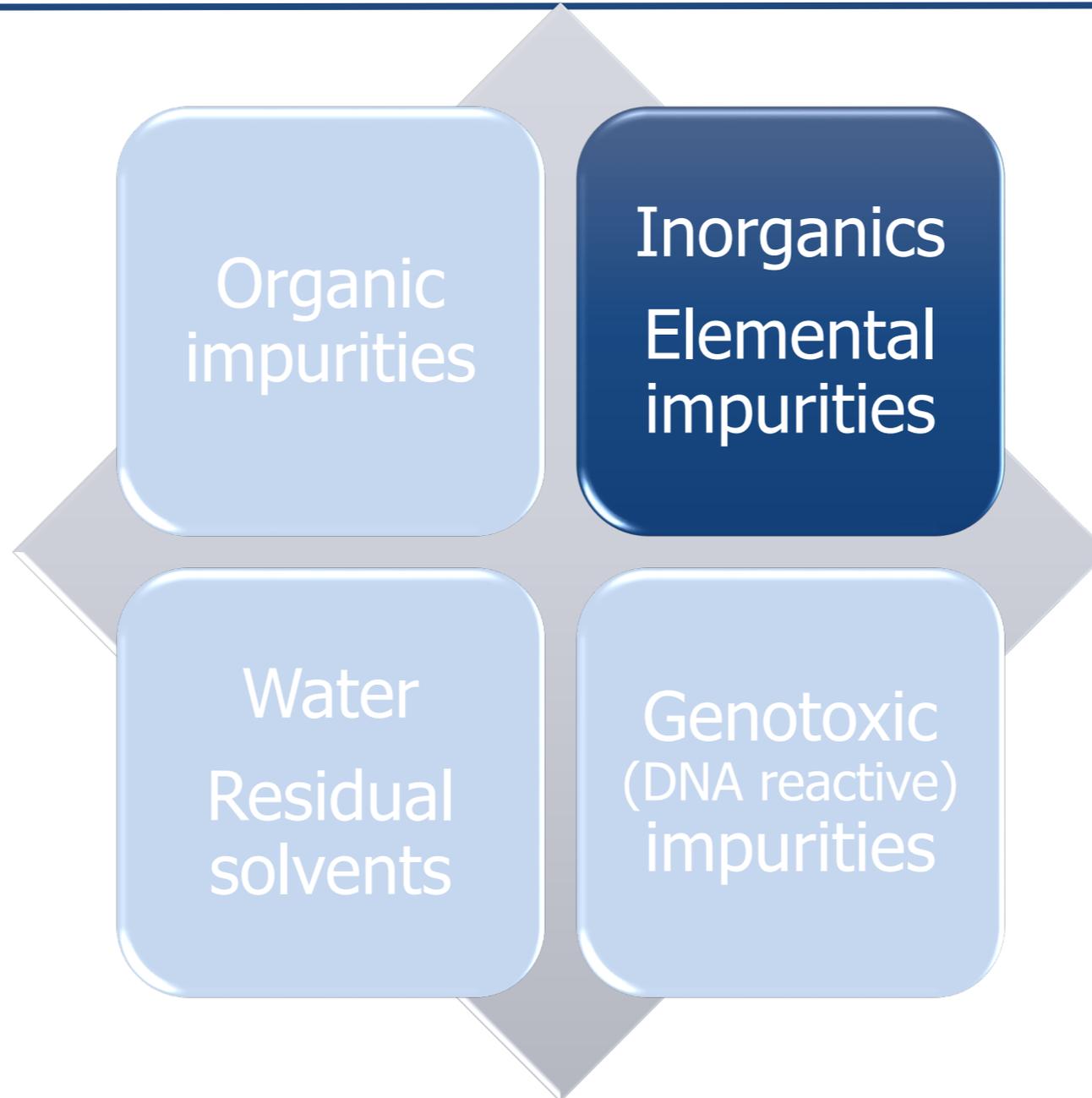**Water** →

- 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 may be controlled by LOD (up to 0.5%)

Control of impurities in Ph. Eur.

Organic impurities

Inorganics
Elemental impurities

Water
Residual solvents

Genotoxic
(DNA reactive)
impurities

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*
↳ currently being harmonised within PDG

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.

