swissmedic

Guidance document
Authorisation radiopharmaceutical

Identification number:	ZL000_00_034
Version:	2.1
Valid from:	24.05.2023

List of contents

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 or therapeutic purposes. As a result of their radioactive labelling, they can be detected externally with suitable measuring devices (radiodiagnostic agents) or, in certain organs, produce a therapeutically desired radiation effect (radiotherapeutic agents).

Annex 1 of the Radiological Protection Ordinance (RPO, Art.4) defines radiopharmaceuticals as follows:

For the purposes of this ordinance, the following are considered to be radiopharmaceuticals:

- medicinal products containing one or more radionuclides in a form which can be directly used in medicine (**ready-to-use radiopharmaceuticals**, e.g. ^{131}I capsules);
- non-radioactive components (kits) used to produce radiopharmaceuticals by reconstitution of, or combination with, radionuclides immediately prior to use in humans (**labelling kits**, e.g. peptide for labelling, tumour scintigraphy);
- radionuclide generators with a fixed parent radionuclide producing a daughter radionuclide which is removed by elution or by any other method and used in a radiopharmaceutical (**generators**, e.g. column with ^{99}Mo, from which ^{99m}Tc is eluted);
- radionuclides used directly or as precursors for the radiolabelling of other substances (carrier compounds, cells, plasma proteins) prior to their administration (**precursors**, labelling solution) (e.g. ^{90}Y solution for the labelling of ligands).

A distinction should be made, both for radiodiagnostic and radiotherapeutic agents, between pure isotopes (e.g. ^{131}I from various sources) and combinations of partially patent-protected molecules ("cold" part) with isotopes/radionuclides.

1.1.2 Radiodiagnostic agents

Radiodiagnostic agents (RD) are radiopharmaceuticals used as in-vivo diagnostic agents to detect diseases. They are used, for example, in scintigraphy, single photon emission computed tomography (SPECT) and in positron emission tomography (PET) in connection with morphological and/or functional investigations.

1.1.3 Radiotherapeutic agents

Radiotherapeutic agents (RT) are radiopharmaceuticals that are used to treat diseases. Systemic administration (usually intravenously) ensures that the radiotherapeutic agent is distributed throughout the body so that, for example, tumour metastases in various sites can be reached. In this procedure, coupling the radionuclide to specific ligands (antibodies, peptides, amino acids) causes the radiotherapeutic agent to bind strongly to certain tumours (e.g. neuroendocrine tumours). This allows the tumour itself and any metastases to be irradiated in a targeted manner with relatively few side effects.

1.1.4 Radiopharmaceuticals with increased hazard potential

According to Annex 1 of the RPO, these are radiolabelling kits for therapeutic purposes, radiodiagnostic agents for PET and radiopharmaceuticals produced in-house (with or without kits). The preparation and synthesis of such radiopharmaceuticals requires considerable technical effort. They must be prepared under the direction of a Responsible Person who satisfies the professional requirements set out in Art. 6 letter d of the Ordinance on Licensing in the Medicinal Products Sector (MPLO) or who has completed equivalent training. This means that they must possess a Certificate in Radiopharmacy issued by the European Association of Nuclear Medicine (EANM), as well as the necessary experience.

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. This extra-parliamentary commission prepares expert reports on applications for the authorisation of radiopharmaceuticals and safety-related questions connected with radiopharmaceuticals. The ECRP is comprised 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). The ECRP must be consulted on authorisation procedures for radiopharmaceuticals (Art. 48 RPO). Their recommendation also forms the basis for the consent of the FOPH on compliance with the requirements of radiological protection legislation.

1.2 Abbreviations

AR	Assessment Report
CA	Clinical Assessment
cGRPP	current Good Radiopharmacy Practice
CTD	Common Technical Document for the Registration of Pharmaceuticals for Human Use
DMF	Drug Master File
EANM	European Association of Nuclear Medicine
ECRP	Expert Commission for Radiopharmaceuticals
FDHA	Federal Department of Home Affairs
FOPH	Federal Office of Public Health
FeeO-Swissmedic	Ordinance on the Fees charged by the Swiss Agency for Therapeutic Products of 14 September 2018 (SR 812.214.5)
GMP	Good Manufacturing Practice
HMP	Human Medicinal Products

HD	Hilfsdokument = support document
HMEC	Human Medicines Expert Committee
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRP	International Commission on Radiological Protection
KAS	Known Active Substances
MPLO	Ordinance of 14 November 2018 Licensing in the Medicinal Products Sector (SR 812.212.1)
NAS	New Active Substance
NCA	Nonclinical Assessment
NTA	Notice to Applicants
ODS	Orphan Drug Status
PBRER	Periodic Benefit-Risk Evaluation Report
PET	Positron Emission Tomography
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PMS	Post Marketing Surveillance
PSUR	Periodic Safety Update Report
QA	Quality Assessment
RA	Regulatory Assessment
RD	Radiodiagnostic agent
RT	Radiotherapeutic agent
RPA	Radiological Protection Act of 22 March 1991(SR 814.50)
RPO	Radiological Protection Ordinance of 26 April 2017 (SR 814.501)
SPECT	Single Photon Emission Computed Tomography
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TPLO	Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 on the Simplified Licensing of Therapeutic Products and the Licensing of Therapeutic Products by the Notification Procedure (SR 812.212.23)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)
UraM	FDHA Ordinance of 26 April 2017 on the handling of radioactive material (SR 814.554)
WEU	Well Established Use

2 Introduction

Radiopharmaceuticals (radiodiagnostic agents and radiotherapeutic agents) are radioactive when administered to patients. They are therefore covered by both medicinal products and radiological protection legislation.
Under Art. 9 para. 1 TPA, radiopharmaceuticals distributed in Switzerland must be authorised by Swissmedic. This does not apply to radiopharmaceuticals that satisfy the criteria for "formula-related medicinal products" and are thus exempt from authorisation (Art. 9 para. 2 a-c^{bis} TPA in conjunction with Art. 37 e TPO)[1] or radiopharmaceuticals used in the course of clinical trials (Art. 9 para. 2 d TPA).

2.1 Legal framework

Medicinal products

- TPA
  Art. 10 Conditions for granting a marketing authorisation
  Art. 13 Medicinal products and procedures authorised in foreign countries[2]
  Art. 14 Simplified authorisation procedure
- TPLRO
  Art. 3 Documentation of analytical, chemical and pharmaceutical investigations
  Art. 12ff. Information and texts on containers and packaging materials
- TPLO
  Art. 4ff. Recognition of the status of an important medicinal product for rare diseases
  Art. 12ff. Simplified authorisation of medicinal products with known active substances
  Art. 24ff. Simplified authorisation of important medicinal products for rare diseases
  Art. 27a Simplified authorisation of radiopharmaceuticals and antidotes in general medical use

Radiological protection

- 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 of radiopharmaceuticals[3]
  Art. 48 Expert Commission for Radiopharmaceuticals
  Annex 1 Definition of technical terms
  Annex 8 Designation of control and monitoring areas
- UraM

Art. 50ff. Protection of patients

[1] In practice, radiopharmaceuticals that are not subject to authorisation almost exclusively involve radionuclides with very short half lives (in the order of minutes) that can be produced and used in centres with a cyclotron and satisfy the criteria for a formula-related medicinal product according to Art. 9 para. 2 TPA in conjunction with Art. 37 e TPO. This guidance document does not cover formula-related medicinal products.
[2] See also guidance document *Authorisation of human medicinal products under Art. 13 TPA HMV4*
[3] See *EANM Guidelines on Good Radiopharmacy Practice (cGRPP) in the Preparation on Radiopharmaceuticals*

3 Objective

This guidance document sets out the specific requirements relating to the authorisation of radiopharmaceuticals in Switzerland. It is aimed primarily at administrative bodies. Swissmedic uses this guidance document first and foremost as a resource for applying the legal provisions in a uniform and equitable manner. For applicants, the document is intended to clarify the specific requirements that must be fulfilled so that corresponding authorisation applications can be processed as quickly and efficiently as possible. Deviations are permitted if the applicants propose equivalent alternatives. Swissmedic, the ECRP and, for radiotherapeutic agents, the Human Medicines Expert Committee (HMEC) as well, evaluate the application documents in the context of this guidance document subject to the latest findings in science and technology and the latest versions of the pharmacopoeia and relevant guidelines (ICH[4], EANM[5] etc.).
Everything connected with radiological protection is dealt with in other documents issued by the Federal Office of Public Health (FOPH)[6] and is not addressed any further in this guidance document . However, the authorisation documentation must take account of radiological protection issues.

