European Pharmacopoeia

New monographs and chapters in the European Pharmacopoeia

European Pharmacopoeia Organisation

- The European Pharmacopoeia contains a large number of monographs, among them about 70 on radiolabelled radio-pharmaceuticals and radioactive precursors and 5 on non-radioactive precursors for radiosynthesis.
- Dr. Ellen Pel has presented on how to use and how to contribute to the European Pharmacopoeia.
- The European Pharmacopoeia has currently three groups working in the area of radiopharmaceuticals:
  - Expert Group 14 (Radioactive Compounds)
  - PRP working Party (Precursors for radiopharmaceutical preparations)
  - CRP working Party (Production and compounding of radiopharmaceutical preparations)

MONOGRAPHS

New/changed monographs published since 2014 (Ed 8.2)

Fludeoxyglucose (^{18}F) injection

A correction was made to the test for chemical purity to have a better system suitability test

Technetium (^{99m}Tc) etifenin injection

The biodistribution test was deleted as an improved identity and RCP test was introduced which is in line with the 3R policy (Replacement, Reduction and Refinement of animal testing).

Fluoroethyl-l-tyrosine (^{18}F) injection

New monograph

Copper tetramibi tetrafluoroborate for radiopharmaceutical preparations

New monograph

New/changed monographs published since 2014 (Ed 8.2)

Technetium (^{99m}Tc) medronate injection

The biodistribution test was deleted as an improved identity test was introduced. Also the limit for Sn was expressed per V. A kit for the determination of Sn was introduced

Gallium (^{68}Ga) edotreotide injection

A correction was made to the amount of sample to be applied for the test for HEPES

Technetium (^{99m}Tc) oxidronate injection

New Monograph

5.19. Extemporaneous preparation of radiopharmaceuticals

This is a guidance monograph (not binding) on the preparation of radiopharmaceuticals in a hospital/radiopharmacy environment

New/changed monographs published since 2014 (Ed 8.2)

Pentetate sodium calcium for radiopharmaceutical preparations

updated to include a 'variable quantity of water' according to current Ph. Eur. policy on hydrates.

Fluorocholine (^{18}F) injection

The monograph has been published in Ed 8.8 of the European Pharmacopoeia. Bur the monograph is under review in order to verify the necessity of inclusion of further impurities, e.g. bromocholine

Chemical precursors for radiopharmaceutical preparations

to be discussed later

Work in Progress on Radiopharmaceutical Monographs

Lutetium (^{177}Lu) solution for radiolabelling

Comments on the draft have been discussed during the Group 14 meeting preceding this symposium. A final draft will be made to be submitted to the commission

Sodium pertechnetate (^{99m}Tc) injection (cyclotron-produced)

Comments on the draft have been discussed during the Group 14 meeting preceding this symposium. A final draft will be made to be submitted to the commission

Yttrium (^{90}Y) solution for radiolabelling

The draft of this monograph will soon be published in Pharmeuropa and will be open for comments

Choline (N-$^{11}C_1$) Injection

The monograph has been published in Pharmeuropa and was open for comments until March 31st 2016

Work in Progress on Radiopharmaceutical Monographs

Fluoro-L-dopa (^{18}F) (prepared by nucleophilic substitution) injection

A start has been made with drafting the monograph. A complicating factor is the many different synthetic pathways used by producers.

Fluciclovine (^{18}F) injection

The latest draft was discussed at the recent meeting of Group 14. It is expected to be published in Pharmeuropa 29.4 (October 2016).

Technetium (^{99m}Tc) succimer injection

Investigation to replace the biodistribution test

Monographs for Precursors for Radiopharmaceutical preparations

Challenges and considerations

- **Impossible to have soon a Ph. Eur. monograph for each currently used precursor**

Therefore ***General Monograph "Chemical Precursors for Radiopharmaceutical Preparations"*** has been finalized in order to provide a self-contained guidance in terms of quality criteria for these precursor substances, taking into account how they are intended to be used

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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:

- the quality of the chemical precursor and the information available for quality evaluation;
- any further processing after radiolabelling (which may or may not include purification before administration to the patient);
- the amount used to prepare a patient dose (e.g. diagnostic

Specific thresholds may be applied for impurities known to be unusually potent or to produce toxic or unacceptable pharmacological effects.

