Specific monographs: a guide through the different sections

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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
APIs, excipients, finished products

Specific monograph(s) → Relevant General monograph(s)

COMPLEMENTARITY

Specific monographs
Finished products (FP)

- Vaccines and sera
- Blood products
- Radiopharmaceuticals
- Insulin preparations

New approach (March 2014)
Monographs on finished products with chemically-defined APIs
Sitagliptin tablets (2927)
Raltegravir tablets (2938)
Raltegravir chewable tablets (2939)
Specific monographs

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

- Definition
- Production (mandatory for manufacturer)

- Potential adulteration (information may be available)
- Characters (for information only)

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)
  → Excipients monographs
DICLOFENAC SODIUM
Dioecfenacum matricum

C16H18Cl2NaN2O3
[5985-76-4]

DEFINITION
Sodium (2-(2,2-dichlorophenyl)phenyl)acetate. Content: 93.0 per cent to 96.0 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 (60 per cent), slightly soluble in acetone.

Identification
First identification. A, D
A. Infrared absorption spectrophotometry (2.2.24).
B. Comparison: diclofenac sodium CRS.
C. Thin-layer chromatography (2.2.37).
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 diclofenacin R in reference solution (a) and dilute to 2 ml with reference solution (a).

Molecular and graphic formulae
- Molecular structure
- Molecular mass
- CAS number

Further information provided on Knowledge database

Reference to general Chapters: 2.2.29
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)**

**DEFINITION (DICLOFENAC SODIUM)**

- **Content**: 99.0 per cent to 101.0 per cent (dried substance).
- **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 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 (“\(xH_2O\)”: “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 (parenteral etc.): pethidine hydrochloride, fructose

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. genotoxic 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)
- 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 and Second identifications → defined in General Notices
Sometimes cross-reference to “Tests”
Reference to Water/ Loss on drying (applicable for a hydrate)

1st identification alone → always sufficient
2nd identification → never mandatory

2nd identification → usually less sophisticated; may be performed in pharmacies e.g. TLC, wet chemical reaction
TESTS

Chemical methods  Physical methods  Chromatographic methods

Organic impurities  Inorganic impurities  Volatile impurities

Impurity testing (in line with ICH Q3A/B) (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)
Knowledge database

Reference standards (CRS)
• Trade names (column, reagents…)

Impurity testing (2): Impurities section

Not necessarily exhaustive
Impurities known to be detected by mono 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**

- Result from the manufacturing process or from raw materials
- Known and identified:
  - Reagents, ligands catalysts
  - Elemental impurities → ICH Q3D Guideline for Elemental impurities
  - Inorganic salts
  - Other materials (e.g. filter aids)
- Atomic absorption spectrometry (2.2.23) or other techniques
- Sulfated ash (2.4.14): global determination of foreign cations

**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** (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}.

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

Unspecific but precise assay (titration), provided sufficiently characteristic and selective related substances test (cf Technical guide)

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

**STORAGE** (DICLOFENAC SODIUM)

In an airtight container, protected from light.

Not mandatory section

Storage of the product → to ensure compliance with the monographs

Competent authority may specify particular storage conditions → may decide to make it 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 (FRCs)**

- Described in monographs on Excipients
- Section is not mandatory
- Provides information on important parameters → Chapter on FRCs 5.15
- Tests are linked to use (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.

**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 5.13). This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however 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. Whenever 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.
CONCLUSION

- Complementarity of specific and general monographs/chapters
- New: Monographs on finished products with chemically-defined APIs (e.g. sitagliptin tablets)
- Not mandatory sections: Characters, Storage, FRC
- Other sections
  - In general mandatory
  - Production (mandatory for manufacturer)
- Knowledge database: SOW, reference standards, CEP-holders, trade names

Thank you for your attention!