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

Individual monographs - Focus on chemically-defined APIs and Medicinal Products (containing chemically-defined APIs)

2024 EDQM virtual training programme, Module 2

3 December 2024, Strasbourg, France

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Individual monographs

SAFETY FIRST!

Products of proven safety, evaluated and approved by competent authorities of Ph. Eur. member states

Impurity profiles for existing, approved manufacturing routes

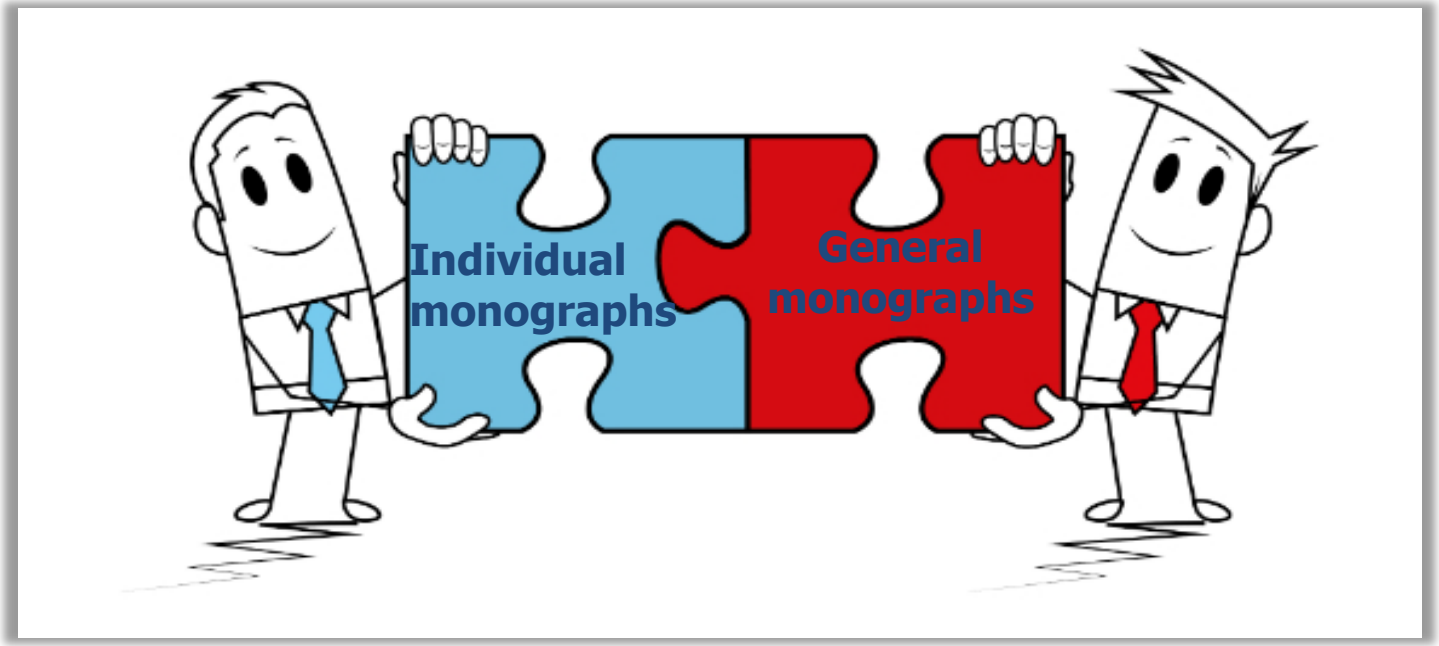
Collaboration with and support from manufacturers

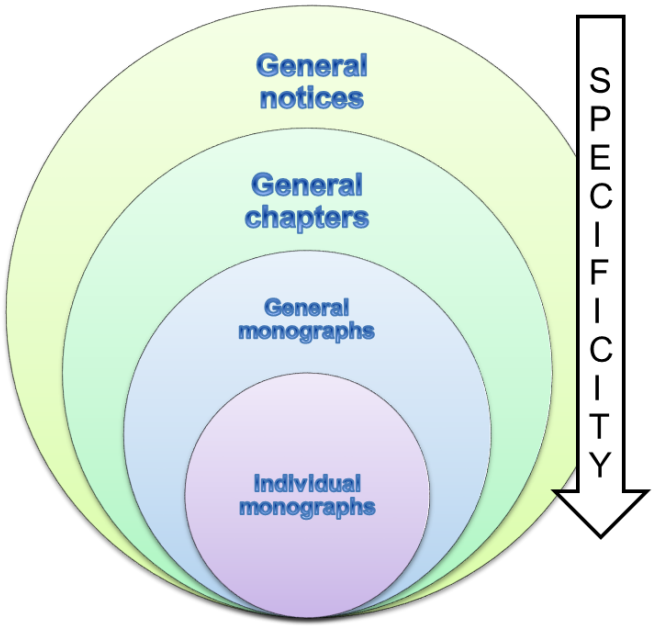
- ❑ **data and samples (active substance and impurities)**

Use of validated analytical procedures

Verification of robustness

General vs. individual monographs





- Complementary
- One not overruling the other
- Exceptions are clearly indicated either in the general monograph or in the individual one

Document en Français PDF Knowledge Database

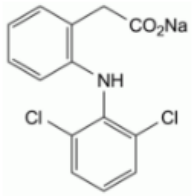
General Notices apply to all monographs and other texts.
See the information section on general monographs.

Tools

01/2017: 1002
corrected 10.0

DICLOFENAC SODIUM

Diclofenacum natricum



$C_{14}H_{10}Cl_2NNaO_2$

M_r 318.1

[15307-79-6]

DEFINITION

Sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate.
Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or slightly yellowish, slightly hygroscopic, crystalline powder.
Solubility: sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), slightly soluble in acetone.
mp: about 280 °C, with decomposition.

IDENTIFICATION

First identification: A, D.
Second identification: B, C, D.

Poll no. 1

Which are the mandatory section(s) in a monograph?

A) Definition and Characters
B) Production
C) Identification
D) Tests and assay
E) Storage and Functionality-related characteristics

(several replies needed)

Demonstration of compliance with the Ph. Eur.