4 Scope

This guidance document is valid for the Authorisation division of Swissmedic and is applicable to human medicinal products (HMP).

5 Description

5.1 Principles of review and general requirements

5.1.1 Principles of review

The applicant must have a registered address or registered office in Switzerland and possess the required operating licences issued by Swissmedic (see Art. 10 TPA) and the FOPH (see Art. 28 RPA).

Radiopharmaceuticals may only be placed on the market or used on humans if they have been authorised by Swissmedic with the consent of the FOPH (see Art. 9 para. 1 TPA and Art. 30 RPO, exceptions are mentioned in section 2). To this end, the authorisation application and corresponding documentation are submitted to Swissmedic.

The authorisation documentation is reviewed by Swissmedic, the ECRP and, for radiotherapeutic agents, by members of the HMEC as well. For both radiodiagnostic and radiotherapeutic agents, Swissmedic takes the final decision (with the approval of the FOPH). The ECRP serves as an advisory body and the HMEC can issue recommendations.

The Regulatory (RA) department at Swissmedic is responsible for the coordination, planning and correspondence for all applications for the authorisation and modification of radiopharmaceuticals and draws up the regulatory evaluation report.

[4] www.ich.org
[5] www.eanm.org
[6] Radiological Protection Act, FOPH Radiation, radioactivity and sound

Applications for the authorisation, authorisation extension and modification (major variations, type II) of **radiodiagnostic agents** are usually reviewed by members of the ECRP, which also draws up the assessment reports (AR). The assessors at Swissmedic (QA, NCA and CA) verify the plausibility of the result of the ECRP's review and carry out a regulatory review of the applications.

When dealing with applications for the authorisation and modification of **radiotherapeutic agents** the ECRP focuses its review on the properties of the radionuclide, particularly the radiological protection aspects, dosimetry and quality documentation of the preparation, and advises Swissmedic in the decision-making process. The assessors at Swissmedic draw up the AR for these applications. The AR for radiological protection is supplemented by ECRP members. The HMEC formulates its assessment of the efficacy and safety and the risk/benefit ratio of the radiotherapeutic agent in the form of a recommendation.

5.1.2 Innovative radiopharmaceuticals (radiodiagnostic and radiotherapeutic agents)

Medicinal products with new radiodiagnostic or radiotherapeutic substances (e.g. new radioisotopes, new synthetically produced peptides, new combinations of ligands and nuclides) and biotech radiopharmaceuticals are considered to be medicinal products with new active substances (NAS). They require full documentation in CTD format (see Annex 9.3 *Authorisation documentation for radiopharmaceuticals with new active substance (NAS)*).
Swissmedic advises applicants with innovative radiopharmaceuticals to obtain scientific advice and arrange a presubmission meeting before submitting their application. This advice does not, however, prejudice the document review or the final authorisation decision, which can only be reached on the basis of the available data (study results).
For innovative **radiodiagnostic agents** which do not produce a pharmacodynamic effect in the body at the administered dosage because of the small quantities involved, simplifications based on a justified risk analysis prepared by the applicant in consultation with Swissmedic are possible. These usually involve a single administration of a short-lived isotope.
The efficacy and safety of **radiotherapeutic agents** in the indications requested in the application must be demonstrated on the basis of comparative, randomised clinical trials.
For certain preparation categories (e.g. orphan drugs), the required data volume can be reduced provided a positive risk/benefit ratio can be demonstrated for the use in question.

5.1.3 Radiodiagnostic agents

The quantity of radiolabelled carrier molecules used in the administration of RD is very low and no pharmacodynamic effect is generally expected. Since radiodiagnostic agents tend not to be administered more than once, the associated toxicity and radiation doses are low, and negative long-term effects are not generally expected. However, adverse drug reactions such as hypersensitivity reactions, which can occur even at low concentrations, should be taken into consideration.
Generally speaking, quality documentation, data on biosafety and the hypersensitivity / sensitisation potential (safety), as well as the results of imaging procedures (criterion of diagnostic efficacy) are sufficient. If a specific diagnosis is to be made indirectly with a radiodiagnostic agent, the sensitivity and specificity of the method and the validity of the diagnosis compared to established standard procedures should be determined. This includes statistical analyses of diagnostic efficiency (e.g. to support medical decisions by correct staging, etc.).
For preparations with nuclides containing carriers,[7] the potential acute toxicity of the element must be evaluated on the basis of appropriate toxicological and clinical data.

5.1.4 Simplified authorisation of radiopharmaceuticals

Simplifications involve an easing of the documentation requirements for data from pharmacological, toxicological and clinical investigations (complete documentation on quality is always required).

Reduced requirements relating to the volume of preclinical and clinical data apply to the radiopharmaceuticals (RD and RT) described in sections 6.4.1 to 6.4.4 and are summarised in the following table. Additional data may need to be requested if something is not clear.

Simplified authorisation	Type	Documentation requirements	
		Preclinical	Clinical
WEU (5.4.1)	RD	Literature data	Images from the target population
	RT	Literature data	Literature data, dosimetry
Authorised in a foreign country (5.4.2)	RD	Preclinical data from the foreign authorisation documentation	Clinical data from the foreign authorisation documentation Images from the target population
	RT	Preclinical data from the foreign authorisation documentation	Clinical data from the foreign authorisation documentation Images from a representative patient population
KAS (5.4.3)	RD	Literature data on biodistribution, if the quality of the RD is not comparable	Results of imaging procedures
	RT	Literature data on biodistribution, if the quality of the RT is not comparable	Clinical trials on therapeutic equivalence with the reference medicinal product Observational studies with a limited number of patients
ODS (5.4.4)	RD	No simplification[8]	Images from the target population Limited data availability due to the rarity of the disease is taken into account
	RT	No simplification[8]	Phase 1 to 3 trials Limited data availability due to the rarity of the disease is taken into account

Table 1: Required preclinical and clinical data for the corresponding simplified authorisation.

[7] Carrier corresponds to an excess of the "cold" nuclide of the element concerned
[8] The ODS does not usually affect preclinical development.

5.1.4.1 Radiopharmaceuticals with active substances that have been used for at least 10 years (Well Established Use, WEU)

Under Art. 27a para. 1 TPLO, radiopharmaceuticals which contain an active substance that is not contained in any other medicinal product authorised by Swissmedic can be authorised in a simplified procedure. This applies provided the active substance has been used for the requested indication and administration route in Switzerland and/or a foreign country for at least 10 years, and its safety and efficacy is generally acknowledged on the basis of accumulated experience in use (Art. 27a para. 1 a TPLO) and if the preparation is, or was, authorised for the requested indication and administration route in a country with a comparable regulatory system for medicinal products, or if the preparation has been approved by the competent foreign authority or by Swissmedic for the treatment of specific patients (Art. 27a para. 1 b TPLO). A list of such active substances will be drawn up by Swissmedic in conjunction with the ECRP (see Annex 9.2 *"Well Established Use" active substances for Radiopharmaceuticals*) and published.
Radiodiagnostic agents with established active substances listed in Annex 9.2 *"Well Established Use" active substances for radiopharmaceuticals* can be authorised in the simplified procedure for the stated indications. These simplifications involve a reduction in the required literature data for the preclinical section and images from the target population with the notified preparation for the clinical section.
Only in exceptional cases may **radiotherapeutic agents** with active substances not yet authorised in Switzerland be considered as preparations with "well established use" active substances and thus qualify for the simplified authorisation procedure (e.g.: ^{32}P-sodium phosphate in polycythaemia vera). Applicants are advised to obtain scientific advice from Swissmedic before submitting their application. Otherwise, the requirements stated in section 6.2 *Innovative radiopharmaceuticals (radiodiagnostic and radiotherapeutic agents)* apply.

5.1.4.2 Radiopharmaceuticals authorised in foreign countries

For radiopharmaceuticals that are already authorised in foreign countries, the provisions of the guidance document *Authorisation of human medicinal products under Art. 13 TPA HMG4* with the corresponding legal articles apply.
In view of the provisions on radiological protection and the obligation to consult the ECRP, radiopharmaceuticals always undergo a separate review by Swissmedic. This may also mean that Swissmedic will request data that is not required in the foreign country (e.g. results of imaging procedures or clinical trials with the relevant preparation).

