Specific monographs on "Substances for pharmaceutical use" and on Finished Products (containing chemically defined APIs)

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**Individual monographs**

**Basis for the elaboration of monographs:**

**SAFETY FIRST!**

- Products of proven safety, evaluated and approved by competent authorities of Member states
- Impurity profiles for existing, approved manufacturing routes
- Use of robust, validated analytical methods

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**General vs. individual monographs**

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

- Title
- Relative atomic and molecular masses
- CAS registry number

- Definition
- Production (mandatory for manufacturer)

- Potential adulteration
- Characters (for information only)

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Individual monographs

- Identification
- Tests
- Assay

- Storage (information and recommendation, but competent authority may make it mandatory)
- Labelling

- Impurities - transparency list
- Functionality - related characteristics (not mandatory)
  → Excipient monographs
DICLOFENAC SODIUM
Diclofenacum natrium

C₁₁H₁₈NaO₃
Mₑ₃ 381.1

DEFINITION
Sodium [2-(2,6-dichlorophenyl)phenol]acetate. Content: 98.4 per cent to 101.0 per cent (dried substance).

CHARACTER
Appearance: white or slightly yellowish, slightly hygroscopic, crystalline powder. Solubility: sparingly soluble in water, freely soluble in methanol, soluble in ethanol (88 per cent), slightly soluble in acetone.

mp: about 280 °C, with decomposition.

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

A. Infrared absorption spectrophotometry (2.2.14).

B. Comparison: Diclofenac sodium CRS.

Further information provided on Knowledge database (http://www.edqm.eu/en/Knowledge-Database-707.html)

Further identification tests

Chromatographic conditions

Assay by titration

Reagent described in the Ph.Eur.; phosphoric acid R
INNs used almost universally (modified to indicate salt)

Includes degree of hydration

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

DEFINITION (1)

• Chemical nomenclature
  
• Assay limits
    - Content expressed on anhydrous or dried basis
    - Solvent-free substance is implied, even where not stated (see Substances for Pharmaceutical Use, 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)

• 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·H₂O"): “It contains a variable quantity of water” (zanamivir 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): pethidine hydrochloride

PRODUCTION

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

Diluting sodium is produced by a validated manufacturing and purification procedure under conditions designed to minimize the presence of NNO groups. The manufacturing procedure must have been shown to reduce any contamination by NNO groups to approved limits using an appropriate, validated quantification method.
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

- No 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)

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 solutions**:
- **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 GF254 plate R.


**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 (2.3.3).
TESTS

Chemical methods  Physical methods  Chromatographic methods

Organic impurities  Inorganic impurities  Volatile impurities

Impurity testing (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 Substances for Pharmaceutical Use)
Impurity testing (2): Impurities section

Not necessarily exhaustive
Impurities **known** to be controlled by monograph tests

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

Based on information obtained and verified during monograph elaboration/revision

**DACARBZanine**

**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 criteria for other unspecified impurities and, or by the general monograph Substances for pharmaceutical use (2018) It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.3. Control of impurities in substances for pharmaceutical use. C.

A. 3,7-dihydroxy-4H-pyran-4-one (isocoumarinone)

B. X = H: 5-amino-1H-imidazole-4-carboxamide
C. X = NH: 1H-imidazole-4-carboxamide
D. N,N-dimethylacetamide

New impurity profiles: Directive 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...”
Specifications

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

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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- approved limit:</td>
<td>0.2 %</td>
</tr>
<tr>
<td>- batch data</td>
<td>0.04 – 0.02 – 0.06 – not detected – 0.01 %</td>
</tr>
<tr>
<td></td>
<td>mean + 3sd = 0.026 % + 0.065 = 0.091 %</td>
</tr>
<tr>
<td>- limit fixed at</td>
<td>0.10 % (unspecified)</td>
</tr>
<tr>
<td></td>
<td>no CRS for peak id needed !</td>
</tr>
</tbody>
</table>

Inorganic impurities

- Result from the manufacturing process or from raw materials
- Known and identified:
  - Reagents, catalysts
  - Elemental impurities → ICH Q3D Guideline for Elemental impurities (general chapter 5.20)
  - Inorganic salts
  - Other materials (e.g. filter material)
- Atomic absorption spectrometry (**2.2.23**), ICP, XRF *and others*
- Sulfated ash (**2.4.14**)
**Inorganic impurities (2)**

**Specific element testing in individual monographs**

- Tests remain when elements are of natural abundance which cannot be eliminated by purification (mined excipients).