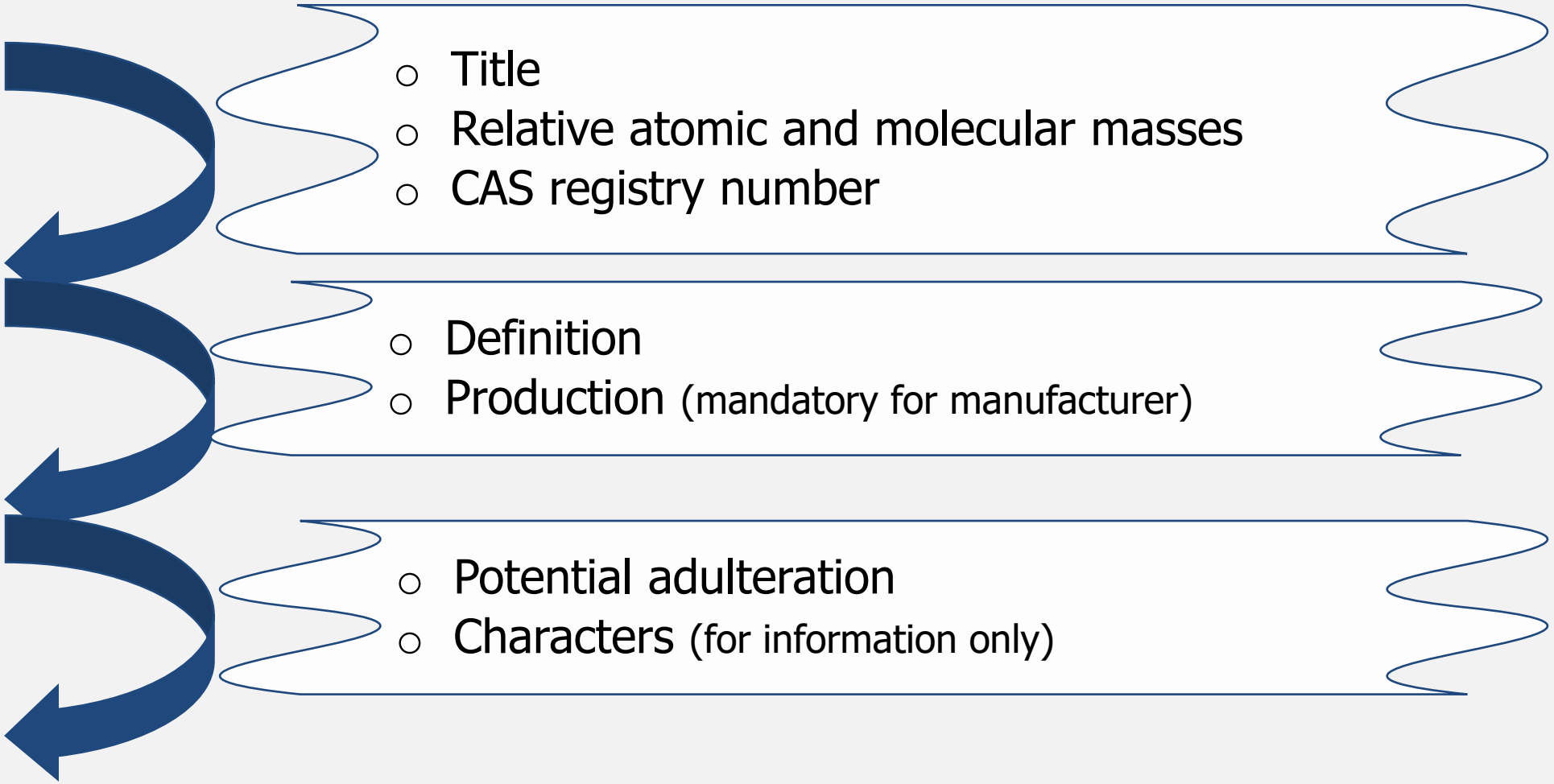
"*Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements.*"

Compliance

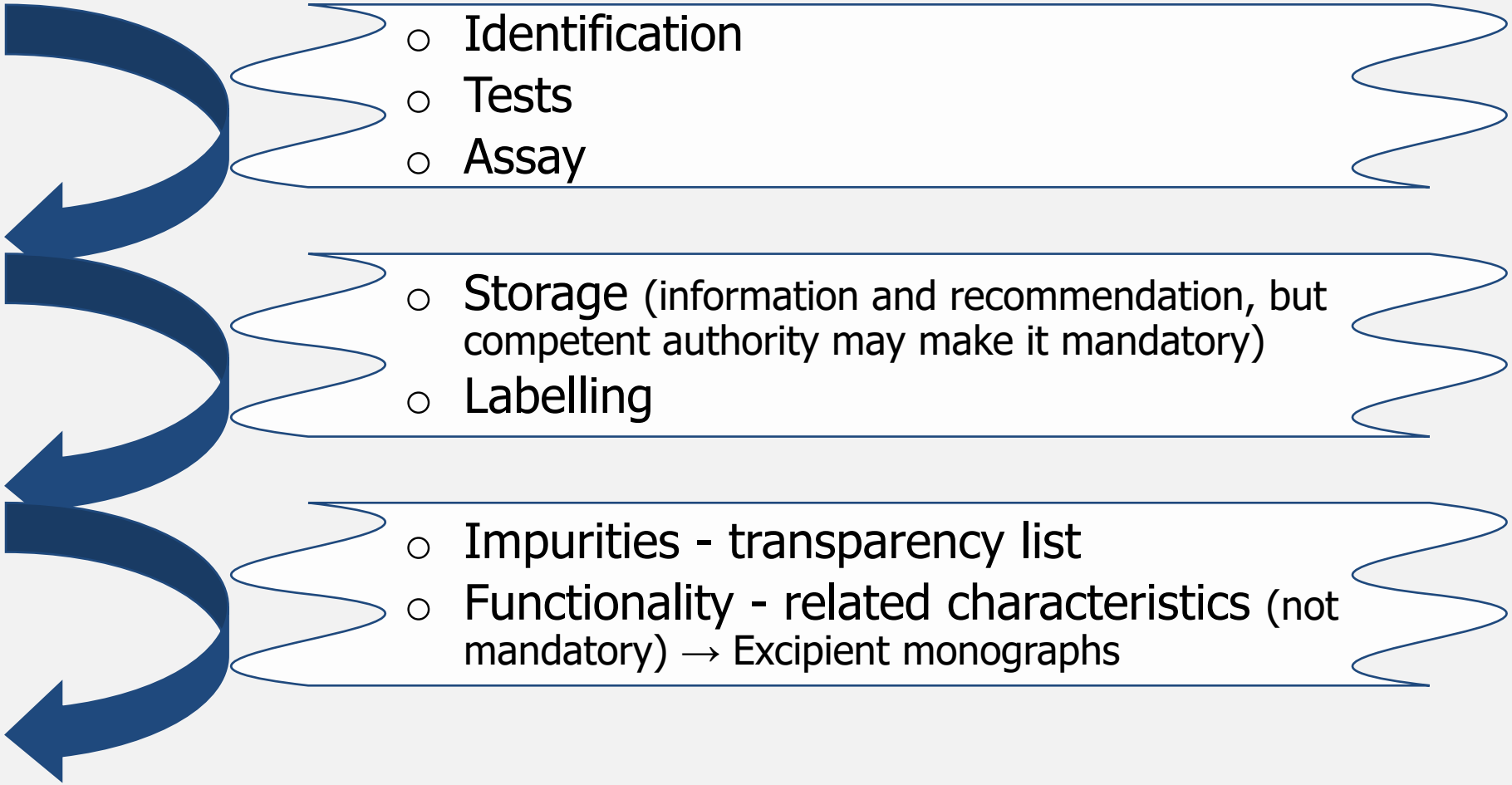
= satisfaction to all **mandatory** parts of a **monograph**

MANDATORY	INFORMATIVE
Definition Production Identification Tests Assay	Characters Storage Functionality-related characteristics

Sections in individual monographs (1)



Sections in individual monographs (2)



TITLE

INNs used almost universally (modified to indicate salt)

Includes degree of hydration

- ❑ **«*x* hydrate»: if well-defined form (x = hemi, mono, di, tri, etc.)**
- ❑ **«hydrate»: if a mixture of hydrates**

- ✓ **DICLOFENAC SODIUM**
- ✓ **AMILORIDE HYDROCHLORIDE DIHYDRATE**
- ✓ **MAGNESIUM ACETATE TETRAHYDRATE**
- ✓ **ALFENTANIL HYDROCHLORIDE HYDRATE**

DEFINITION (1)

DEFINITION (DICLOFENAC SODIUM)
Sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate.
Content: 99.0 per cent to 101.0 per cent (dried substance).

- Chemical nomenclature
- Assay limits
  - Content expressed on anhydrous or dried basis
  - Solvent-free substance is implied, even where not stated

  (see 2034 Substances for Pharmaceutical Use, 5.4 Residual solvents)

  - LC assay: reflect assay variability and purity

    (e.g.: 96.0-102.0 % means 2 % assay variability and minimum 2.0 % total impurities)
  - Volumetric titration: usually 99.0 to 101.0 %
  - Microbiological assay: minimum activity (IU/mg, as is)
  - Biological assay: specific activity (e.g.: IU/mg)

DEFINITION (2)

DEFINITION (DICLOFENAC SODIUM)
Sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate.
Content: 99.0 per cent to 101.0 per cent (dried substance).