5.1.4.3 Radiopharmaceuticals with known active substances (KAS with/without innovation)

Simplified authorisation is also occasionally possible if a comparable preparation is already authorised in Switzerland and its protection period has expired or its authorisation holder has explicitly consented to the referral to its authorisation documentation (Art. 12 TPA). In such cases, an essentially identical preparation can be authorised with reduced application documentation (Art. 14 para. 1 a TPA and Art. 12ff. TPLO). In evaluating the efficacy and safety of the medicinal product, Swissmedic relies indirectly on the documentation and the review of the reference medicinal product. In order to link the reference medicinal product to the preparation with a known active substance (KAS), the second applicant must submit corresponding comparative studies (bridging). In the specific case of

radiopharmaceuticals, it should be noted that even the smallest variations in quality (e.g. isotope impurities), synthesis or labelling can have far-reaching clinical consequences. It is particularly difficult to provide evidence of bioequivalence for composite molecules (radionuclide and carrier molecules). Therefore, in addition to comprehensive quality documentation, the following additional data should always be submitted for radiopharmaceuticals with known active substances:

Radiodiagnostic agents: Literature data on biodistribution (PK), if the quality is not comparable, and the results of imaging procedures (incl. data on distribution in the body, dosimetry).

Radiotherapeutic agents: Biodistribution and clinical studies of therapeutic equivalence with the reference medicinal product.

Deviations from the reference medicinal product should be documented comprehensively in respect of their effects on the quality, efficacy and safety of the preparation.

5.1.4.4 Radiopharmaceuticals with Orphan Drug Status (ODS)

Appropriate consideration is given to the rarity of the diagnosis / disease during the review of the clinical data. In particular, the limited data availability and the increased difficulty of conducting studies are taken into account. For Orphan Drugs therefore, Swissmedic also accepts, in justified cases, published results in addition to complete study reports with the notified preparation.
The ODS does not usually affect the preclinical study programme. This is the same as for an innovative preparation (cf. section 6.2).

5.1.5 Radiological protection

The authorisation documentation must demonstrate that the preparation is safe for patients and third parties and is not harmful to the environment. The corresponding precautions and dosimetry data must be included in the Information for healthcare professionals. The radiological protection aspects are reviewed by the ECRP and checked by the FOPH.

5.1.6 Document protection

Document protection for radiopharmaceuticals is granted on the basis of the same requirements as for non-radioactive medicinal products. They are regulated in the guidance document *Document protection HMV4*.

5.1.7 Product information

Radiopharmaceuticals are used exclusively by specialists in correspondingly licensed facilities and are the subject of Information for healthcare professionals (SmPC), but not a Patient Information leaflet. Information for healthcare professionals is enclosed in the packs in accordance with Art. 14 para. 2 TPLRO.
The requirements to be fulfilled by this Information for healthcare professionals are derived from the guidance document *Product information for human medicinal products HMV4*. The special features of radiopharmaceuticals are described in the related Annex 4 *Requirements for Information for*

healthcare professionals for radiopharmaceuticals. The guidelines of the umbrella organisations (e.g. EANM[9]) should also be taken into account.
The description of any use in paediatrics should take particular account of the relevance and prevalence of the claimed indications in this population. Exposure data must conform to the latest publications of the ICRP[10]. The publications of the EANM should be taken into account for administration and dosage.

5.1.8 Pharmacovigilance

Since the above-mentioned practice relating to simplified authorisation is based on a general risk assessment and since comprehensive preclinical and clinical documentation is often not available, pharmacovigilance is particularly important. Consequently, Swissmedic can make authorisation subject to special pharmacovigilance conditions.

5.2 Time limits

The time limits are based on the guidance document *Time limits for authorisation applications HMV4*.

5.3 Fees

The fees are charged at cost in accordance with the Ordinance on Fees Levied by the Swiss Agency for Therapeutic Products (FeeO-Swissmedic). Owing to the importance of radiodiagnostic agents, fees may be reduced for individual authorisation or variation applications in accordance with Art. 12 FeeO-Swissmedic.

5.4 Requirements for documents to be submitted

5.4.1 General

Complete documentation on quality is always required both for radiodiagnostic and radiotherapeutic agents, regardless of whether authorisation is requested in the ordinary or simplified procedure. The documentation of radionuclide identity and purity, radiochemical and chemical purity, stability, sterility and apyrogenicity (for injectable preparations) is a key quality-related factor for all radiopharmaceuticals.

In justified cases, Swissmedic can ease the documentation requirements for **pharmacological, toxicological and clinical studies** (simplified authorisation according to Art.14 TPA, see section 6.4).

[9] www.eanm.org
[10] www.icrp.org

5.4.2 Administrative documents (Module 1 CTD / Part I NTA)

The formal requirements for Module 1 are based on the corresponding specifications for non-radiopharmaceuticals (see guidance document *Formal requirements HMV4* in conjunction with the Directory *Overview of documents to be submitted HMV4*.). Specifics for radiopharmaceuticals are laid down in annex 9.3 *Authorisation documentation for radiopharmaceuticals with new active substance (NAS)* of this guidance document at hand as well as in chapter 3.22.1 *Radiopharmaceuticals* of the guidance document *Formal requirements HMV4*.

5.4.3 Overviews and summaries (Module 2 CTD / Part II NTA)

Preclinical: For radiopharmaceuticals, a Nonclinical Overview (Module 2.4) with a critical assessment of all the available data should be prepared by an expert in accordance with ICH M4S(R2)[11]. A summary of the experimental investigations should be presented in the corresponding Nonclinical Written/ Tabulated Summaries (Module 2.6).

Clinical: A summary assessment in the form of a Clinical Overview (Module 2.5) based on the study reports and publications of Module 5 of the CTD should be prepared. The data on the efficacy and safety of the preparation and the risk/benefit ratio compared to existing alternative diagnostic or therapeutic agents (gold standard / standard treatment) should be critically evaluated and discussed.

The most important studies should presented in tabular form in the Clinical Overview.

5.4.4 Quality (Module 3 CTD / Part II NTA)

5.4.4.1 Guidelines

In addition to the specification documents that apply generally to the compilation of the authorisation documents on quality (see guidance document *Authorisation of human medicinal product with a new active pharmaceutical ingredient HMV4* and guidance document *Variations and extensions HMV4*), the following radiopharmaceutical-specific guidelines apply:

EMA:

- Quality: see *Quality: specific types of products, Radiopharmaceuticals* und *Radiopharmaceuticals Based on Monoclonal Antibodies*

European Pharmacopoeia (Ph. Eur.):

- Methods: 01/2014:20266; 2.2.66; Detection and Measurement of Radioactivity
- General text: 01/2008:50700; 5.7 Table of physical characteristics of Radionuclides

5.4.4.2 Active substances

Details of all the manufacturing processes (for nuclides: from the target or starting nuclide to the active substance) should be provided and DMFs should be included if applicable.

[11] www.ich.org

5.4.4.3 Composition of the preparation

Ready-to-use radiopharmaceuticals:
Information on activity, specific activity, carriers[12], excipients, with details of function, purity specifications, pH, etc. should be provided.

Kits:
The information required includes precise details on the active substance and all excipients and their functions, including in connection with labelling.

Generators:
A description of the generator with illustrations, activity, purity specifications, etc. is expected.

Precursors:
Details on activity and purity specifications should be provided.

5.4.4.4 Specifications

It should be stated whether Ph. Eur. or the company's own specifications are used; an explanation is required for the latter. The specifications that are relevant for the user (radionuclide purity, radiochemical purity, specific activity, pH etc.) must be mentioned in the Information for healthcare professionals.

5.4.4.5 Administration, labelling specification and quality control

Kits:
The specifications of the nuclide, generator eluate / precursor required for labelling should be validated and stated in the Information for healthcare professionals or reference should be made to the pharmacopoeia monograph, if available.

The completely validated labelling procedure (materials and methods) should be described in full in the Information for healthcare professionals.

The quality control of kits that are labelled on site prior to administration to the patient must be validated and described in detail in the Information for healthcare professionals.

The minimum labelling yield / radiochemical purity must satisfy pharmacopoeia requirements. For kits which are not described in a pharmacopoeia, a rationale should be provided for the proposed specifications in relation to efficacy and safety.