- Tests for elements are suppressed when they have been « intentionally added », i.e. reagents or catalysts used in synthesis.

- Tests may remain when important to ensure the quality.

- Special cases: Methylthioninium chloride (methylene blue)
  (Elements may have an effect on therapeutic activity (API is a chelating agent)

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**Residual solvents**

- 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: not included in a specific monograph; limit set by option 2 (cf. 5.4 Residual solvents)

  - **Class 3** solvents are only named and limited 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:

- Tests described if **proof for genotoxicity available** (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 C14H10Cl2NNaO2.

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

Unspecific but precise assay (titration), often 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)

Described in monographs on Excipients
Section is not mandatory

Provides information on important parameters
⇒ Chapter on FRCs 5.15 (revised in 9.2)

Tests are linked to use, in line with ICH Q8
(lubricant, tablet compression, etc.)

SORBITOL

FUNCTIONALITY-RELATED CHARACTERISTICS
This section provides information on characteristics that are recognized 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 recognized 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).
CONCLUSION

- Ph. Eur. Monographs are legally binding
- General chapters are mandatory when referred to in a monograph
- Complementarity of specific and general monographs/chapters
  Non mandatory sections: Characters, Storage, FRC
- Other sections of the monograph
  - In general mandatory
  - Production (mandatory for manufacturer)
- Alternative methods can be used provided they lead to the same pass-fail decision
- Knowledge database: reference standards, CEP-holders, trade names
Specific monographs on Finished Products (containing chemically defined APIs)

Ph. Eur. Training Webinar
Strasbourg, 7-8 July 2020

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Development of monographs on finished products

2012: Ph. Eur. Commission reconsidered its strategy
   ⇒ Pilot phase initiated with 2 examples:
      1 single-source (P4) product and 1 multi-source product (P1)

2014: Strategy decided to widen the scope of Ph. Eur.:
   ⇒ Start with focus on single-source products, first monograph
      Sitagliptine tablets published in Pharmeuropa (26.3 - July 2014)

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

2016: 1st monograph came into force on 1st April 2016

2019: Adoption of the 1st P1 monograph: Rosuvastatine tablets
Current focus

Chemically defined active substances

Single-source products (Group P4)

Elaboration of FP monographs

Multisource products (Group 17 – P1)

Finished product monographs (FPMs)

15 adopted & published:
- Sitagliptin tablets (8.7)
- Raltegravir tablets (9.5)
- Raltegravir chewable tablets (9.5)
- Difluprednate oral solution (9.7)
- Lacosamide oral solution (9.7)
- Lacosamide infusion (9.7)
- Deferiprone tablets (9.8)
- Lacosamide tablets (9.8)
- Rosuvastatin tablets (10.1)
- Dronedronate tablets (10.3)
- Regorafenib tablets (10.4)
- Riociguat tablets (10.4)
- Rivaroxaban tablets (10.4)
- Sorafenib tablets (10.4)
- Ticagrelor tablets (10.5)