- Chemical nomenclature
- Assay limits

Volumetric titration: usually 99.0% to 101.0 % (cf. Technical guide)

VOLUMETRIC TRITRATION	CONTENT LIMITS (%)	REPEATABILITY (RSD)	RELATIVE ACCURACY (%)
Acid/base	± 1.0	0.33	± 0.67
Non-aqueous	± 1.0	0.33	± 0.67
Conjugate acid of base	± 1.0	0.33	± 0.67
Redox	± 1.5	0.5	± 1.0
Argentometric	± 1.5	0.5	± 1.0
Complexometric	± 2.0	0.67	± 1.33

DEFINITION (3)

DEFINITION (DICLOFENAC SODIUM)
Sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate.
Content: 99.0 per cent to 101.0 per cent (dried substance).

- Chemical nomenclature
- Assay limits
  - LC assay: reflect assay variability and purity

(e.g.: 96.0-102.0 % means 2 % assay variability and 2.0 % total impurities)

2.2.46. Chromatographic separation techniques

Table 2.2.46.-1. – *Repeatability requirements*

	Number of individual injections			
	3	4	5	6
B (per cent)	Maximum permitted relative standard deviation			
2.0	0.41	0.59	0.73	0.85
2.5	0.52	0.74	0.92	1.06
3.0	0.62	0.89	1.10	1.27

DEFINITION (4)

- Statements on scope (e.g. route of synthesis, degree of hydration):
  - A well-defined hydrate (mono, di, tri, etc.): no specific statement, cf. chemical nomenclature (meldonium dihydrate, caffeine monohydrate)
  - A mixture of different hydrate forms ("$x H_2 0$"): "It contains a variable quantity of water" (zanamavir hydrate, thiocolchicoside hydrate, valaciclovir hydrochloride hydrate)
  - Water- free **and** hydrate form: "It may be anhydrous or contain a variable quantity of water" (fluvastatin sodium, saccharin sodium)
- Monograph applies to all grades, unless otherwise stated
- Special grades may be mentioned in body of monograph (e.g. special requirements for parenteral use)

PRODUCTION

Pethidine hydrochloride (0420)

PRODUCTION

If intended for use in the manufacture of parenteral preparations, the manufacturing process is validated to show that the content of impurity B is not more than 0.1 ppm.

Instructions

for manufacturers

Source materials,

manufacturing process,

validation, control,

in-process testing

Cannot necessarily be verified by independent analyst

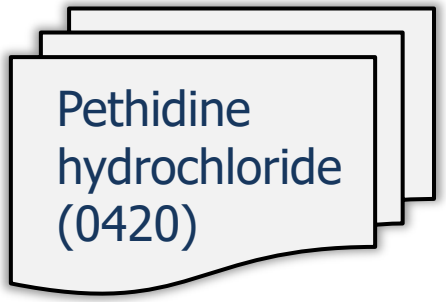
Compliance established by competent authorities

→ e. g. DNA reactive (mutagenic) impurities

Absence of a Production section does not imply that attention to above features is not required

PRODUCTION

It is produced by highly stereoselective methods of manufacture; consideration must be given to the formation of potential stereoisomeric impurities during the manufacturing process, and procedures must be implemented for the appropriate control of these impurities.



In the manufacture of parenteral preparations, the manufacturing process is validated to show that the content of impurity B is not more than 0.1 ppm

CHARACTERS (1)

CHARACTERS (DICLOFENAC SODIUM)
Appearance: white or slightly yellowish, slightly hygroscopic, crystalline powder.
Solubility: sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), slightly soluble in acetone.
mp: about 280 °C, with decomposition

- Not analytical requirement
- Useful information for the analyst

- Polymorphism, where known, is mentioned (cf *5.9 Polymorphism*, IR-spectrophotometry)
- Physical properties may be mentioned (melting point, density)
- See also chapter *5.11. Characters section in monographs*

  (methods to determine hygroscopicity, crystallinity, solubility)

CHARACTERS (2)

11th Ed.

NEW

As of 11th Ed., **'ethanol' and 'alcohol' without qualification**: sentence deleted and terms replaced in monographs by 'anhydrous ethanol' and 'ethanol (96 per cent)'.

Hygroscopicity, crystallinity, solubility: transfer of information to chapter *5.11 Characters section in monographs*

IDENTIFICATION (1)

- First and Second identifications → defined in General Notices (cf. Supplement 10.7)
- Sometimes cross-reference to "Tests" (e.g. Enantiomeric purity, HPLC assay)
- Reference to Water/ Loss on drying (applicable for a hydrate)

1st identification → may be used in all circumstances

2nd identification → implementation of the tests subject to national regulation (2034, Supp. 10.3)

IDENTIFICATION
First identification: A, D.
Second identification: B, C, D.
A. Infrared absorption spectrophotometry (2.2.24).
Comparison: diclofenac sodium CRS.

B. Thin-layer chromatography (2.2.27).
Test solution. Dissolve 25 mg of the substance to be examined in methanol R and dilute to 5 mL with the same solvent.
Reference solution (a). Dissolve 25 mg of diclofenac sodium CRS in methanol R and dilute to 5 mL with the same solvent.
Reference solution (b). Dissolve 10 mg of indometacin R in reference solution (a) and dilute to 2 mL with reference solution (a).
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).

IDENTIFICATION (2)

First identification series → ex. IR, HPLC, TLC

In case of statement: '*Carry out either tests A, B or tests C, D*'.

≠ Second identification series

These **two (or more) sets** of identification tests are equivalent and may be used independently, at user's discretion.

Fosinopril sodium (1751)

A. Specific optical rotation (2.2.7): – 6.7 to – 4.7 (anhydrous substance).
Dissolve 0.500 g in methanol R and dilute to 25.0 mL with the same solvent.
B. Infrared absorption spectrophotometry (2.2.24).
Comparison: fosinopril sodium CRS.
If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in a 2 per cent V/V solution of water R in methanol R, evaporate to dryness and record new spectra using the residues.
C. It gives reaction (a) of sodium (2.3.1).

Levetiracetam (2535)

Carry out either tests A, B or tests B, C.

A. Specific optical rotation (2.2.7): – 82 to – 76.
Dissolve 0.500 g in water R and dilute to 25.0 mL with the same solvent.
B. Infrared absorption spectrophotometry (2.2.24).
Comparison: levetiracetam CRS.
C. Enantiomeric purity (see Tests).

