Guidance document
Maintenance and updating of Annex 1

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1 Terms, definitions, abbreviations

1.1 Definitions and terms

1.1.1 Radiopharmaceuticals

Radiopharmaceuticals are medicinal products containing radionuclides whose radiation is used for diagnostic (radiodiagnostic agents) or therapeutic (radiotherapeutic agents) purposes. Annex 1 of the Radiological Protection Ordinance (RPO) defines radiopharmaceuticals based on the Ph. Eur. *General Monograph on Radiopharmaceuticals,* such that the immediate non-radioactive and radioactive precursors are considered to be radiopharmaceutical preparations.

1.1.2 Formula-related radiopharmaceuticals

Formula-related radiopharmaceuticals are radiopharmaceuticals that may be prepared for own use without authorisation in accordance with Art. 9 TPA. They are subject to certain preconditions and restrictions. In view of their properties, radiopharmaceuticals are predominantly prepared according to a *magistral formula*. Formula-related radiopharmaceuticals are not dispensed to patients or their carers, but administered to patients in hospital under the responsibility of a specialist in nuclear medicine.

1.1.3 Active substances for formula-related radiopharmaceuticals according to Annex 1 TPO

Art. 37 para. 1, let. e TPO specifies the legal basis for establishing additional active substances for formula-related radiopharmaceuticals that do not satisfy the criteria of lets. a and d. While a Ph. Eur. monograph does not (yet) exist for these active substances at the time of inclusion in the list, their safety and quality has been confirmed in a review procedure, and the clinical data confirm considerable benefit compared to established treatments in treating life-threatening illnesses.

1.1.4 Good Manufacturing Practice for radiopharmaceuticals in small quantities

In Switzerland, the rules of Good Manufacturing Practice apply to the preparation of formula-related medicinal products in small quantities (section 20 of Pharmacopoea Helvetica).
In 2019, a supplementary subsection, 20.3, comes into force for radiopharmaceuticals. Together with sections 20.1 and 20.2, this is binding for all radiopharmaceuticals prepared on the basis of Annex 1.

1.1.5 Expert Commission for Radiopharmaceuticals (ECRP)

The ECRP advises Swissmedic, the Swiss Agency for Therapeutic Products, and the Federal Office of Public Health (FOPH) on radiopharmaceutical matters. The non-parliamentary commission consists of specialists from the scientific fields of nuclear medicine, pharmaceutics, chemistry and radiological protection. The Federal Council appoints the ECRP members on the basis of proposals submitted by the Federal Department of Home Affairs (FDHA). According to Art. 79 TPO, its remit also includes advising on the updating of Annex 1 TPO.

1.1.6 Hospital-based radiopharmaceutical facility

According to Art. 38 TPO, a hospital-based radiopharmaceutical facility for the preparation of radiopharmaceuticals according to Art. 9 para. 2 lets. a–c_{bis} and para. 2_{bis} TPA is considered to be a hospital pharmacy as defined in Art. 4 para. 1 let. j TPA. This applies only if the radiopharmaceutical facility is part of the hospital. A facility that is not part of a Swiss hospital can prepare formula-related medicinal products only if contracted to do so by a hospital pharmacy.

1.2 Abbreviations

ECRP	Expert Commission for Radiopharmaceuticals
FDHA	Federal Department of Home Affairs
FOPH	Federal Office of Public Health
GMP	Good Manufacturing Practice
Ph. Eur.	European Pharmacopoeia
Ph. Helv.	Pharmacopoeia Helvetica
RPA	Radiological Protection Act of 22 March 1991(SR 814.50)
RPO	Radiological Protection Ordinance of 26 April 2017 (SR 814.501)
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, SR 812.21)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (Therapeutic Products Ordinance) (SR 812.212.21)

2 Introduction

This guidance document describes the rules and procedures for maintaining and updating Annex 1 of TPO, in particular the list of active substances, restrictions on use and quality requirements (para. 3 of Annex 1 TPO, subsequently referred to as the *list*).

2.1 Legal framework

- **TPA**
  Art. 9 para. 2 let. a-c^{bis}, 2bis and 2ter, Medicinal products for which authorisation is not required
- **TPO**
  Art. 35 Dispensing restrictions
  Art. 36 Quantitative restrictions
  Art. 37 Permitted active substances (especially let. e)
  Art. 38 Radiopharmaceuticals
  Art. 79 Updating of annexes (especially para. 3)
  Ann. 1 Permitted active substances for the preparation of radiopharmaceuticals according to Art. 9 para. 2 lets. a-c$_{bis}$ and para. 2$_{bis}$ TPA
- **TPLRO**
  Art. 3 Documentation of analytical, chemical and pharmaceutical investigations
  Art. 12ff. Information and texts on containers and packaging materials