Generators:
Generators must conform to the Ph. Eur. monograph (if available) or evidence must be provided to demonstrate that the eluate is suitable for labelling authorised kits or for direct administration. Corresponding labelling reports should be submitted.
The elution plan (with frequency of elutions) for obtaining eluates with the appropriate activity and purity should be investigated and described in detail in the Information for healthcare professionals.

[12] These involve an excess of the "cold" nuclide of the element concerned.

Precursors:
Evidence should be provided to show that the precursors are suitable for labelling authorised kits. Corresponding labelling reports should be submitted.

5.4.4.6 Radionuclide purity, radiochemical purity, chemical purity

These criteria determine patient exposure and must be specified. They must satisfy pharmacopoeia requirements or – if no monograph is available – the company's own test methods must be fully validated and the specifications justified.
The impurity spectrum affects safety, and the effect of all critical impurities (particularly long-lived impurities) should be considered. Metallic impurities can also impair the labelling of **kits**. The impurity profile for nuclides produced with fission differs from that of nuclides produced without fission.
Chemical purity must be investigated in full and in detail during the course of validation.
The radionuclide purity of "non-pharmacopoeial preparations" must be investigated, validated, specified and justified.

Additionally for **generators**:
The quality controls to be carried out by the user should be described in the Information for healthcare professionals.

Breakthrough of parent nuclide:
For generators which are not described in Ph. Eur., this parameter must be specified and the specification justified on the basis of toxicological and dosimetry data. The manufacturing process must be carefully validated in order to ensure reproducibility of quality and safety.

Presence of column material in the eluate:
This parameter must be specified and the specification justified.

5.4.4.7 Virology (incl. prions), DNA content

This information is essential for biotech radiopharmaceuticals or for radiopharmaceuticals from human blood.

5.4.4.8 Containers, syringes, accessories

Kits, generators and precursors:
In particular, possible interferences with labelling should be documented. This applies especially if substances such as plastic, metal are capable of interfering with labelling or adsorbing the active substance.

5.4.4.9 Stability

Ready-to-use radiopharmaceuticals, generators and precursors:
Particular attention should be paid to radiolysis. Furthermore, breakdown behaviour due to radiolysis should also be investigated.

Kits:
The labelling yield should be tested at regular intervals throughout the storage period.

5.4.4.10 Clinical trial preparations

If a formulation other than the preparation notified for authorisation was investigated in clinical trials, all attributes of the test preparation should be stated and the applicability of the data to the notified preparation should be demonstrated by means of bridging studies and critically discussed.

5.4.5 Preclinical (Module 4 CTD / Part III NTA)

5.4.5.1 Guidelines

In addition to the specification documents that apply generally to the compilation of the authorisation documents on preclinical data (see guidance document *Authorisation of human medicinal product with new active substance HMV4* and guidance document *Variations and extensions HMV4*), the following radiopharmaceutical-specific guidelines apply:

EMA:

- *Radiopharmaceuticals*, see www.ema.europa.eu

FDA:

- *Guidance for Industry, Non-clinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals*

5.4.5.2 Data on toxicology and pharmacology

The toxicological, pharmacokinetic (and, where relevant, pharmacodynamic) properties of the radionuclide, carrier molecule and labelled compound should be documented separately, because these involve three different entities (among other things in respect of pharmacokinetics and specificity). Absorption, distribution, metabolism and excretion (ADME) are of primary importance. For colloids, biodistribution must be investigated separately, since it directly influences safety (and also efficacy in the target organ – e.g. in connection with a synoviorthesis).
Good-quality images of scintigrams, scans and histology findings should be provided (e.g. on CDs/DVDs).

5.4.6 Clinical (Module 5 CTD / Part IV NTA)

5.4.6.1 Guidelines

In addition to the specification documents that apply generally to the compilation of the authorisation documents on clinical data (see guidance document *Authorisation of human medicinal product with a new active pharmaceutical ingredient HMV4* and guidance document *Variations and extensions HMV4*), the following radiopharmaceutical-specific guidelines apply:

EMA:

- *Radiopharmaceuticals*, see www.ema.europa.eu
- *Points to Consider on the Evaluation of Diagnostic Agents*, see www.ema.europa.eu
- *Guideline on Clinical Evaluation of Diagnostic Agents*, see www.ema.europa.eu

FDA:

- *Guidance for Industry: Developing Medical Imaging Drug and Biological Products*, Parts 1 – 3, see www.fda.gov (Part 1), www.fda.gov (Part 2) und www.fda.gov (Part 3)

5.4.6.2 Study selection and design

The applicant should justify the choice and design of its studies.

5.4.6.3 Radiodiagnostic agents

Imaging:
High-quality images (scans/scintigrams) obtained during the use of the notified preparation / comparison method (e.g. CDs/DVDs). The methods and equipment used for imaging, as well as the anonymised patient data, should be described in detail and statistically analysed. A critical evaluation is required, usually versus the gold standard, focusing on validity, sensitivity and specificity and including a discussion of the test results.

Specific diagnosis of a disease:
Sensitivity, specificity compared to a recognised reference method and validity of the diagnosis (where possible with the gold standard, if available).

Functional, physiological, biochemical tests:
Details of the normal values, variability and interpretation.

5.4.6.4 Radiotherapeutic agents

Imaging:
Imaging is usually required prior to treatment in order to verify the indication, distribution and dosimetry. The modalities of imaging should be validated and described in detail in the Information for healthcare professionals. The corresponding scintigrams / scans should be submitted. A critical evaluation is required, usually versus the gold standard, focusing on correctness, accuracy, validity, sensitivity and specificity.

Therapeutic efficacy:
The efficacy should be demonstrated on the basis of randomised studies; if an open study design is used, an evaluation of objective parameters by blinded reviewers (Independent Review Committee) must be provided. The number of enrolled study patients should ensure a sufficient statistical test power to detect a significant difference between the treatment groups or by demonstrating statistical equivalence. Appropriately adapted statistical hypotheses must be used for the equivalence studies or non-inferiority studies.

Statistical report:
A statistical analysis of the study results is essential.

Modalities of treatment:
It must be established whether the treatment is to be administered on an inpatient or outpatient basis, taking into consideration the administered activity, the attributes of the preparation and legal provisions (incl. in respect of excreta). The "Further information" section of the Information for healthcare professionals must contain precise instructions for nuclear medicine specialists on the information to be provided to the patient, including the modalities to be followed after the patient's death.

5.4.6.5 PMS experience if already authorised in foreign countries

PSUR / PBRER reports, incl. data on all officially required, relevant measures implemented in the foreign country.

5.4.6.6 Radiation exposure

Detailed dosimetry figures from reference sources (e.g. ICRP[13]) and clinical trials – also taking account of isotope impurities – should be included.

5.4.6.7 Immunogenicity

Immunogenicity should be additionally investigated for biotech preparations (e.g. antibodies, proteins, peptides) and blood products as carrier substances.

[13] www.icrp.org

6 Annex

6.1 Special aspects of certain product groups

6.1.1 Ready-to-use radiopharmaceuticals

Group	Examples	Difficulties	Comment and specific requirements
Therapeutic finished preparations	Iodine capsules	Radiation exposure	Dosimetry, applicator required for oral forms
Colloid suspensions for synoviorthesis	Yttrium citrate	Particle size / pharmacokinetics (diffusion from the joint)	The safety of the preparation should be demonstrated on the basis of analytical data on particle size distribution and on the basis of pharmacokinetic data (on distribution), sterility
Diagnostic finished preparations	^{123}I	Radionuclide purity	Specific activity, applicator required for oral forms

6.1.2 Labelling kits

Labelling kits are regarded as ready-to-use radiopharmaceuticals. They are not radioactive themselves and are used for combining with radionuclides (usually eluates from generators). Manufacture within the meaning of therapeutic products legislation refers to all manufacturing steps, from the active substances to the release of the kit for distribution as part of authorisation. The radiolabelling of the kit by the user and the subsequent quality control (determination of radiochemical purity) are regarded as preparation – not manufacturing – steps, regardless of the complexity of the methods used. These preparation and control steps must be carried out by qualified personnel in accordance with the methods described in the Information for healthcare professionals and in accordance with the cGRPP guidelines for radiopharmaceuticals[14] (otherwise off-label use applies, for which the user is wholly responsible). The use of the kits is described in the Information for healthcare professionals. The Information for healthcare professionals is reviewed by Swissmedic and the ECRP on the basis of the submitted quality documentation. The specific provisions relating to radiopharmaceuticals with an elevated hazard potential should be observed.