IDENTIFICATION (3)

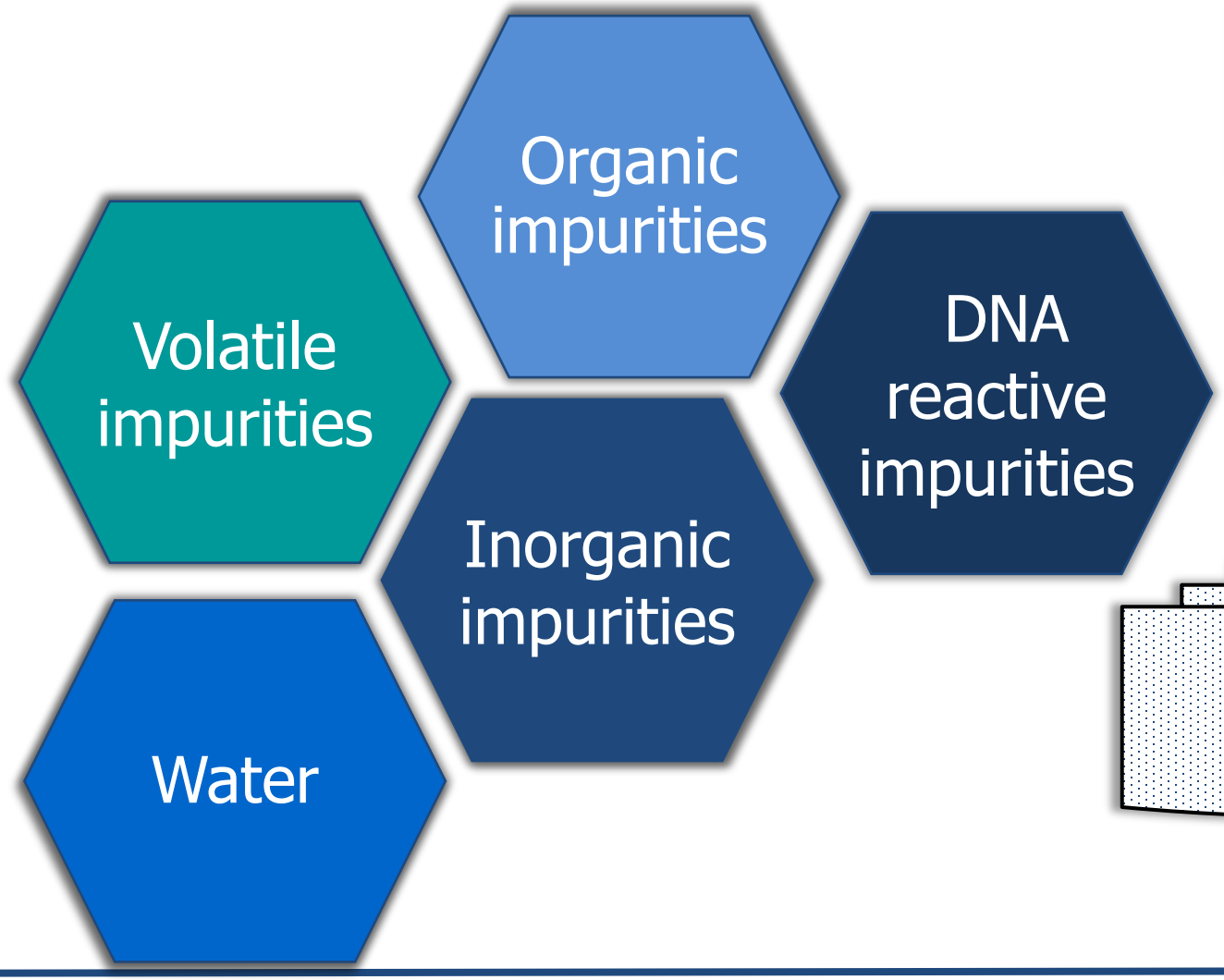
Second identification series → ex. TLC, chemical reactions, mixed melting point

may be used in community or hospital **pharmacies** provided it can be demonstrated that the substance or preparation is fully traceable to a batch certified to comply with all the other requirements of the monograph

Prednisolone acetate (0734)

Second identification: B, C.
B. Thin-layer chromatography (2.2.27).
Test solution. Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.
Reference solution. Dissolve 10 mg of prednisolone acetate CRS in the mobile phase and dilute to 10.0 mL with the mobile phase.
Plate: TLC silica gel F254 plate R.
Mobile phase: methanol R, methylene chloride R (10:90 V/V).
Application: 5 µL.
Development: over 3/4 of the plate.
Drying: in air.
Detection: spray with a solution prepared as follows: dissolve 0.25 g of 2,4-dihydroxybenzaldehyde R in glacial acetic acid R, dilute to 50 mL with the same solvent and add a mixture of 12.5 mL of sulfuric acid R and 37.5 mL of glacial acetic acid R; heat at 90 °C for 35 min or until the spots appear, allow to cool and examine in daylight and in ultraviolet light at 365 nm.
Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.
C. Add about 2 mg to 2 mL of sulfuric acid R and shake to dissolve. Within 5 min, an intense red colour develops. When examined in ultraviolet light at 365 nm, a reddish-brown fluorescence is seen. Add the solution to 10 mL of water R and mix. The colour fades and there is an intense greenish-yellow fluorescence in ultraviolet light at 365 nm.

TESTS



Chemical methods

Physical methods

Chromatographic methods

Organic impurities (in line with ICH Q3A) (1)

Specified impurities

- detected, identified by SST/ peak identification CRS
- individual acceptance criteria

Unspecified impurities ("ODIs")

- impurity is detected, but not individually identified
- limit for "unspecified impurities" (or *2034 Substances for Pharmaceutical Use*)

Organic impurities (2): Impurities section

Not necessarily exhaustive

Impurities **known** to be controlled by monograph tests

Usually controlled by the related substances test, but may be other tests, e. g. UV absorbance ratio

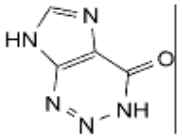
Based on information obtained and verified during monograph's elaboration/revision

DACARBAZINE

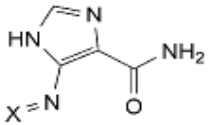
IMPURITIES

Specified impurities: *A*, *B*, *D*.

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

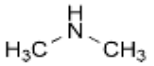


A. 3,7-dihydro-4*H*-imidazo[4,5-*d*]-1,2,3-triazin-4-one (2-azahypoxanthine),



B. X = H_2: 5-amino-1*H*-imidazole-4-carboxamide,

C. X = NH: 5-diazenyl-1*H*-imidazole-4-carboxamide,



D. *N*-methylmethanamine.

New impurity profiles: Directive 2001/83/EC as amended (2003/63/EC)

- "However, where a starting material in the European Pharmacopoeia … has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described."

- In cases where a specification contained in a monograph of the European Pharmacopoeia (…) might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder…"

- "The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied"

also included in the General Notices, *1.1.2.3 Demonstration of suitability of monographs*

Organic impurities (in line with ICH Q3A) (3)

- specifications and batch analysis data for approved products (European market)
- revision of monographs with "area comparison style"→ fully quantitative approach

« Area comparison » expression ⟹ ***« Quantitative » expression***

Finasteride (1615)

Limits:

- *impurity A*: maximum 0.3 per cent, calculated from the area of the corresponding peak in the chromatogram obtained with reference solution (b) and taking into account the assigned value of impurity A in *finasteride for system suitability CRS*,
- *impurity B*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent),
- *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent),
- *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent),
- *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.6 per cent),
- *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Calculation of percentage contents:

- *correction factor*: multiply the peak area of impurity A by 2.4;
- for each impurity, use the concentration of finasteride in reference solution (c).

Limits:

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

Inorganic impurities (1)

- Result from the manufacturing process or from raw materials
- Known and identified:
  - Elemental impurities → ICH Q3D Guideline for Elemental impurities (partly reproduced in general chapter 5.20)
  - Inorganic salts
  - Other materials (e.g. filter material)

- Determination of elemental impurities (2.4.20), AAS (2.2.23), ICP (2.2.57 & 2.2.58), XRF (2.2.37) and others
(e.g. Cisplatin: Ag max 250 ppm; Calcium acetate: Mg max 500 ppm; Dalteparin sodium: Boron max 1 ppm)
- Sulfated ash (*2.4.14*)

Inorganic impurities (2)

❑ Tests are **suppressed** when elements have been « intentionally added » in the production process, i.e. reagents or catalysts used in synthesis. (e.g. Ni in prazosin hydrochloride)

➔ Covered by a general statement in general monograph on Substances for Pharmaceutical use (2034)

❑ Tests **remain** when elements are of natural origin and cannot be easily eliminated by purification (e.g. mined excipients)

❑ Tests may remain when important to ensure the quality

❑ Special cases: e.g. Methylthioninium chloride hydrate (methylene blue)

(Elements may have an effect on therapeutic activity (API is a chelating agent)

Residual solvents (in line with ICH Q3C)

- Individual monographs do not include a test for residual solvents, *except*:

Class 1 solvents are always named and limited in monographs

Ethambutol hydrochloride (0553): Impurity D (1,2-dichloroethane): maximum 5 ppm

Class 2 solvents are not included in an individual monograph; limit set by option 2 (cf. general chapter *5.4. Residual solvents*)

Class 3 solvents are named and limited individually in monographs when they exceed 0.5% (impact on assay results)

Olmesartan medoxomil (2600): Acetone: maximum 0.6 per cent

DNA reactive (mutagenic) impurities

Ph. Eur. follows ICH M7 for active substances:

- Tests described if **proof for genotoxicity available** (e.g. Ames test, toxicological studies…), 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.»