Organic impurities

Inorganics
Elemental impurities

Water
Residual solvents

Genotoxic
(DNA reactive)
impurities
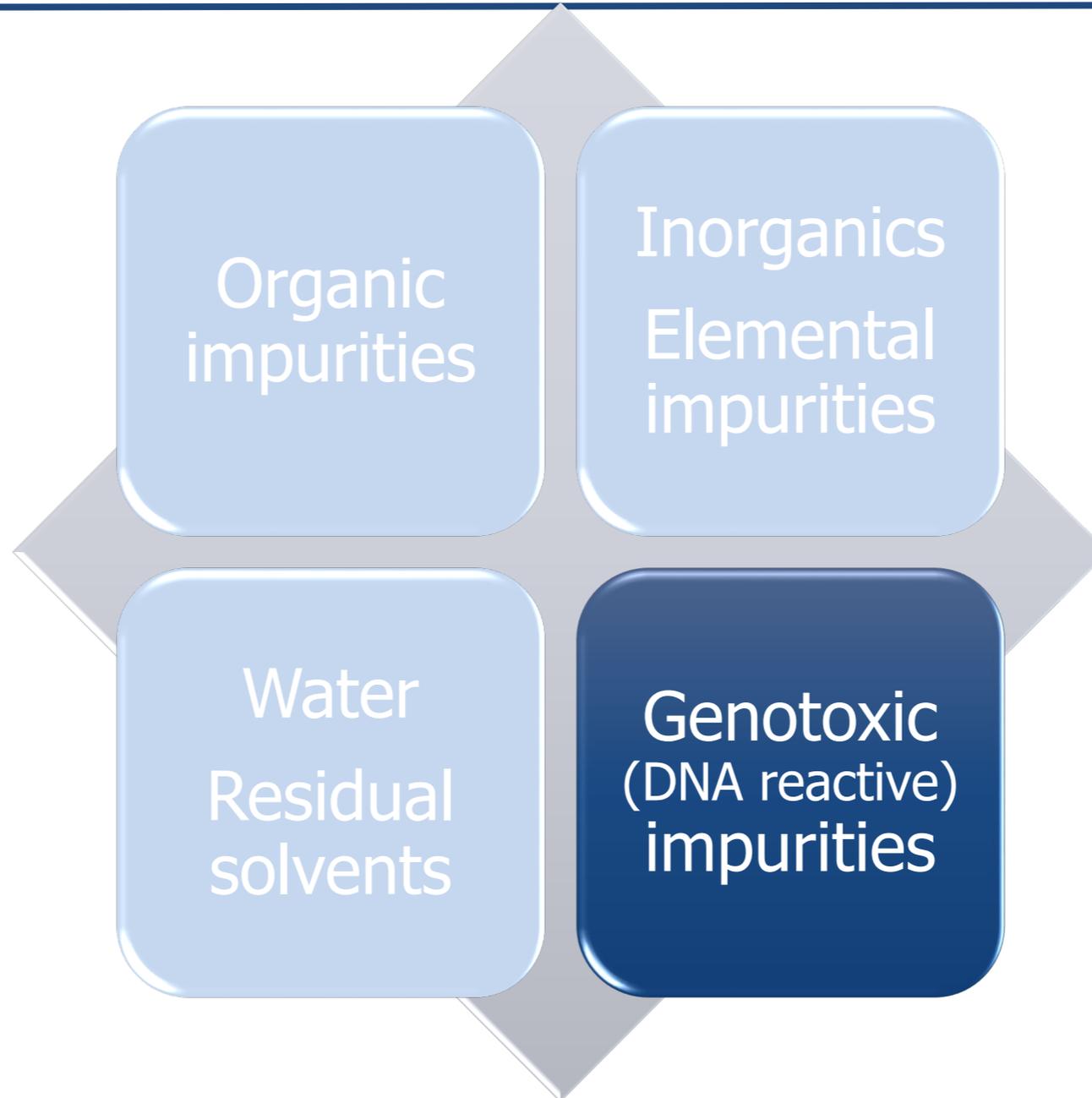
# DNA reactive (mutagenic) impurities

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 in Sartans: monographs & *2.5.42*
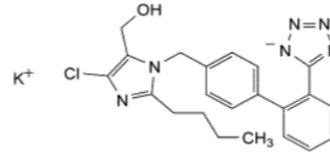
Sartan monographs:
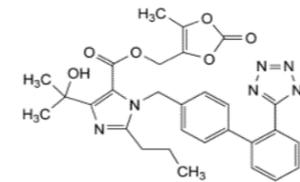
✓ Several revisions (latest in Supplement 10.6)
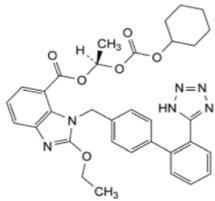
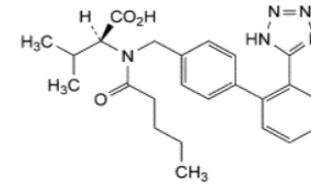Candesartan cilexetil   Irbesartan   Losartan potassium   Olmesartan medoxomil   Valsartan
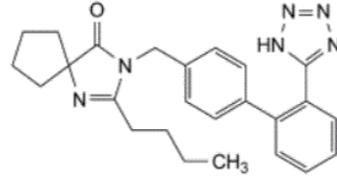
✓ General chapter *2.5.42. N-Nitrosamines in active substances:*

- 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

- Under revision to extend the scope to cover medicinal products

Nitrosamines: general monographs *2034* & *2619*

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

- ✓ 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

- ✓ Adopted in November 2022, published in 11.3. (See wording in [News](#))

- ✓ Statement in General Monograph 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."

Nitrosamines: impact on individual monographs

Two cases to be distinguished:

A. Individual monographs having "just" a statement in Production section

B. Individual monographs having a test (and a limit) prescribed

PROPOSAL

A. Production section
⇨ Delete (no introduction) as covered by the general monograph

B. Test (and a limit)
⇨ Keep/Introduce a test in Test section only if nitrosamine = confirmed risk from the API manufacturing/stability

Next step:

✓ External consultation on detailed strategy planned in the coming weeks

✓ Consultation of Groups of Experts in September/October 2023

✓ Final decision by the Commission in November 2023

Conclusions

✓ Ph. Eur. impurity control strategy in line with relevant ICH guidelines

✓ Ph. Eur. texts kept up to date to be in line with new regulations/recommendations (e.g. nitrosamines)

✓ Analytical procedures developed/verified are regularly revised by expert groups which ensures that they reflect the quality of substances/products on the European market

✓ Limits based on specifications as approved by competent authorities and taking into account batch/stability data

✓ Transparent and collaborative process: texts published for public consultation

✓ Impurity tests validated but implementation necessary

Thank you for your attention

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