Group	Examples	Difficulties	Comment and specific requirements
Kits, therapeutic	Zevalin (ibritumomab tiuxetan)	Labelling quality Proportion of free nuclide *Pre-imaging* required	Preclinical, clinical: scope depends on the carrier molecule Comprehensive validation of the labelling procedure
Biotechnologicals	Zevalin (ibritumomab tiuxetan)	Safety in respect of DNA, viruses, prions, immunogenicity, immunological activity of antibodies/proteins/peptides	Complete, orderly documentation to the NAS standard is required.
Tc kits, diagnostic	All kits labelled with ^{99m}Tc	Oxidation status and structure of the complex Radiochemical purity Labelling procedure and yield	Validation of the labelling procedure Tin content The stability of the labelled kit and the corresponding storage conditions should be stated and validated and must be included in the Information for healthcare professionals
Tc kits in particle form, diagnostic	Nanocoll, MAA	Particle size, particle distribution and particle count per administration (aliquot withdrawal) with consequences for biodistribution	Instructions for use and validation of the manufacturing and labelling procedure The analytical methods and results of several batches must be submitted

(Tab. continuation)

Group	Examples	Difficulties	Comment and specific requirements

[14] European Association of Nuclear Medicine - Guidelines

Phosphate kits, diagnostic	HDP, MDP	Instability, oxidation, colloid formation	Protective atmosphere Tin content Validation of the labelling procedure
"Difficult" Tc kits[15], diagnostic	MAG3, HMPAO	Labelling (excessive pertechnetate, formation of a by-product). Instability of the labelled preparation.	Special documentation on the labelling, radiochemical purity and characterisation of the complex Radiochemical purity should be verified for each labelling in accordance with cGRPP[16]
Labelled peptides	DOTATOC, DOTATATE	Manufacture Pharmacology	Detailed quality Preclinical, affinity studies, imaging

Particular attention should be paid to impurities that could interfere with labelling (e.g. with indium kits).

[15] "Difficult kits": kits whose labelling involves several steps or critical steps (e.g. heating) or whose post-labelling stability is low.

[16] See Art. 47 RPO and cGRPP

6.1.3 Generators

Generators are devices for repeatedly separating a short-lived daughter nuclide from a long-lived parent nuclide and then using this for diagnostic or therapeutic purposes. The manufacturer fills the generators with parent substance. The separation of the daughter radionuclide, which is constantly produced from the parent nuclide, is carried out at the site of use. The best known example is the ^{99}Mo-/^{99m}Tc-generator. PET generators (e.g. ^{68}Ge/^{68}Ga, ^{82}Sr/^{82}Rb) have also been available for some time. A generator-elution system usually consists of a glass column containing a specific adsorbent on which the parent nuclide is fixed. The daughter nuclide formed has new adsorption properties and can be eluted from the column using a suitable solvent. Care should be taken during the quality control of the eluate to ensure that no parent nuclide is eluted at the same time (check for breakthrough) and that no column material is present in the eluate. For generators, information on the following points in particular should be provided in the authorisation documentation:

- Description and design of the generator, including shielding
- Mode of use and safe use
- Breakthrough of the parent nuclide, radionuclide purity
- Validation of use with elution plan and
- Quality control by the user.

For the investigation of the operational safety of generators, refer to Annex 9.3 *Authorisation documentation for radiopharmaceuticals with new active substances (NAS)*.

6.1.4 PET preparations

PET preparations (also known as tracers) are radiodiagnostic agents and can be used to provide functional depictions of metabolic processes. In view of the short half-life of certain nuclides (e.g. ^{18}F), it is not possible to carry out all quality control tests prior to batch release (parametric release). Validation of the manufacturing process is therefore particularly important.

Group	Examples	Difficulties	Comment and specific requirements
Cyclotron-produced PET preparations	^{18}F e.g. in the form of fluorodeoxyglucose (FDG)	Short half-life High activity Parametric release before the completion of all quality tests	Provided that the preparation does not produce any appreciable toxicological or pharmacological effects at the recommended dosage, the documentation focuses on the following aspects: ▪ **Quality:** Validation, risk analysis ▪ **Safety:** Radiation dose ▪ **Efficacy:** Image quality

(Tab. continuation)

Group	Examples	Difficulties	Comment and specific requirements
Cyclotron-produced PET preparation	^{18}F e.g. in the form of fluorodeoxyglucose (FDG)	Manufacturing risk analysis	Tabular compilation of the synthesis stages, stating the critical stages and the technical and analytical safety measures (in-process controls). Reference should be made in the table to the relevant validation documents.
		Synthesis yield	The toxicological and pharmacological effects of any by-products from defective synthesis and the tests capable of identifying incidents during the course of synthesis should be included. This is particularly important for PET preparations, because the synthesis processes are complex and it is not possible to carry out all tests on the manufactured batch prior to administration because of the short half-life of the nuclide. Synthesis yield depends on the synthesis pathway. The following limits must be specified and justified on the basis of the validation of the manufacturing process and the analytical results for the pilot batches: ▪ Minimum yield (specification) ▪ Warning limit: (above the minimum yield specification), below which release is not possible. The process should be verified (despite compliance with the specifications) before the next batch is produced.
Extremely short-lived cyclotron-produced PET preparations	^{15}O, ^{13}N, ^{11}C[17]	These preparations have nuclide half-lives in the order of minutes and are generated (by the cyclotron) and administered to the patient on the spot before quality control is possible.	Validation of the manufacturing process and the manufacturing risk analysis are extremely important
Generator-produced PET preparations	^{68}Ga- or ^{82}Rb-labelled compounds	Since the activity administered by the parent nuclide (^{68}Ge, ^{82}Sr) is non-specific, its breakthrough constitutes a critical safety risk.	Focus on breakthrough of the parent nuclide, elution plan and validation, ensure the manufacturing process is robust and quality is reproducible. Require regular quality control by the user, particularly in respect of radionuclide purity.

6.1.5 Carrier-containing preparations

Group	Examples	Difficulties	Comment and specific requirements
Carrier-containing radionuclides	^{186}Re	Acute toxicity of the metal and the labelled compound Interaction of the carrier with kit labelling	Extended preclinical data, i.e. including toxicity clarification for the "cold" nuclide of the element concerned. Meticulous validation of the labelling procedure

6.1.6 Precursors

Precursors are radioactive precursors of radiopharmaceuticals which are used for radiodiagnostic or radiotherapeutic purposes and which are combined, usually with labelling kits, before administration. The minimum specifications for kit labelling are crucial here.

[17] These preparations are not subject to authorisation if they are described in a pharmacopoeia monograph and satisfy the formula-related criteria (Art. 9 para. 2 TPA).

Group	Examples	Difficulties	Comment and specific requirements
Precursors	Yttrium chloride, Indium chloride	Radiation toxicity of the free nuclide (yttrium) and the labelled compounds Any pharmacological activity	Adequate preclinical documentation
		Chemical purity	The absence of metallic impurities should be documented.
		Adequate labelling of existing kits	Data on the labelling of authorised kits

6.1.7 Blood preparations

Product group	Examples	Difficulties	Comment and specific requirements
Radiodiagnostic agents with human albumin	Seralb-I-125, Nanocoll, Maasol	Safety in respect of viruses and prions	Comprehensive specific documentation, as for blood preparations Plasma Master File required

6.2 "Well Established Use" Active Substances for Radiopharmaceuticals

The Annex lists the active substances that have been used for the cited indications for at least 10 years and whose safety and efficacy are generally acknowledged on the basis of the experience acquired in use. As such, the corresponding radiopharmaceuticals are eligible for simplified authorisation under Art. 27a para. 1 TPLO

