Specific monographs: APIs

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Content of the presentation

- Sections:
  - Identification
  - Related substances
  - Assay
  - Non-mandatory sections
  - FRC
- Elemental impurities
- Specification setting

General vs. individual monographs

- Complementary
- One not overruling the other
- Exceptions are clearly indicated either in the general monograph or in the individual one
**General vs. individual monographs**

**Example:**
- « The thresholds indicated under Related substances (Table 2034-1) in the general monograph 2034 *Substances for pharmaceutical use (2034)* do not apply ».

  e. g. :
  - Deferoxamine mesilate (limit for unspecified imps. 0.20 %)
  - Certain antibiotics, bacitracin, bacitracin zinc (reporting threshold, limits for unspecified impurities)

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**Specific 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
**Specific 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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**Specific 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 natricum

C_21H_21NO_3SNa_2 [M 318.1]

DEFINITION
Sodium [2-(2,6-dichlorophenyl)phenyl]acetate. Content: 98.0 per cent to 101.0 per cent (dry substance).

CHARACTER
Appearance: white or slightly yellowish, slightly hygroscopic, crystalline powder.
Solubility: sparingly soluble in water, freely soluble in methanol, soluble in ethanol (86 per cent), slightly soluble in acetone.
mp: about 280 °C, with decomposition.

IDENTIFICATION
First identification: A, B.
Second identification: B, C, D.
A. Infrared absorption spectrophotometry (2.2.14).
Comparison: Diclofenac sodium CRS.

Further identification tests

Chromatographic conditions
Assay by titration

Reference to general Chapters: 2.2.29

Reagent described in the Ph.Eur.: phosphoric acid R

Further information provided on Knowledge database (http://www.edqm.eu/en/Knowledge-Database-707.html)
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.: 1U/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 ("xH₂O"): "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): 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
CHARACTERS

**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 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 the solution add 0.3 mL of a mixture, prepared immediately before use, of equal volumes of a 6 g/L solution of potassium hexacyanoferrate(III) and a 9 g/L solution of ferric chloride R. Allow to stand protected from light for 5 min. Add 3 mL of a 10 g/L solution of hydrochloric acid R. Allow to stand, protected from light, for 15 min. A blue colour develops and a precipitate is formed.

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

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

Inorganic impurities (1)

- Result from the manufacturing process or from raw materials
- Known and identified:
  - Reagents, catalysts
  - Elemental impurities → ICH Q3D Guideline for Elemental impurities
  - 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)

Inorganic impurities (3)

Specific element testing in individual monographs

Methylthioninium chloride (methylene blue)

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

<table>
<thead>
<tr>
<th>Element</th>
<th>Maximum content (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>100</td>
</tr>
<tr>
<td>Cadmium</td>
<td>1</td>
</tr>
<tr>
<td>Chromium</td>
<td>100</td>
</tr>
<tr>
<td>Copper</td>
<td>300</td>
</tr>
<tr>
<td>Iron</td>
<td>2000</td>
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<td>Lead</td>
<td>10</td>
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<td>Manganese</td>
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<td>Molybdenum</td>
<td>10</td>
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<tr>
<td>Nickel</td>
<td>10</td>
</tr>
<tr>
<td>Tin</td>
<td>10</td>
</tr>
<tr>
<td>Zinc</td>
<td>100</td>
</tr>
</tbody>
</table>
Residual solvents

• Specific 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

### 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\(_2\)NNaO\(_2\).
Assay methods

- **Assays by chromatography** preferred when API + FP monograph
  - Then ideally the same assay method should be used
- **Volumetric titrations** still used for monographs on APIs:
  - Advantage: rapid, precise, simple, cheap, combined with selective impurity test
- **UV-Vis assays**: less often used nowadays, occasional use in monographs on herbals for group determination (e.g. flavonoids)

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**STORAGE**

**STORAGE (DICLOFENAC SODIUM)**

In an airtight container, protected from light.

- **Non mandatory** section
  - Storage of the product → to ensure compliance with the monographs

- Competent authority may specify particular storage conditions
  - → may decide to make the conditions mandatory

- Conventional expressions
  - → defined in the General Notices (e.g. *in an airtight container, protected from light*)
LABELLING

Covered by national and international regulations

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)

Informational items or recommendations included

FUNCTIONALITY-RELATED CHARACTERISTICS

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

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.

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)

Informational items or recommendations included

FUNCTIONALITY-RELATED CHARACTERISTICS

(FRCs)

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).
Specifications

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

**Example:** Request for revision to include impurity X in an API monograph
- Approved limit 0.2 %
- Batch data 0.04 – 0.02 – 0.06 – not detected – 0.01 %
- Mean + 3sd = 0.026 % + 0.065 = 0.091 %
- Limit fixed at 0.10 % (unspecified)

no CRS for peak id needed!

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
Thank you for your attention

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