26 monographs under elaboration:
- Abiraterone tablets
- Atazanavir capsules
- Atazanavir oral powder
- Brivaracetam infusion
- Brivaracetam oral solution
- Brivaracetam tablets
- Cabazitaxel concentrate for infusion
- Colistimethate injection
- Daptomycin powder for injection
- Darunavir oral suspension
- Darunavir tablets
- Decitabine powder for infusion
- Deferasirox dispersible tablets (32.2)
- Dolutegravir tablets
- Etoposide powder for infusion
- Etravirine tablets
- Fosaprepitant powder for infusion
- Fulvestrant injection
- Lenalidomide capsules
- Micafungin powder for infusion
- Plerixafor injection
- Pirfenidone capsules
- Pirfenidone tablets
- Saxagliptin tablets
- Sunitinib capsules
- Teriflunomide tablets (32.2)
**General principles**

- Monographs based on currently approved specifications in Europe
- Provide shelf-life specifications
- Monograph tests are mandatory, unless otherwise specified
- Flexibility offered by 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. dissolution, related substances)
General documents

- General policy paper:
  « General principles for Monographs on Finished Products (FPs) containing chemically defined active substances »
  Adopted

- Derived from this policy paper:
  « Technical Guide for the elaboration of Monographs on Finished Products containing chemically defined active substances »
  (Still under discussion, not yet approved)
  Draft

Structure of FP monographs

- Follows general structure of API monographs
- Cover different formulations and strengths
- All tests are mandatory, unless otherwise specified
**Title and Definition**

**Title:** Combination

**Active moiety name:**
- INNs used
- Degree of hydration and salt are omitted

**Pharmaceutical form:**
- Derived from the dosage form monograph (title or subtitles)

**Definition:** includes statement on the scope:
- The exact pharmaceutical form
- The API covered: specific salt and/or hydrate
- For human use

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

**Identification tests**

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

- **Combination LC method + UV-DAD:**
  - **LC method:** \( t_R \) & size of the main peak
  - **UV-DAD** spectrum of the main peak (Assay)

- **Other options:**
  - **LC + IR** (Direct or after extraction)
  - **LC + UV-DAD versus LC + IR** (Alternative)
Tests

• All tests are mandatory, these typically include:
  ➢ Related Substances test
  ➢ Dissolution test (e.g. for tablets, capsules)

• If not product specific, additional tests to control specific quality parameters (e.g. water, pH)

• Bacterial endotoxin test, Microbial testing, Sterility, Uniformity of Dosage units/Content uniformity...:
  ⇒ Not included as referenced and covered by general texts 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
- Individual acceptance criterion

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 CRS or reagent)
  - 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: Deferiprone tablets**

*How impurities are identified and limited?*

*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.

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

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

*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.

*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.

*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:* 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 test**

**Current policy** follows the **General Principles**:

- **Mandatory testing procedure** (test conditions + acceptance criteria), unless otherwise justified and authorised:
  - Flexibility given with the statement: "The tablets comply with the test and the acceptance criterion/criteria described below, unless otherwise justified and authorised".
- Provided for quality control only
- Should be sufficiently **discriminatory** to assure batch-to-batch consistency
  - Not intended to demonstrate bioequivalence
- **Quantitation**: by LC or UV-Vis, using either a CRS with assigned content (e.g. Rosuvastatin tablets) or value for specific absorbance (e.g. Dronedarone tablets)

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**Disintegration test**

Disintegration may be substituted:
(in accordance with ICH Q6A)

- For **rapidly dissolving** 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 monograph)
**Assay**

- **Specific, stability-indicating assay for content** (usually HPLC)
- Standard specification: 95.0 to 105.0 % of the content stated on the label
- **Repeatability** requirements of chapter 2.2.46. *Chromatographic separation techniques* only valid for APIs:
  ⇒ Standard RSD max. 1.5% (n=6), based on case-by-case decision
- 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 finished product are designated by “FP-” followed by a letter (e.g. FP-A, FP-B)
Conclusion

• A number of FP monographs has been elaborated under the P4 procedure (Single source products)

• Several monographs are elaborated under the P1 procedure (Multi-source products)

• A first monograph under P1 has been adopted: Rosuvastatin tablets

• Policies for identification, impurities, assay are clear and agreed

• Revision of the current policy of dissolution test still under discussion

Thank you for your attention

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