Active substance	Indication
^{14}C-aminopyrine (aminophenazone)	Breath test for hepatocellular function
^{57}Co-cyanocobolamin	Schilling test
^{51}Cr-chromate	Labelling of red blood cells for the determination of platelet survival time, determination of erythrocyte mass
^{51}Cr-chromium-EDTA	Glomerular filtration
^{18}F-DOPA	Diagnosis of neuroendocrine tumours, differential diagnosis of Parkinson syndrome via presentation of presynaptic decarboxylase activity
^{18}F-fluoromisonidazole (F-MISO)	Hypoxia
^{123}I-IBZM (iodobenzamide)	Parkinson syndrome, movement disorder, impaired pre- or postsynaptic dopamine transmission, multisystem atrophy
^{131}I-norcholesterol	Diagnosis of relapse in Conn's disease, investigation of corticosterone-producing tumours, hyperaldosteronism, adrenal adenoma
^{111}In-oxinate	Platelet scintigraphy
^{15}O-water	Blood flow
^{32}P-sodium phosphate	“Maladie de Vaquez", polycythaemia vera, myeloproliferative syndrome
^{99m}Tc-hepatate agent	Hepatosplenic scintigraphy, labelled meal, "fuite péritonéale", reflux
^{99m}Tc-mebrofenin	Scintigraphy of the hepatobiliary system, liver function, biliary atresia
^{99m}Tc-DMSA (dimercaptosuccinic acid, DE: Dimercaptobernsteinsäure)	Detection / exclusion of scarring in the renal parenchyma, renal malformations, kidney localisation, kidney position and shape
^{99m}Tc-tin-colloid	Hepatosplenic scintigraphy, labelled meal
^{68}Ga from generator	PET generator

6.3 Authorisation documentation for radiopharmaceuticals with new active substance (NAS)

The Annex provides an overview of all scientific requirements governing quality and the preclinical and clinical situation that are relevant to radiopharmaceuticals. These requirements apply both to radiopharmaceuticals with new active substances (NAS) and innovative radiopharmaceuticals with known active substances (innovations compared to the original preparation should be substantiated on the basis of proprietary data) and biotechnological radiopharmaceuticals, if applicable.

The Annex also contains information on the testing and documentation of the operational safety of generators.

For details of the content and format of the CTD documentation, refer to ICH-Guidelines M4Q, M4S and M4E (www.ich.org). The rest of this document covers points to be observed specifically for radiopharmaceuticals.

6.3.1 Documentation

Administrative documents (Module 1)

The formal requirements for Module 1 are based on the corresponding specifications for non-radiopharmaceuticals (see guidance document *Formal requirements HMV4* in conjunction with the Directory *Overview of documents to be submitted HMV4*.).

Specifics for radiopharmaceuticals are laid down hereinafter (see also chapter 3.22.1 *Radiopharmaceuticals* of the guidance document *Formal requirements HMV4*).

a) Form *Declaration of radiopharmaceuticals HMV4*

Detailed information on the radiochemical aspects of the preparation, incl. specific activity.

b) Form *Manufacturer information HMV4*

For preparations containing radionuclides, all manufacturers / manufacturing sites for all manufacturing steps (from target / precursor to the nuclide contained in the preparation) must be stated in the "Active substances" section.

c) GMP certificate

A GMP certificate must be provided for each manufacturer of the finished product and active substance (GMP certificate no more than three years old).

Overviews and summaries (Module 2)

a) Summary of analytical, chemical and pharmaceutical documents (Module 2.3 CTD)

Particular attention should be paid to impurities, kit labelling and the corresponding quality controls, validation and the manufacturing safety analysis, as well as the corresponding consequences for the safety and efficacy of the preparation.

b) Summary of toxicology and pharmacology (Module 2.4 *Nonclinical Overview* / Module 2.6 *Summary*)

For innovative radiopharmaceuticals, a *Nonclinical Overview* (Module 2.4) containing a comprehensive and critical appraisal of all the available data should be prepared by an expert. A summary of the experimental investigations should be presented in the corresponding *Nonclinical Written / Tabulated Summaries* (Module 2.6).

For preparations subject to the simplified procedure or containing KAS, a scientific discussion in the form of a non-clinical overview based on the latest relevant literature data and taking account of the quality of the preparation, particularly its impurity profile, should be submitted. Nonclinical Summaries should only be prepared in connection with experimental data.

c) Clinical summary (Module 2.5 *Clinical Overview* and Module 2.7 *Summary*)

This document should provide a critical discussion of the risk/benefit ratio and the diagnostic / therapeutic value of the preparation. For diagnostic agents, the validation (sensitivity and specificity, etc.) compared to a recognised method (gold standard) is of prime importance. The study results should be subjected to a statistical analysis.

Quality documentation (Module 3)

As a general rule, all the requirements relating to pharmaceutical and chemical quality documentation contained in the relevant specification documents (ICH, EMA, etc.) apply without reservation to radiopharmaceuticals. The chemical, analytical and biological tests must satisfy GMP requirements.

a) Active substances

Naming:

INN, name according to a pharmacopoeia, chemical name, development code, other non-proprietary names, CAS number.

Structure:

Structural formula, stereochemistry, molecular weight. For peptides: Amino acid sequence, secondary to quaternary structure.

Physicochemical properties:

Additionally for biotech preparations: Biological activity and characterisation.

Manufacture:

Since alternative manufacturing processes usually result in preparations of differing radiochemical quality, including in respect of impurities, only one synthesis route can be authorised for an individual preparation.

The following special factors also apply to the manufacture of radionuclides:

Production of the radionuclide:

The nuclear reactions used, including those leading to by-products and impurities, should be described in detail, including in respect of the half-life, type and energy of the irradiation and the interference effects caused by the impurities.

Nuclides produced by target bombardment: Target material and target shell:

- Composition, chemical form, chemical purity, physical condition and any chemical additives that may influence the product
- Irradiation method, physical and chemical environment (target holder)
- Yield

Nuclides produced by fission:

The whole nuclide chain, from the first starting material (incl. impurities) through to the corresponding stable daughter nuclides should be stated, incl. half-life, type and energy of irradiation. The interference effects caused by impurities or the starting material must be discussed.

Preparation of the radionuclide:

Detailed description of the isolation (separation from target material) and enrichment of the desired radionuclide; yield

Physical properties of the radionuclide:

Half-life, type and energy of the irradiation, as well as the course over time from the preparation of the radionuclide until the expiration of the medicinal product and the aspects that are important for its disposal should be stated in detail.

Process validation and/or evaluation:

Focusing on the sterile preparation and apyrogenicity. The results of a suitable number of representative batches should be submitted (for PET preparations usually 10 batches).

Manufacturing safety analysis: The critical steps and corresponding in-process controls in terms of ensuring quality and safety should be evaluated in detail.

Characterisation:

For biotech preparations: Characterisation of the primary to quaternary structure, biological activity and immunochemical properties.

Impurities:

The impurities, including nuclides and metals should be investigated and quantified comprehensively as part of validation on the basis of a minimum of 3 representative batches. The consequences for preparation quality, kit labelling, safety, and possibly efficacy / image quality should be discussed critically.

If certain impurities (e.g. γ-radiating impurities in weak β-radiating preparations) interfere with the measurement of the activity to be administered, this should be discussed comprehensively and mentioned in the Information for healthcare professionals.

Specifications:

The selected specifications must be suitable for ensuring that safety-relevant quality deficiencies can be detected before active substance is released. This is particularly important for short-lived nuclides and PET preparations.

Analytics:

The measures for protecting the tester against radiation should be factored in.

Batch analysis:

The results of at least 3 representative batches must be available (at least 10 batches for PET preparations).

b) Finished product

The following specific information should also be provided for generator systems:

- a general description of the system;
- detailed description of system components that are capable of influencing the quality or composition of the daughter nuclides / eluate
- detailed instructions for use, incl. validation
- detailed data on elution, incl. elution plan
- confirmation that operational safety requirements according to section 6 are fulfilled
- detailed composition of the eluate, incl. chemical analysis of at least 3 representative batches

Biotechnology / genetically engineered medicinal products:

The following aspects in particular should be considered:

- biological activity and the specificity of antibodies or peptides
- absence of pathogenic agents
- absence of contaminating DNA or of foreign proteins

Composition:

For radionuclides, the activity per dosage form (in Bq) and the specific activity (at the time of calibration) should be stated.

For biomolecules, the biological activity should be stated.

All compounds required for labelling should be stated (e.g. tin salts for reducing pertechnetate).

In generators, parent and daughter nuclides are regarded as active constituents.

For excipients (e.g.: colouring agents, stabilisers, etc.), the Euro numbers should be stated if available.

The compatibility of the active substance with the excipients should be discussed. The chemical/physical properties of the active substance that are important for quality, safety and efficacy should be stated and discussed.