If the individual monograph does not provide suitable control for a new impurity, a suitable test for control must be developed and included in the specification for the substance.

Residual solvents. Residual solvents are limited according to the principles defined in chapter *5.4* using general method *2.4.24* or another suitable method.

Class 1 solvents must not be employed in the final step of the manufacturing process of chemical precursors. If the use of a Class 1 solvent in an earlier step in the production process is unavoidable, the limits stated in chapter *5.4*, Table 1 apply.

Based on the permitted daily exposure (PDE), Class 2 and Class 3 solvents are limited to 0.5 per cent.

For Class 2 and Class 3 solvents, a test for loss on drying or a specific determination of the solvent may be carried out. If for a Class 2 or a Class 3 solvent, a justified and authorised limit greater than 0.5 per cent is prescribed, a specific determination of the solvent is required.

Metal catalysts or metal reagent residues. If the production processes of chemical precursors are known or suspected to lead to the presence of metal residues due to the use of a specific metal catalyst or metal containing reagent, the chemical precursors comply with the limit of 0.01 per cent for each of the following metals: Pt, Pd, Ir, Rh, Ru, Os, Mo,

General monograph on precursors for RP

Some particular requirements

TESTS

Related substances. Unless otherwise prescribed or justified and authorised, organic impurities in chemical precursors and inorganic impurities present in inorganic chemical precursors are to be reported, identified and controlled as follows:

Reporting threshold	0.2 per cent
Identification threshold	2.0 per cent
Total unspecified impurities	maximum 3.0 per cent

It is seen that the requirements for precursors for radiopharmaceutical use are more relaxed than those for 'substances for pharmaceutical use'.

General monograph on precursors for RP

Some particular requirements

Metal catalysts or metal reagent residues. If the production processes of chemical precursors are known or suspected to lead to the presence of metal residues due to the use of a specific metal catalyst or metal containing reagent, the chemical precursors comply with the limit of 0.01 per cent for each of the following metals: Pt, Pd, Ir, Rh, Ru, Os, Mo, Ni, Cr, V, Pb, Hg, Cd and Tl, unless stricter limits are stated in an individual monograph.

The methodology described in general chapter *2.4.20. Determination of metal catalyst or metal reagent residues* is to be applied wherever possible.

General monograph on precursors for RP

Some particular requirements

Microbial contamination

TAMC: acceptance criterion 10^3 CFU per gram for bulk material or maximum 10^2 CFU per container for chemical precursors packed in single and multidose containers (*2.6.12*).

TYMC: acceptance criterion 10^2 CFU per gram for bulk material or maximum 10^1 CFU per container for chemical precursors packed in single-dose and multidose containers (*2.6.12*).

Bacterial endotoxins (*2.6.14*). Unless otherwise justified and authorised, bacterial endotoxins are limited to a maximum 100 IU per gram for bulk material or maximum 10 IU per container for chemical precursors packed in single-dose and multidose containers.

These requirements are not repeated in individual monographs!

THE FUTURE

Work program:

Indium (^{111}In) Pentetreotide, Fluoro-L-dopa (^{18}F) (prepared by nucleophilic substitution) injection, Yttrium (^{90}Y) Edotreotide, replacement of the TBA test in fluorine-18 monographs, Betiatide (S-benzoyl-MAG3), Succimer (DMSA), Sodium pyrophosphate, ^{68}Ga-PMSA

Potentially:

- PSMA-11 and PSMA-617
- ^{68}Ga produced by cyclotron

Your input is valuable: what monographs do YOU need? Please let us know!

How can you help us making better monographs?

1) If you are a manufacturer or compound for your own use any of the products that we are working on, please let us know so we can invite you to work with Group 14/PRP group to elaborate the monographs and do experimental verification
2) Provide your comments on the drafts published in Pharmeuropa Online, freely available on line: http://pharmeuropa.edqm.eu/home/

THANK YOU