How to use the European Pharmacopoeia and how to contribute

18th European Symposium on Radiopharmacy and Radiopharmaceuticals

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Outline

• Purpose of the European Pharmacopoeia (Ph. Eur.)
• Place of the Ph. Eur. in the regulatory network
• General principles – general organisation
• Elaboration of Ph. Eur. Texts
• Setting of limits
• Opportunities for you to contribute to the Ph.Eur.
The purpose of the European Pharmacopoeia is to promote public health by the provision of recognised common standards for the quality of medicines and their components. Such standards are to be appropriate as a basis for the safe use of medicines by patients.
Place of the Ph. Eur. within the regulatory network

- Lays down common, compulsory quality standards for all medicinal products in Europe.
- Mandatory on the same date in 37 states (CoE) and the EU.
- The Ph. Eur. is legally binding. The legislation also includes a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market;
- The European Pharmacopoeia needs to keep pace
  - with the regulatory needs of licensing, control and inspection authorities in the public health area,
  - with technological and scientific advances, and with industrial constraints.
Ph. Eur. – General organisation

- Introduction
- General notices
- General chapters
- General monographs
- Individual monographs
Ph. Eur. – General organisation

1. General notices

- apply to all monographs and other texts of the Ph. Eur.
- instructions to understand texts, conventional expressions
- essential reading before starting to use general chapters and monographs
Flexibility in the Ph. Eur.
– Alternative methods

- **Ph. Eur. tests are reference methods**, essential in cases of dispute.
- Compliance is required, but **alternative methods** may be used as long as they lead to the **same pass/fail result**.
- It is the responsibility of the user to demonstrate their suitability. **Approval of the competent authority** is necessary in many cases.
“An article is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. **This does not imply that performance of all the tests** in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality from data derived, for example, from **validation of the process** and from **validation studies of the manufacturing process** and from **in-process control**.”

**General Notices** (3rd Edition to Supplement 8.1)
Ph. Eur. – General organisation

Introduction
General notices
General chapters
General monographs
Individual monographs

2 - Methods of analysis
2.2.66 – Detection and measurement of radioactivity
DETECTION AND MEASUREMENT OF RADIOACTIVITY
Detection and measurement of radioactivity are carried out according to general chapter 2.2.66. Detection and measurement of radioactivity.
Ph. Eur. – General organisation

- Introduction
- General notices
- General chapters
- General monographs
- Individual monographs

2 - Methods of analysis
3 - Materials for containers and containers
4 - Reagents
5 - General texts
Ph. Eur. – General organisation

Introduction
General notices
General chapters
General monographs
Individual monographs

2 - Methods of analysis
3 - Materials for containers and containers
4 - Reagents
5 - General texts

5.19 – Extemporaneous preparation of radiopharmaceuticals
5.19. EXTEMPORANEOUS PREPARATION OF RADIOPHARMACEUTICALS

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This general chapter is published for information.

1. SCOPE AND DEFINITION

Many radiopharmaceuticals are prepared on-site on a regular basis, typically as doses for a few patients based...
Ph. Eur. – General organisation

Introduction
General notices
General chapters
General monographs
Individual monographs

23 general monographs + Dosage forms monographs in Ph. Eur. 8.8

- Pharmaceutical preparations
- Radiopharmaceutical preparations
- Parenteral preparations
- Chemical precursors for radiopharmaceutical preparations

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RADIOPHARMACEUTICAL PREPARATIONS

Radiopharmaceutica

DEFINITIONS

Radiopharmaceutical preparations or radiopharmaceuticals are medicinal products which, when ready for use, contain 1 or more radionuclides (radioactive isotopes) included for a medicinal purpose.

For the purpose of this general monograph, radiopharmaceutical preparations also cover:

- radionuclide generators: any system incorporating a fixed parent radionuclide from that is produced a daughter radionuclide that is to be obtained by elution or by any other method and used in a radiopharmaceutical preparation;
- kits for radiopharmaceutical preparation: any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical preparation, usually prior to its administration;
- radionuclide precursors: any radionuclide produced for radiolabelling of another substance prior to administration.

Radionuclide precursors may be supplied as solutions for
CHEMICAL PRECURSORS FOR 
RADIOPHARMACEUTICAL 
PREPARATIONS

Praecursores chimici ad radiopharmaceutica

DEFINITION AND SCOPE

Chemical precursors for radiopharmaceutical preparations, hereinafter referred to as ‘chemical precursors’, are non-radioactive substances obtained by chemical synthesis for combination with a radionuclide.

Where a chemical precursor not described in an individual monograph of the European Pharmacopoeia is used in a radiopharmaceutical preparation prepared for the special needs of individual patients, the need for compliance with this general monograph is decided in the light of a risk assessment.