<u>Radiological protection</u>

- **RPA**
  Art. 15 Medical radiation applications
  Art. 28ff. Mandatory licensing

- **RPO**
  Art. 46 Placing on the market and use of radiopharmaceuticals
  Art. 47 Preparation and quality control
  Art. 48 Expert Commission for Radiopharmaceuticals

Ann. 1 Determination of technical terms

3 Objective

As this is a guidance document aimed at administrative bodies, it does not directly specify the rights and obligations of private individuals. The Radiation Protection Division of the Federal Office of Public Health (FOPH), the Expert Commission for Radiopharmaceuticals (ECRP) and the Authorisation Division at Swissmedic use this document first and foremost as a resource for applying the legal provisions relating to amendments to the list in a uniform and equitable manner. For third parties, the publication of the guidance document is intended to clarify the specific requirements that must be fulfilled for maintaining and updating the list according to the practice of the FOPH, ECRP and Swissmedic.

4 Scope

The guidance document applies to the maintenance and updating of Annex 1 of the TPO for radiopharmaceuticals.

5 Description

5.1 Annex 1 TPO: Principles and criteria

The principles and criteria for permitted active substances for the preparation of radiopharmaceuticals (diagnostic and therapeutic agents) are stated in paras. 1 and 2, respectively, of Annex 1 TPO.

a) **Active substances:** The active substances listed in section 3 of Annex 1 TPO may be used for preparing and using radiopharmaceuticals according to Art. 37 let. e TPO. The restrictions on use and quality requirements specified therein should be taken into account.
b) **Preparation documentation:** Documentation that satisfies the requirements of section 4 of Annex 1 should be produced for the preparation of a radiopharmaceutical according to Annex 1 TPO.
c) **Instructions for use:** Instructions for use should be produced and approved by the hospital's responsible nuclear medicine specialist for each preparation prepared according to Annex 1 TPO.
d) **Criteria:** The active substances are included in this Annex 1 TPO on the basis of the latest scientific findings, particularly on the basis of the available data on quality, safety and efficacy.

5.2 Updating Annex 1 TPO

The Ordinance gives the FDHA the option to update Annex 1 TPO and to receive corresponding advice from the ECRP. The FDHA office responsible for this task is the FOPH. However, since the secretariat of the ECRP is managed by Swissmedic, this guidance document is valid for several offices.

5.2.1 Updating the list according to section 3 of Annex 1 TPO

On behalf of the FDHA, the FOPH ensures that the list according to section 3 of Annex 1 TPO (Active substances, restrictions on use and quality requirements) accords with the latest scientific and technical findings. After receiving advice from the ECRP, the FOPH proposes amendments to the FDHA, particularly on the restrictions on use and the quality requirements, when this is necessitated by new data on quality, safety and efficacy. Active substances for which a Ph. Eur. has been issued are deleted from the list.

5.2.2 Application for the inclusion of a new active substance in the list according to section 3 of Annex 1 TPO

Expert groups can submit applications for the inclusion of a new active substance in the list. The ECRP and the FOPH review the applications and forward their recommendation to the FDHA.

5.2.2.1 Documentation requirements

Applications can be submitted informally (without forms but with a covering letter). The accompanying documentation must demonstrate that the criteria stated in para. 2 of Annex 1 TPO are met.
If helpful, it is recommended to submit the documentation in the CTD format for Module 2. Summaries of the data situation are expected for the clinical and preclinical parts. The underlying data, reports and publications must be made available in annexes.
The quality part can also be submitted in the form of preparation documentation according to para. 4 of Annex 1 TPO so that subsequent reformatting is not required. In this case the validation of the test methods should be described as part of the validation of the manufacturing process.

5.2.2.2 Application submission

An application to amend the list should be submitted to Swissmedic, Authorisation Division. Swissmedic forwards the application to the FOPH and ECRP.
It is possible to submit a query initially in order to clarify whether a new active substance is appropriate for inclusion in Annex 1 TPO. Any available preclinical and clinical data and a justification with a benefit-risk assessment can be submitted for this purpose. In the event of a positive assessment by the ECRP, the quality part and the instructions for use can then be submitted.

5.2.2.3 Review

The submitted documentation is reviewed by the ECRP and FOPH in respect of safety, efficacy and quality, taking radiological protection into account.
The reviewers can request further documents in connection with a List of Questions. The Authorisation Division at Swissmedic will manage the correspondence.

5.2.3 Time limits

No time limits apply to the processing of applications for modification of Annex 1 TPO.

5.2.4 Fees

No fees are charged for the processing of applications for modification of Annex 1 TPO.

Change history

Version	Change	sig
1.2	New layout, no content adjustments to the previous version.	dei
1.1	Formal adjustments to the header and footer No content adjustments to the previous version.	dei
1.0	Implementation of TPO4	fua