The function, selection and properties of the excipients should be stated and explained.

Manufacturing or stability surpluses should be justified.

Physicochemical and biological properties:

The physicochemical properties of the preparation should be stated and a commentary provided. These should include pH, osmolarity, solubility, polymorphisms (e.g. for complexes), particle size distribution (suspensions, colloids) etc.

The biological / immunological activity of biotech preparations should be stated.

Container and closure:

The manufacturer must provide data on all materials that come into contact with the radiopharmaceutical and on their interaction.

For standardised containers, it is sufficient to state the applicable underlying pharmacopoeia. Detailed information on **all non-standardised containers** should be provided, including:

- name of the material and reference number
- manufacturer
- structure, presentation
- composition
- chemical and physical properties

This information should likewise be provided for **accessories**, particularly for:

- infusion kits
- syringes
- accessories for generators (e.g. columns, containers, stoppers)
- Substances added (e.g. for siliconising) during the manufacture of the containers (glass vials, ampoules, stoppers, etc.) must be stated.
- Vessel materials and/or accessories that may not be used for further processing (labelling) should be mentioned.

Manufacture:

All manufacturers involved should be identified. The manufacturing chain should be traceable, particularly for radionuclides. The responsibilities for the respective stages should be clearly stated. The Responsible Person (Qualified Person) at the marketing authorisation holder for the finished product should be stated in the form *Manufacturer information HMV4*.

The manufacturing process should be described in detail in prose and graphically (flowcharts).

The critical steps must be identified and discussed.

The following must be described in detail for **kits** (labelling kits):

- manufacture of the (non-radioactive) substance to be labelled (kit)
- labelling specification (preparation process)
- specification for the quality control of the labelled, ready-to-administer preparation

All steps in the manufacturing process should be validated.

For kits, the labelling process and quality inspection of the labelled, ready-to-administer preparation must likewise be validated.

The critical steps and their inspection (in-process control) should be described and justified in a manufacturing safety analysis.

Specifications:

Specifications that are relevant for the user should be mentioned in the Information for healthcare professionals.

The specifications should be justified in respect of the reproducibility of quality and safety. Ideally, recognised methods should be used (e.g. Ph. Eur.). All test methods not described in pharmacopoeias should be comprehensively validated.

Control of the finished product:

The attributes to be specifically verified for radiopharmaceutical medicinal products also include:

- Nuclide identity
- Nuclide purity
- Radiochemical purity
- Chemical purity
- Specific activity

And additionally for **generators**:

- Tests for parent nuclide breakthrough in the generator system

For kits, the minimum specifications for the generators used for labelling and the labelling preparations must be stated and validated.

Batch control:

All tests that are routinely performed on each batch of the finished product should be stated. The frequency of tests that are not routinely performed should be stated. The corresponding monographs should be used for end products cited in the relevant pharmacopoeias. Test methods other than those cited in pharmacopoeias or internationally recognised recommendations must be validated according to ICH recommendations.

For authorisation purposes, the results of controls on the end product from at least 3 representative batches should be substantiated.

Information on special precautions for storage and on the earliest and latest use should be mentioned in connection with the activity reference time (calibration time).

Characterisation of impurities:

The impurities in the finished product / ready-to-administer medicinal product should be carefully identified, and their effect on the quality, safety and efficacy (e.g. imaging) of the preparation should be discussed.

The selected specifications must be capable of ensuring that all possible manufacturing failures identified during the manufacturing safety analysis can be determined before the preparation is released.

Stability:

State the tests and their results (original data) including critical assessment and schedule for further ongoing stability studies.

The shelf life, recommended storage conditions and specifications at the end of shelf life should be substantiated on the basis of the stability documents.

If it is possible for degradation products to form, methods for characterising them / test methods for quantifying them should be stated. The maximum tolerable quantity of degradation products should be stated and substantiated, taking account of the pharmacopoeia and ICH guidelines.

A description of how the radiopharmaceutical and container can reciprocally affect each other should be presented in all cases in which a risk of this kind exists (particularly if injectable preparations or aerosols are involved).

Shelf life data for generators, labelling kits and radiolabelled products should be stated. Shelf life (and storage instructions) in multidose ampoules should be documented.

The conditions (temperature, physical condition, etc.) for storage before and after the preparation is prepared should be stated.

Preclinical documentation (Module 4)

Apart from investigations of primary and secondary pharmacodynamics, non-clinical tests for determining properties or safety should be carried out in accordance with the principles of Good Laboratory Practice. The raw images (e.g. photographs, scintigrams, histology images) should be submitted in electronic form (on CD or DVD). The image files must be provided both in the original format (e.g. DICOM) and in a widely used image format that can be read on Windows PCs; the image quality must be sufficient to allow optimal evaluation.

The preclinical documentation should particularly take into account and document the points listed in sections 6 and 8 and the following aspects that are specific to radiopharmaceuticals:

a) Radiodiagnostic agents

Pharmacokinetics, particularly biodistribution in connection with imaging and dosimetry.

Clinical documentation (Module 5)

Clinical studies must satisfy the current Good Clinical Practice requirements. All documentation sets must contain original images (e.g. scintigrams, histology images) or high-quality copies amenable to evaluation. The scintigrams / scans can also be submitted in electronic form (on DVDs). The anonymised patient data and the imaging modalities must be stated.

The choice and design of the clinical studies should be justified for each individual preparation (diagnostic or therapeutic agent, indications). The optimal dosage and activity should be investigated and explained. The clinical studies should be statistically evaluated.

The safety and efficacy, risk/benefit ratio and medical value of the diagnosis or treatment in the claimed indications in the relevant patient population should be comprehensively and critically evaluated in comparison to existing alternatives.

a) Radiodiagnostic agents

For diagnostic agents, the investigation conditions should be validated and described in detail. All factors (e.g. co-medication) that could interfere with the results must be discussed and mentioned in the Information for healthcare professionals. The main focus is on validating the diagnostic method (conditions and quality of imaging, sensitivity and specificity of diagnosis, target values and variability of functional investigations, interpretation of the results, required user experience, etc.).

b) Radiotherapeutic agents

The dosimetry and chemical and radiation-related toxicity are particularly important. The potential for interaction between a radiotherapeutic agent and other medicinal products, and the effect of the irradiation on organ toxicity (in monotherapy or in combination with other medicinal products, e.g. cytotoxic agents) should be investigated.

6.3.2 Preclinical and clinical studies with radiodiagnostic agents

Pharmacokinetics

Pharmacokinetic parameters should be investigated in the same animal species that was used for the toxicology studies. The species should be one that permits extrapolation of the results to humans (including distribution and elimination).

Safety and dose finding

Radiodiagnostic agents can be divided into the following safety classes depending on their composition:

Class 1: Radiodiagnostic agents with carrier molecules that are administered in such small quantities that pharmacological effects are not expected.

Class 2: Radiodiagnostic agents with biological carrier molecules that are administered in such small quantities that pharmacological effects are not expected, but which may nevertheless cause hypersensitivity reactions due to the biological nature of the substances. The risks of sensitisation associated with radiodiagnostic agents in this class should be evaluated.

Class 3: Radiodiagnostic agents with carrier molecules that are administered in fairly large quantities and are thus theoretically expected to produce pharmacological effects. The safety of this class of radiodiagnostic agents should be investigated in a Phase I study involving a limited number of patients.

Maximum doses should be determined for class 3 radiodiagnostic agents, not this is not necessary for classes 1 and 2.

The dose of radiodiagnostic agent to be administered is derived primarily from the expected and necessary radiation dose that the patient will absorb. Although considerations related to pharmacology and potential side effects (including hypersensitivity reactions and allergic potential) are secondary for dose-finding purposes with radiodiagnostic agents, they should nevertheless be considered in the safety documentation.

Dose-finding studies must satisfy the following requirements, depending on the safety class in question:

Class 1: Dose-finding studies are not generally necessary for this class. Minimum doses can be derived from physical and /or mathematical models, while the maximum acceptable radiation dose is relevant for maximum doses.

Class 2: Due to a possible immune response to biological radiodiagnostic agents, the appropriate dose here should be derived from a minimum protein dose with maximum radioactive dose (preparations with high specific activity).

Class 3: Maximum doses for this class of radiodiagnostic agents are derived from the potentially observable pharmacological effects of the carrier molecules above a certain quantity, while the required radiation dose for confirming the diagnosis is relevant for the minimum dose.