ASSAY

ASSAY (DICLOFENAC SODIUM)

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 $C_{14}H_{10}Cl_2NNaO_2$.

Often physico-chemical assay methods, but also bio/immuno and microbiological assays

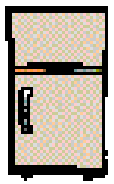
Unspecific but precise assay (titration), may be combined with selective related substances test (cf. Technical guide)

Selective chromatographic assays: assay standards + repeatability requirements (cf. general chapter 2.2.46)

STORAGE

STORAGE (DICLOFENAC SODIUM)
In an airtight container, protected from light.

Non mandatory section



Competent authority may specify particular storage conditions

→ may decide to make the conditions mandatory

Storage of the product

→ to ensure compliance with the monographs

Conventional expressions

→ defined in the General Notices

(e. g. *in an airtight container, protected from light)*

FUNCTIONALITY-RELATED CHARACTERISTICS (FRCs) (1)

Described in monographs on Excipients

Section is not mandatory

Provides information on important parameters

⇨ More info in general chapter on FRCs 5.15

Tests are linked to use, in line with ICHQ8

(lubricant, tablet compression, etc.)

SORBITOL

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). Some of the characteristics described in the Functionality-related characteristics section may also be present in the mandatory part of the monograph since they also represent mandatory quality criteria. In such cases, a cross-reference to the tests described in the mandatory part is included in the Functionality-related characteristics section. Control of the characteristics can contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for sorbitol used as filler and binder in tablets.

Particle-size distribution (*2.9.31* or *2.9.38*).

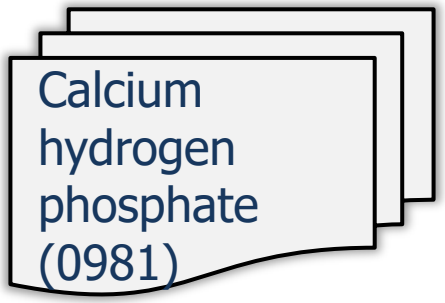
Powder flow (*2.9.36*).

FUNCTIONALITY-RELATED CHARACTERISTICS (FRCs) (2)

Characteristics may be relevant for sorbitol used as filler and binder in tablets.

Particle-size distribution (2.9.31 or 2.9.38).

Powder flow (2.9.36).

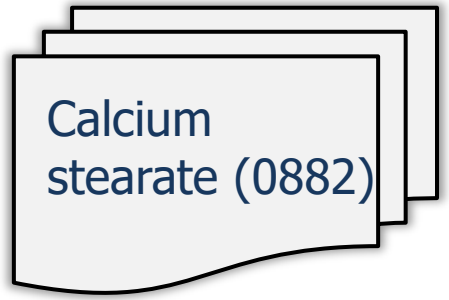


Characteristics may be relevant for calcium hydrogen phosphate used as filler in tablets and capsules.

Particle-size distribution (2.9.31 or 2.9.38).

Bulk and tapped density (2.9.34).

Powder flow (2.9.36).



Characteristics may be relevant for calcium stearate used as a lubricant in tablets and capsules.

Particle-size distribution (2.9.31).

Specific surface area (2.9.26, Method I). Determine the specific surface area in the P/Po range of 0.05 to 0.15.

LABELLING

SORBITOL

LABELLING

The label states:

- where applicable, the maximum concentration of bacterial endotoxins,
- where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

Covered by national and international regulations

Informational items or recommendations included

Information provided with the product included in “labelling”:

package, leaflet, certificate of analysis

Labelling items needed for the application of monographs,

e.g. nominal values (especially excipients)

SUMMARY

- Ph. Eur. Monographs are legally binding
- General chapters are mandatory when referred to in a monograph
- Complementarity of individual and general monographs/chapters
- Sections of the monograph
  - In general, mandatory
  - Non mandatory sections: *Characters, Storage, FRC*
  - Production (mandatory for manufacturers)
- Ph. Eur. is regularly updated to keep pace with the regulatory requirements, technological and scientific advances: any interested party can propose a new monograph elaboration or revisions of already published monographs (via the NPAs or the Secretariat)

Individual monographs on Medicinal Products (containing chemically defined APIs)

2024 EDQM virtual training programme, Module 2

Strasbourg, 3 December 2024

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How it started…

2012: Ph. Eur. Commission reconsidered its strategy about products

⇨ Pilot phase initiated

2014: Strategy decided to widen the scope of Ph. Eur.:

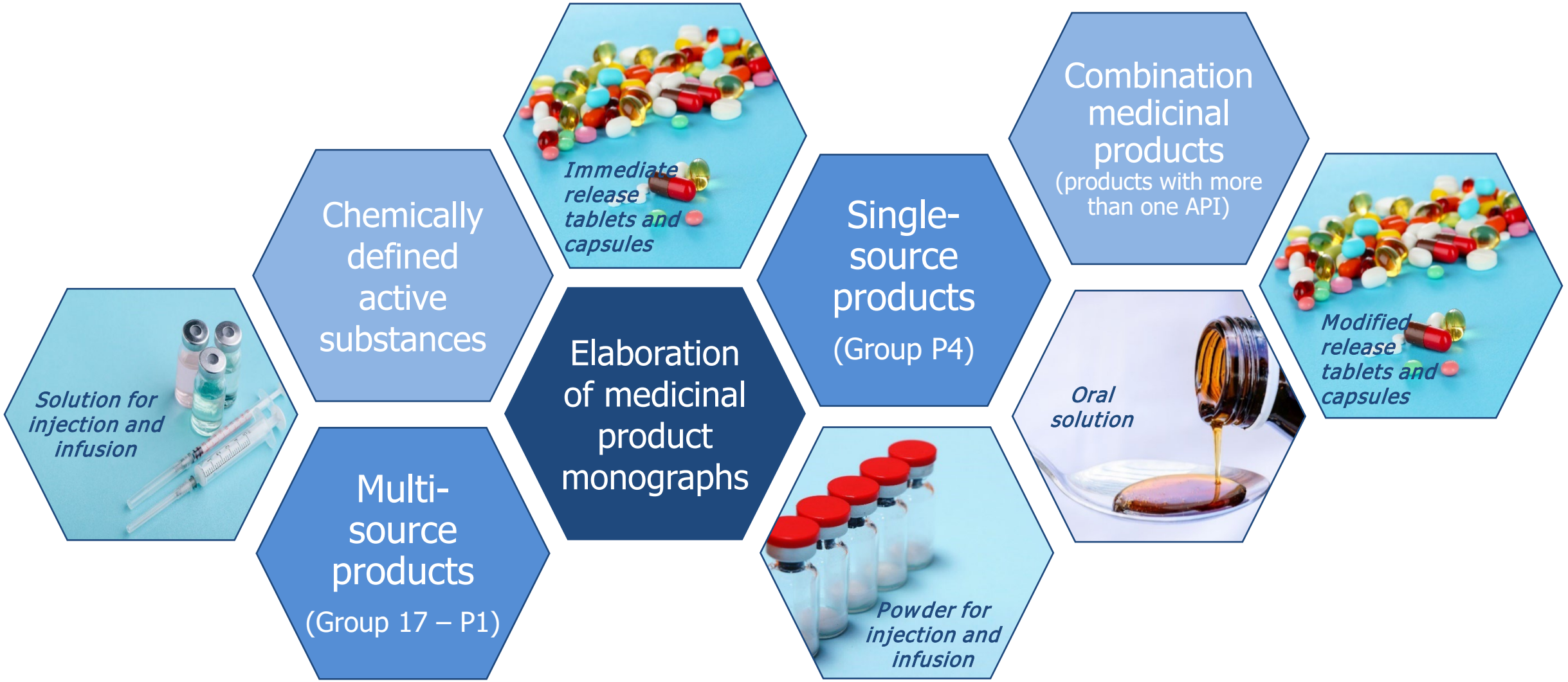
⇨ Start with focus on single-source products, **first P4** monograph Sitagliptin phosphate tablets published in Pharmeuropa 26.3 (July 2014)