This risk assessment takes account of:
Ph. Eur. – General organisation

Introduction
General notices
General chapters
General monographs
Individual monographs

More than 2500 monographs
- Chemicals
- Herbals
- Antibiotics
- Biologicals
- Vaccines
- Fats
- Radiopharmaceuticals
- ....
Elaboration of monographs (1):

- Ideally monographs cover the preparations used all over Europe, produced by different routes of synthesis.

- Individual routes are not explicitly mentioned in a monograph, but a hint to the routes examined during the elaboration might be given in the knowledge database.

- Knowledge about the routes of synthesis, starting materials, intermediates, by-products, degradants (potential impurities/efficiency of the purification procedure) is needed.

=> Input from producers is crucial
Elaboration of monographs (2)

Preparation having a marketing authorisation

- Specifications and tests are based upon those of the marketed preparations.
- But specifications can be different, in case batch data support this and if there is no objection from e.g. efficacy or (radio)toxicological side.
- Validation data are examined. Methods are validated in case of changes.
- Methods are experimentally verified.

Preparation without a marketing authorisation

Note: it is exceptional that monographs are elaborated on substances/preparations not already authorised in at least one Ph. Eur. member state.

- Elaboration often „from scratch“.
- Methods are developed and validated.
- Limits are based upon efficacy, toxicology considerations and analytical method capabilities and supported by batch data.
- Methods are verified in a second laboratory.
Basis for limit setting

- Authorised specifications
- Batch data of frequently used preparations
- Toxicology data
- Efficacy data
- Analytical method capabilities

**Quality systems.** The quality standards represented by monographs are valid only where the articles in question are produced within the **framework of a suitable quality system.** The quality system must assure that the articles **consistently** meet the requirements of the Pharmacopoeia.
Example for limits: Alovudine (18F) injection

**Limits:** in the chromatogram obtained with the spectrophotometer:

- **alovudine:** not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 mg/V);

- **impurity C:** not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 mg/V);

- **any other impurity:** for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 mg/V);

- **total:** not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 mg/V);

- **disregard limit:** 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 mg/V).

**Pass/fail decision**
Participating in the work of the European Pharmacopoeia

Knowledge Database

Knowledge database: new version released

A new version of the Knowledge Database has been released: please read the instructions given under "How to read this table" immediately underneath the information displayed for the monograph. The new feature provides detailed information on work on-going either for a new monograph under elaboration or for a published monograph under revision with a view to being more transparent to our users. This will also allow Ph.Eur users to contribute to the work of the European Pharmacopoeia more easily.

▶ “How to read this table”

Search Database online

https://www.edqm.eu/Knowledge-Database-707.html
Participating in the work of the European Pharmacopoeia

<table>
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<td>Al洛vudine (18F) injection</td>
<td>2793</td>
<td>Fluorocholine (18F) injection</td>
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<td>Fluclidovine (18F) injection</td>
<td>1918</td>
<td>Fluorodopa (18F) (prepared by electrophilic substitution) injection</td>
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<td>2466</td>
<td>Fluoroethyl-L-tyrosine (18F) injection</td>
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<td>2481</td>
<td>Fluoro-L-dopa (18F) (prepared by nucleophilic substitution) injection</td>
<td>2100</td>
<td>Sodium fluoride (18F)</td>
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</table>
Knowledge database: example of additional information

**FLUOROCHOLINE \(^{18}\text{F}\) INJECTION (2793)**

The radionuclide fluoride-18 is most commonly produced by proton irradiation of water enriched in oxygen-18.

\(^{18}\text{F}\)Fluorocholine may be produced by nucleophilic substitution of dibromomethane with fluoride yielding bromo[\(^{18}\text{F}\)fluoro]methane which is then used for \(N\)-alkylation of dimethylaminoethanol.

Generally, \(^{18}\text{F}\)fluoride is adsorbed on an anion-exchange resin and eluted with a solution of potassium carbonate, which is then evaporated to dryness. Addition of a phase-transfer catalyst, such as an aminopolyether or a tetra-alkyl ammonium salt in dry acetonitrile, may be used to enhance the nucleophilicity of the \(^{18}\text{F}\)fluoride so that it reacts easily with dibromomethane at elevated temperatures. The subsequent reaction with dimethylaminoethanol can be performed in solvents such as DMSO or without solvents, or by passing bromo[\(^{18}\text{F}\)fluoro]methane over a solid phase extraction column (SepPak C18) on which dimethylaminoethanol or a solution of dimethylaminoethanol and DMSO is adsorbed.

The preparation can be purified by liquid chromatography or by trapping the product on a cation-exchange cartridge (SepPak CM) followed by elution with saline.

The substance fluoroethyl(2-hydroxyethyl)dimethylammonium chloride may be referred to in other sources as fluoromethylcholine or fluoroethylcholine; to avoid confusion it has been decided not to use either of these names in the European Pharmacopoeia.
**Contributions depend on state of work**

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<th>Description</th>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<td>Draft adopted by the Ph.Eur. Commission</td>
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<tr>
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<td>Monograph is published</td>
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http://pharmeuropa.edqm.eu/home/
Thank you very much!