Toxicity studies

Preclinical studies on chronic toxicity, reproductive toxicity and carcinogenicity (exception: mutagenicity) are not required for the safety evaluation of radiodiagnostic agents. Acute toxicity studies may be required for new radiodiagnostic agents in Class 3.

Side effect profile

Data on possible allergic, immunological or hypersensitivity reactions should be included here.

Dosimetry: estimated absorbed radiation dose

Pharmacokinetic information should be sufficient for calculating the dosimetry of radiodiagnostic agents. Data from animal studies (extrapolated to estimated doses in humans) should be confirmed as relevant or superseded by data measured in humans. The effects of age, clinical condition and, importantly, impairment of hepatic or renal function should be factored into dose estimations.

Reference to the *Medical Internal Radiation Dosimetry* (MIRD) schedule is recommended when calculating the absorbed doses. The model used to calculate cumulative activity (time integral of the activity) in the source organs should be explained, and the data source (animal experiments or studies in humans) stated. Physical parameters, e.g. absorbed dose in the target organ per unit of cumulative activity in the target organ should be taken from the MIRD tables.

The weighting factors established by the *International Commission on Radiological Protection* (ICRP) should be used when calculating the effective doses. Since these factors do not apply to children, pregnant women or the elderly, appropriate adjustments should be made for these patient groups.

If other methods are used to calculate the doses absorbed by organs, corresponding details should be provided and enclosed with the original reports.

The dose absorbed by the organ receiving the highest exposure and by all other organs relevant to the calculation of the effective dose-equivalent should be stated (units: mGy/MBq, mGy per unit of activity). The estimation of the radiation dose must be summarised in terms of the effective dose-equivalent in relation to the ICRP weighting factors, stated in Sv/MBq.

6.3.3 Preclinical and clinical studies with radiotherapeutic agents

The preclinical and clinical requirements for radiotherapeutic agents are based on the current international guidelines of the EMA and FDA. These include, in particular:

a) EMA:

- 3AQ20a Radiopharmaceuticals of the EMA[18]
- Points to Consider on the Evaluation of Diagnostic Agents[19]
- Guideline on Clinical Evaluation of Diagnostic Agents[20]

b) FDA:

- Guidance for Industry on Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals of the FDA[21] in relation to possible late radiation damage
- Guidance for Industry: Developing Medical Imaging Drug and Biological Products, Parts 1 – 3[22]

[18] www.ema.europa.eu
[19] www.ema.europa.eu
[20] www.ema.europa.eu
[21] www.fda.gov
[22] www.fda.gov (Part 1), www.fda.gov (Part 2), www.fda.gov (Part 3)

Dosimetry: estimated absorbed radiation dose

The same applies here as to dosimetry of radiodiagnostic agents (see above).

6.3.4 Testing the operational safety of generators

The RPO and the requirements of the FOPH should be taken into account.

Introduction

Testing the operational safety of radionuclide generators is designed to ensure that the generators do not expose the operating personnel or the environment to an inadmissible level of radiation when they are used correctly, when disposed of at the end of their useful life or in the event of possible incidents.

Proper functioning and the reliability of the activity readings should also be ensured by means of a suitable quality control process.

The overall testing of a radionuclide generator involves the evaluation of a number of individual criteria. However, there is only a small number of criteria for which the requirements can be specified in sufficient detail to allow a clear decision as to whether or not the tested generator satisfies the criteria in every case. Such criteria are concerned with, for example, shielding, compliance with transport requirements, the labels affixed to the generator and the operating instructions. By contrast, rigid requirements cannot be specified for other criteria. In these cases, the generally known principles of radiological protection should be applied.

Every criterion must satisfy the radiological protection regulations and be adequately assessed and justified by the applicant. The authorisation documentation must be accompanied by all available technical documents, including operating instructions, labels, construction drawings and measurement records.

Checks

The following three groups of criteria must be checked and evaluated:

a) Checking formal requirements

Transport regulations:

Radionuclide generator, shipping packaging and accompanying documents must comply with national / international transport regulations:

- ADR/SDR road transport regulations
- RID/RSD rail transport regulations
- IATA regulation for air freight

In particular, it should be established whether the packaging material is sufficiently strong and that the local dose rate at its surface and at a distance of 1 m does not exceed the corresponding limits. It should also be established whether the generator is shipped in certified containers.

Labelling on the radionuclide generator:

Labels on the transport container, generator and the shielding in operation must be provided by the supplier and must include the following information in clearly legible text:

- manufacturer, supplier and service centre in Switzerland
- parent and daughter nuclides
- loading activity of the parent nuclide and calibration date and time
- batch number
- expiry date

- the inscription "Warning: radioactive" and the radiation hazard warning symbol in accordance with Annex 6 of the RPO, short operating instructions
- manufacturer's / supplier's note concerning the taking back of the generator

Accompanying documents:

Accompanying documents containing the following information should be provided with each radionuclide generator:

- parent and daughter nuclides
- chemical and physical forms of the radionuclides
- activity of the parent nuclide
- calibration date and time of the activity, expiry date
- results of function and activity checks during shipment
- shipment date
- signature of checker

Adhesive labels for the elution:

Adhesive labels for the elution vials and/or their shielding must be packed with the generator. These must have fields for entering the following information:

- radionuclide,
- date and time of elution,
- activity,
- volume,
- activity concentration,
- chemical form.

Operating instructions:

Operating instructions must be provided in German and French at the minimum. Preparations for putting the generator into service, and the steps involved in elution should be described clearly and simply. The procedure in the event of operational problems should also be specified: in particular, the instructions should clearly show what operating personnel should do to rectify such problems, and how far staff should go before informing the competent service centre (address and phone number of the nearest service centre should be provided).

Disposal of used radionuclide generators:

Used generators must be returned to the supplier or manufacturer. It should be verified whether the manufacturer or distributor of the generator has made the necessary provisions for this purpose and provided corresponding instructions both in the operating instructions and on the generator itself.

b) Checking the shielding

Shielding of the radionuclide generator:

The shielding supplied by the manufacturer with the radionuclide generator or the fixed shielding at the customer's premises prescribed by the manufacturer for operation of the generator must be able to reduce the local dose rate to 0.01 mSv/h at a distance of 1 m from the surface of the generator at the time of delivery.

Shielding for the elution vials:

Shielding for elution vials must be provided whenever a radionuclide generator is delivered for the first time. Evidence must be provided to demonstrate that the shielding is designed so that the eluate can be removed easily, safely and without unnecessarily exposing staff to radiation. It should be designed such that the dose rate at the surface never exceeds 1 mSv/h and such that the eluted volume can be read easily.

c) Checking technical and operational criteria
Generator system:

The various commercially available generator systems involve a variety of operational risks. Thus, for example, contamination is always possible with gravity-operated and pressurised systems (in contrast to a vacuum system). Pumps and other movable parts are generally prone to faults. If the entire supply of eluent is integrated into the generator, there is a risk of leakage and thus corrosion. Applicants should demonstrate that the generator system, both in principle and in its current form, provides the necessary assurance of safe, contamination-free operation.

Handling the radionuclide generator:

The radionuclide generator should be simple and safe to handle. If handled correctly, it should not be possible to make mistakes during operation.

Applicants should demonstrate that:

- fractionated elutions can be carried out simply and safely,
- individual manipulations are sufficiently simple and safe to ensure that incorrect operation does not lead to malfunctions or even contamination and / or that the carrier column cannot be inadvertently exposed as a result of incorrect use,
- the eluent container and the elution vials cannot be mixed up.

Quality control by the manufacturer:

The quality controls performed by the generator manufacturer must guarantee that the generator is safe to use. These quality controls must cover at least the following points:

- the activity written on the generator must be checked by measuring parent nuclide activity in the primary container after it has been loaded
- the whole (elutable) activity of the daughter nuclide present in the radionuclide generator at the time of calibration must be stated as a percentage of the declared parent nuclide activity
- control of other factors that are critical for the generator system concerned
- The results of the controls should be traceably documented and recorded on the delivery note (certificate).

Change history

Version	Change	sig
2.1	New layout, no content adjustments to the previous version.	dei
2.0	Adjustments to the department names	ski, fua
1.1	Formal adjustments to the header and footer No content adjustments to the previous version.	dei
1.0	Implementation of TPO4	ze