2015: Adopted and published in Ph. Eur. (Supplement 8.7)

2016: Coming into force on 1st April 2016

2019: Adoption of the **first P1** monograph Rosuvastatin calcium tablets

How it's going...



Medicinal product (MP) monographs

with chemically defined active substances

26 adopted and published:

Sitagliptin phosphate tablets (8.7/11.7)

Deferiprone oral solution (9.7/10.3)

Lacosamide oral solution (9.7/10.3)

Lacosamide infusion (9.7/10.3)

Deferiprone tablets (9.8/10.6)

Lacosamide tablets (9.8/10.6)

Rosuvastatin calcium tablets (10.1/11.7)

Dronedarone hydrochloride tablets (10.3/11.7)

Regorafenib tablets (10.4/11.1)

Riociguat tablets (10.4/11)

Rivaroxaban tablets (10.4/10.6)

Sorafenib tosilate tablets (10.4/11.7)

Ticagrelor tablets (10.5/10.6)

Deferasirox dispersible tablets (10.7)

Teriflunomide tablets (10.7)

Fulvestrant injection (11.1)

Raltegravir potassium tablets (9.5/11.3)

Raltegravir potassium chewable tablets (9.5/11.3)

Brivaracetam tablets (11.4)

Brivaracetam oral solution (11.4)

Brivaracetam solution (11.4)

Cabazitaxel acetone concentrate for infusion (11.4)

Pirfenidone capsules (11.5)

Etravirine tablets (11.7)

Pirfenidone tablets (11.7)

Dapagliflozin propylene glycol tablets (11.8)

* Monographs based on single-source products * Monographs based on multi-source products

Medicinal product (MP) monographs

with chemically defined active substances

35 monographs under elaboration:

Abiraterone acetate tablets
Alectinib hydrochloride capsules
Apixaban tablets
Atazanavir sulfate capsules
Atazanavir sulfate oral powder
Cabazitaxel concentrate for infusion
Ceritinib tablets
Ceritinib capsules
Colistimethate sodium powder for injection
Dabrafenib mesilate capsules
Daptomycin powder for injection or infusion
Darunavir ethanolate oral suspension
Darunavir tablets
Darunavir ethanolate tablets
Dolutegravir sodium tablets
Eltrombopag olamine tablets
Eltrombopag olamine powder for oral suspension
Esomeprazole gastro-resistant tablets
Fosaprepitant dimeglumine powder for infusion
Indigotindisulfonate disodium injection
Lenalidomide capsules
Lenalidomide hydrochloride capsules
Macitentan tablets
Metformin hydrochloride and Dapagliflozin propylene glycol tablets
Micafungin sodium powder for infusion
Olaparib tablets
Plerixafor injection
Pretomanid tablets
Saxagliptin hydrochloride tablets
Selexipag
Selexipag tablets
Sunitinib capsules
Sunitinib malate capsules
Trabectedin powder for concentrate for infusion
Vismodegib capsules

* Monographs based on single-source products
* Monographs based on multi-source products
* First modified release product
* First combination single-source product

General policy and approaches

- General policies are captured in the Technical Guide for the elaboration of monographs on medicinal products containing chemically defined active substances (3rd Edition, 2023)
- Recent updates of the guide include:
  - elaboration of combination medicinal products
  - policy on repeatability criterion (Assay/Dissolution) – **RSD value of 1.0% (n=6)** as a general rule confirmed after the trial period (ended in March 2023)
  - indication of the strength(s) of the medicinal product considered during the elaboration of the monograph is provided to users in the EDQM Knowledge database (for information) once a monograph is published (FAQ, March 2023)

- Policy is evolving to best tackle the needs and reflect the regulatory requirements and scientific progress

General policy and approaches (cont'd)

Important aspects defined in the past years include:

- adoption of the revised general monograph Pharmaceutical preparations (2619), clarifying widening of limits of impurities, in exceptional cases (adopted by the EPC in June 2023, published in Supplement 11.5)

▸**Related substances**◂ ▸. Medicinal products containing one or more chemically defined active substances comply with the test(s) for related substances in the relevant individual monograph.

In exceptional circumstances and if justified by the applicant to the satisfaction of the competent authority, the latter may approve a wider limit than that described in the monograph. In these rare cases, the competent authority shall bring this to the attention of the Ph. Eur. Commission for review of the monograph and, where appropriate, its revision.

◂

General policy and approaches (cont'd)

- policy for the development of monographs on medicinal products containing chemically defined **active substance hydrates or solvates** (News, May 2022)
- policy for the development of monographs on medicinal products containing chemically defined **active substance salts or bases/acids** (News, May 2021)
- adoption of the revised General Notices chapter (News, May 2021) with the addition of a section on monographs for medicinal products containing chemically defined active substance
- policy for **dissolution and disintegration testing** in individual monographs (News, December 2020)

Prospective harmonisation

- Initiated with the USP in 2008, on new active substance monographs, followed by medicinal product monographs for products still under patent (P4 procedure)*
- Regarding medicinal product monographs, 11 projects are ongoing with the USP and 10 have been finalised
- In 2023, projects expanded to bilateral harmonisation with the WHO and the JP under P1 procedure (multi-source active substances and medicinal products)
- Goal is to align test procedures and limits to a common quality standard (final respective texts do not have to be identical)

Advantages:

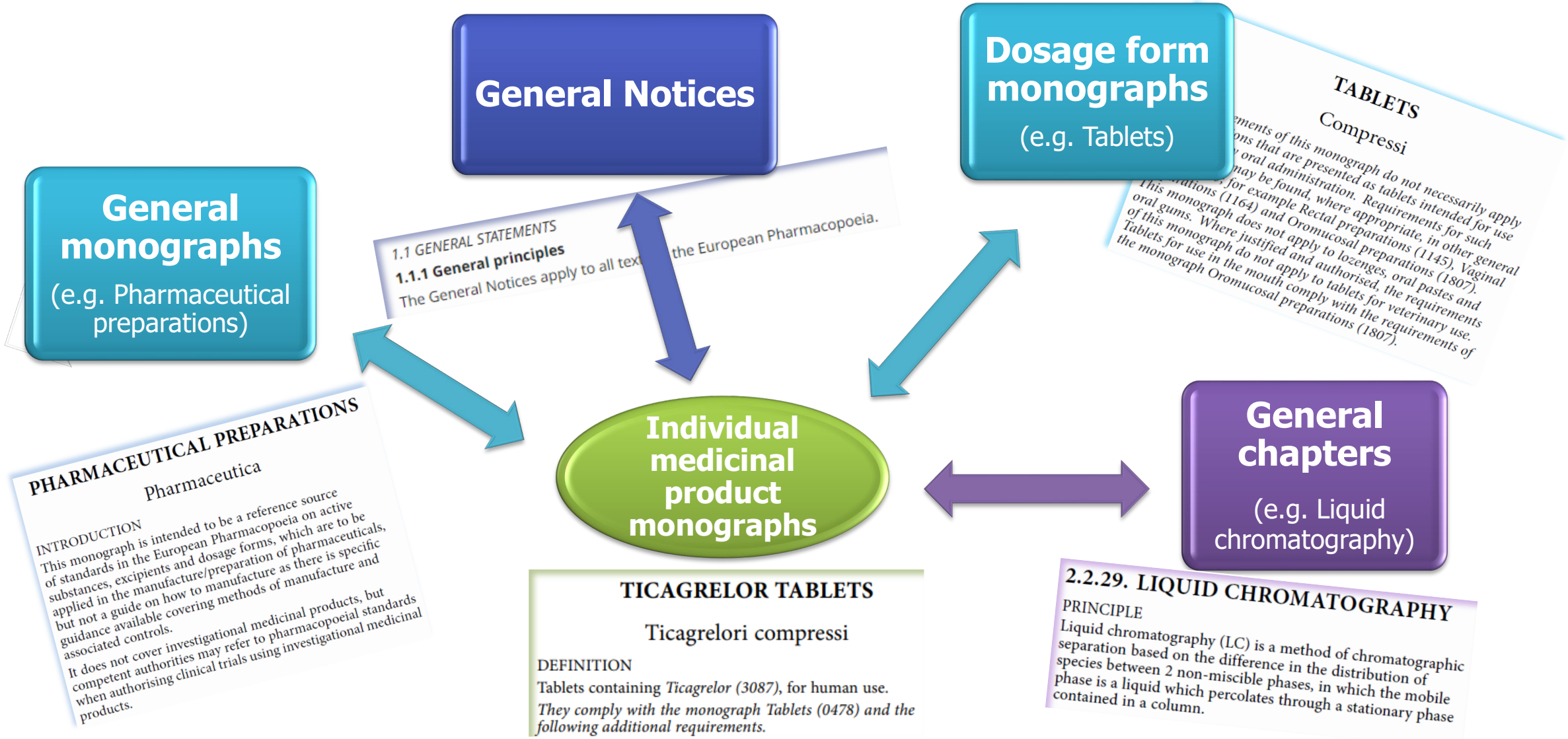
* More information available at: Prospective harmonisation of quality standards: a model for pharmacopoeial convergence

General principles for medicinal product monographs

- Monographs based on currently approved specifications in Europe
- Provide shelf-life specifications
- Monograph tests are mandatory, unless otherwise specified
- Flexibility offered by the Ph. Eur. (see General Notices)
- The choice of analytical procedures may be affected by the formulation and/or the manufacturing process

  ⇨ Each MAH must demonstrate, in the MAA, that tests in the monograph are appropriate for the quality control of their product (e.g. related substances)

General principles



Medicinal product (MP) monographs

- TITLE
  - DEFINITION
  - PRODUCTION
  - IDENTIFICATION
  - TESTS
    - Related Substances
    - Dissolution / Disintegration
  - ASSAY
  - IMPURITIES
  - STORAGE / LABELLING

- Follow general structure of API monographs
- Cover different formulations and strengths of the same dosage form
- One monograph per active substance (e.g. one for the product containing the salt form and one for the base/acid) ⇒ **Policy approved in March 2021**
- Separate monographs for medicinal products containing different active substance solvates ⇒ **Policy approved in March 2022**
- One monograph for medicinal products containing one or several hydration forms of the active moiety

Title

Active substance name

INN* or INNM** is used:

– salt mentioned in the title

– hydrate form omitted

– other solvates mentioned in the title

+

Dosage form

(Titles/sub-titles of the dosage form monographs)

EXAMPLES

- Deferiprone oral solution
- Lacosamide infusion
- Raltegravir potassium chewable tablets
- Cabazitaxel acetone concentrate for infusion
- Dronedarone hydrochloride tablets
- Dapagliflozin propanediol tablets
- Fosaprepitant dimeglumine powder for injection
- Deferasirox dispersible tablets

* INN – The International Nonproprietary Name

** INNM – The International Nonproprietary Name Modified

Definition

Includes statement on the scope:

- The exact pharmaceutical form
- The API covered: specific salt, hydrate and/or solvate (i.e. reference to API monograph)
- "*For human use*"

- If appropriate states that the preparation is sterile
- Cross-reference to the relevant dosage form monograph
- Content as percentage of active moiety declared on the label (e.g. 95.0% - 105.0%)

RALTEGRAVIR ▸POTASSIUM◂ TABLETS

Raltegraviri ▸kalici◂ compressi

DEFINITION

Tablets containing *Raltegravir potassium (2887)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content: 95.0 per cent to 105.0 per cent of the content of raltegravir ($C_{20}H_{21}FN_6O_5$) stated on the label.

LACOSAMIDE INFUSION

Lacosamidi praeparatio ad infusionem

DEFINITION

Sterile solution for infusion of *Lacosamide (2992)*, for human use.

It complies with the monograph Parenteral preparations (0520) and the following additional requirements.

Content: 95.0 per cent to 105.0 per cent of the content of lacosamide ($C_{13}H_{18}N_2O_3$) stated on the label.

REGORAFENIB TABLETS

Regorafenibi compressi

DEFINITION

Tablets containing *Regorafenib monohydrate (3012)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content: 95.0 per cent to 105.0 per cent of the content of regorafenib ($C_{21}H_{15}ClF_4N_4O_3$) stated on the label.

Production

- Included in the monographs of medicinal products containing an active substance in solvate form (for solvates other than hydrates)

- No test for the control of the organic solvent will be described, but the following statement published in the monograph:

> PRODUCTION
>
> Manufacturers are expected to evaluate whether the presence of the active substance as a solvate is critical to the quality, efficacy and/or safety of the medicinal product and, where applicable, implement a control strategy for the corresponding solvent in the medicinal product, to the satisfaction of the competent authorities.

Identification

Provides confirmation of the identity of the product, e.g.:

- Combination LC method + UV-DAD:
  - LC method: t_R and size of the main peak
  - UV-DAD spectrum of the main peak (Assay)
- Other options:
  - LC + IR (Direct or after extraction)
  - LC + UV-DAD or LC + IR (Alternative)

IDENTIFICATION

Carry out either tests A, B or tests B, C.

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay with a diode array detector in the range of 190-400 nm.

Results: the UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

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

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation: crush a tablet to a powder and homogenise.

Comparison: *raltegravir potassium CRS*.

Results: the spectrum obtained shows absorption maxima at about 1633 cm^{-1}, 1515 cm^{-1}, 1188 cm^{-1}, 810 cm^{-1} and 728 cm^{-1}, similar to the spectrum obtained with *raltegravir potassium CRS*.

Other absorption maxima may be present in the spectra.

Tests

- This section typically includes:
  - ➢ Related substances test
  - ➢ Dissolution / Disintegration test (e.g. for tablets, capsules)

- If not product specific, additional tests to control specific quality parameters (e.g. pH for liquid or semi-liquid dosage forms when it is indicative of stability)

- Bacterial endotoxins test, Microbial testing, Sterility, Uniformity of dosage units/Content uniformity…:

  ⇨ Not included as referenced and covered by general texts, general monographs and dosage form monographs, **unless** specific individual limit or specific method prescribed

Impurity policy (in line with ICH Q3B*/Q6A**)

Degradation products

Controlled

Arising during the manufacturing process and throughout shelf-life, including impurities of synthesis that are also degradation products

Acceptance criterion: individual (for specified impurities) or general (for all unspecified impurities)

Impurities of synthesis

- Not controlled in MP monographs *(controlled in API monographs)*
- If detected by the method, they are included in the transparency list
- If present at a level greater than the reporting threshold, they are:
  1. identified (e.g. using a reference standard (CRS) or reagent)
  2. 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 »

Impurity policy: example of Deferiprone tablets

How impurities are identified and limited?

Related substances

Test solution (a). Crush 20 tablets to obtain a homogeneous powder. Dissolve an amount of the powder containing the equivalent of 100 mg of deferiprone in the mobile phase by sonicating for approximately 15 min and dilute to 100.0 mL with the mobile phase.

Assay

Test solution (b). Dilute 5.0 mL of test solution (a) to 200.0 mL with the mobile phase.

Related substances

Reference solution (a). Dilute 2.0 mL of test solution (b) to 50.0 mL with the mobile phase.

SST

Reference solution (b). Dissolve 2 mg of ***maltol R*** **(impurity B)** in the mobile phase and dilute to 100 mL with the mobile phase. Mix 5 mL of the solution and 10 mL of test solution (a) and dilute to 100 mL with the mobile phase.

Assay

Reference solution (c). Dissolve 50.0 mg of ***deferiprone CRS*** in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 5.0 mL of the solution to 200.0 mL with the mobile phase.

Impurity policy: example of Deferiprone tablets (cont'd)

Identification of impurities: use the chromatogram obtained with reference solution (b) to identify the peak due to impurity B.

Relative retention with reference to deferiprone (retention time = about 12 min): impurity B = about 0.5.

System suitability: reference solution (b):

– *resolution:* minimum 5.0 between the peaks due to impurity B and deferiprone.

Calculation of percentage contents:

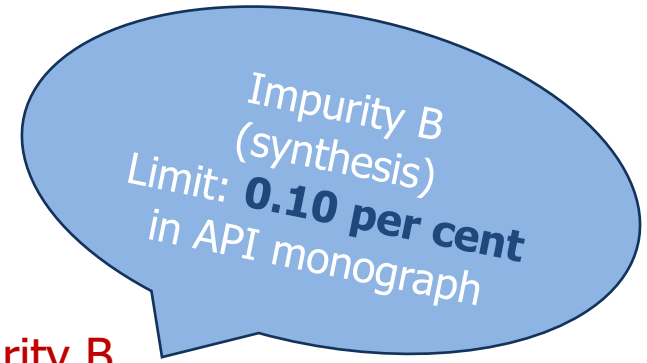
– for each impurity, use the concentration of deferiprone in reference solution (a).

Limits:

– *unspecified impurities:* for each impurity, maximum 0.10 per cent;

– *total:* maximum 0.3 per cent;

– *reporting threshold:* 0.05 per cent; disregard the peak due to impurity B.



Dissolution (1/2)

- Policy on Dissolution/Disintegration (adopted in November 2020) described in the General Notices (Supplement 10.6):

The following terms are used hereafter:

- **Monograph dissolution test**: analytical procedure and acceptance criteria described in the individual monograph;
- **Product-specific dissolution test**: analytical procedure and acceptance criteria proposed by the applicant in a Marketing Authorisation Application (MAA) for a medicinal product;
- **In-house dissolution test:** analytical procedure developed and acceptance criteria defined by the applicant.

In line with the relevant guidelines applied nationally or regionally (such as the ICH Q6A guideline) and with the relevant Ph. Eur. dosage form monograph, a suitable product-specific dissolution test has to be proposed by the applicant for routine quality control to confirm batch-to-batch consistency. This test must be described in the MAA for submission to the competent authority, unless there is data justifying the replacement of the dissolution test by a disintegration test (see below). The demonstration of the suitability of the dissolution test has to be made by the applicant to the satisfaction of the competent authority.

Where appropriate, a dissolution test is described in an individual monograph on a medicinal product. In such cases, the applicant may either select the monograph dissolution test or develop an in-house dissolution test as the product-specific dissolution test. In any case, the applicant has to demonstrate the suitability of the selected test to the satisfaction of the competent authority.

If an in-house dissolution test is proposed, justification for not selecting the monograph dissolution test and demonstration of compliance with the monograph dissolution test is normally not requested in the MAA.

However, when tested, the medicinal product has to comply with the monograph dissolution test, unless otherwise justified by the applicant.

Where a given medicinal product does not comply with the monograph dissolution test and this product is approvable by a competent authority, then the competent authority shall bring this to the attention of the Ph. Eur. Commission so it can review the monograph and revise it where appropriate.

Dissolution (2/2)

- A suitable product-specific dissolution test has to be proposed by the applicant for routine quality control to confirm batch-to-batch consistency
- Where appropriate, a test is included in individual monographs
- The applicant may either select the monograph dissolution test or develop an in-house dissolution test. In all cases, the applicant has to demonstrate the suitability of the selected test to the satisfaction of the competent authority.
- If an in-house dissolution test is proposed, justification for not selecting the monograph dissolution test is not requested in the MAA
- However, when tested, the medicinal product has to comply with the monograph dissolution test, unless otherwise justified by the applicant
- Quantitation: by LC or UV-Vis, using either a reference standard with assigned content (e.g. Rosuvastatin tablets) or specific absorbance value (e.g. Dronedarone tablets)

Disintegration

- Disintegration test may be substituted for a dissolution test (in accordance with ICH Q6A), as outlined in the General Notices (Supplement 10.6):
  - For rapidly dissolving medicinal products containing highly soluble active substances throughout the physiological range and,
  - When relationship to dissolution is established **or** when disintegration is more discriminating (e.g. Sitagliptin tablets)
- Such a substitution has to be justified by the applicant to the satisfaction of the competent authority

Assay

- Specific, stability-indicating assay for content (usually HPLC)
- Standard specification: 95.0 to 105.0 per cent of the content stated on the label
- Repeatability requirements of chapter *2.2.46. Chromatographic separation techniques* only valid for APIs, therefore an individual criterion is introduced into each MP monograph:

Policy approved in March 2023

  - *repeatability:* maximum relative standard deviation of 1.0 per cent determined on 6 injections *(general rule that could be adapted depending on the values reported)*

- When the CRS of the API monograph is used, a conversion factor may be required (e.g. *Rosuvastatin calcium CRS* used for determination of rosuvastatin in Rosuvastatin tablets ⇨ conversion factor 0.96)

Impurities

- Transparency list as for API monographs
- List all impurities, independent of their nature (degradant or synthetic) that are known to be detected
- Impurities also relevant to the API keep their designation (e.g. A, B)
- Impurities specific to the medicinal product are designated by "FP-" followed by a letter (e.g. FP-A, FP-B)

Conclusions

- A number of monographs has been elaborated under the P4 procedure (Single-source products) – Procedure 4 - Everything you always wanted to know
- Increasing number of monographs are elaborated under the P1 procedure (Multi-source products)
- Prospective harmonisation with the USP, JP and WHO ongoing for various projects to reach aligned standards
- Policies for different parts of a monograph e.g. titles, definition, identification, assay, impurities, dissolution/disintegration are now well defined
- An indication of the strength(s) of the medicinal product considered during the elaboration provided to users for information (EDQM Knowledge database)
- Ph. Eur. is regularly updated to keep pace with the regulatory requirements, technological and scientific advances: any interested party can propose a new monograph elaboration or revisions of already published monographs (via the NPAs or the Secretariat)

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