Ethiopian Food and Drug Authority (EFDA)

Medicine Evaluation and Marketing Authorization Led Executive office

Guideline for Registration of Radiopharmaceuticals

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Contents

ABBREVIATIONS

API:	Active Pharmaceutical Product
EFDA	Ethiopian Food and Drug Authority
ERPA	Ethiopian Radiation Protection Authority
ETA	Ethiopian Technology Authority
PET	Positron emission tomography
SPECT	Single-photon emission computed tomography
EMA	European Medicine Agency
EURATOM	European atomic energy community
FPP	Finished Pharmaceutical Product
eRIS	Electronic Regulatory Information System
GMP	Good Manufacturing Practices
GLP	Good Laboratory Practices
QC	Quality Control
MA	Market Authorization
IR	Immediate Release
NMT	Not More Than
U.S. FDA	United States Food and Drug Administration
CHMP	Committee for Human Medicinal Products
USP	United States Pharmacopeia
WHO	World Health Organization

Definition

Radiopharmaceuticals

Radiopharmaceuticals are defined as "medicines which have one or more radionuclide substances combined with pharmaceutical agents (cold kits) used in the diagnosis and treatment of human diseases. However, some radionuclides may be used as Radiopharmaceuticals without being combined with pharmaceutical agents.

Radionuclide generator

Radionuclide generators are devices that produce a useful short-lived medical radionuclide (known as "daughter") from the radioactive transformation of a non-medical long-lived radionuclide (called a "parent").

Scintigraphy

Scintigraphy is a diagnostic imaging technique in which an image of internal body tissues is produced through the detection of radiation emitted by a radioactive substance administered into the body.

Becquerel

The becquerel is the unit of radioactivity in the International System of Units (SI). One becquerel is defined as the activity of a quantity of radioactive material in which one nucleus decays per second.

Curie

Curie is an alternative unit of radioactivity.

Radiopharmaceutical kit (pharmaceutical cold kit)

A radiopharmaceutical kit is actually used to prepare a radiopharmaceutical and consists of a vial containing non-radionuclide chemical components, usually in the form of lyophilized or appropriately sterilized product ready to be chemically combined with the appropriate radioisotope to be converted to the radiopharmaceutical.

Radioactive decay

Radioactive decay is the process by which an unstable nucleus emits radiation to become stable or more stable.

Radionuclide Precursors: is any Radionuclides produced for the radiolabeling of another substances to prepare radiopharmaceuticals prior to administration.

Theranostics: also called **theragnostics**, is the term used to describe the combination of diagnostic with therapeutic radiopharmaceuticals that share a specific target in disease cells or tissues.

Medical Cyclotron: is a particle accelerator, a machine that uses electromagnetic field to propel charged particles to very high speeds and energies, used to produce radioisotopes for the preparation of radiopharmaceuticals, which diagnose and treat disease.

1. INTRODUCTION

The radiopharmacy/radiopharmaceuticals regulatory legal frame work and the associated regulatory activities are generally observed to be not well versed, developed and organized in most African countries. Articles 2(13) of Ethiopia's Food and Medicine Administration Proclamation (Proclamation No. 1112/2019) defines radiopharmaceuticals as "medicine which has one or more radionuclide substance used in the diagnosis and treatment of human disease and includes non-radioactive reagent kit used for a preparation of medicine and radionuclide generator". In addition, Articles 29(1-3) Ethiopia's Food and Medicine Administration Proclamation (Proclamation No. 1112/2019) highlighted the need for Certificate of Competence from Ethiopia FDA to manufacture, import, export, wholesale or store, extemporaneous preparation. Furthermore, article 20 (4) of Proclamation No. 1112/2019 stated Medicine manufacturers should comply with good manufacturing practices (GMP), dossiers evaluation and Quality control testing as appropriate to fulfill safety, quality and efficacy or effectiveness in order to grant Market Authorization (MA) certificate. Moreover, in effectively regulating radiopharmaceuticals or radiation emitting medical devices, Ethiopia FDA shall work together with the appropriate body such as Ethiopian Radiation Protection Authority (ERPA).

According to Article 19(1) of Ethiopia's Food and Medicine Administration Proclamation (Proclamation No. 1112/2019) illustrate the rigor of regulatory assessment of a medicine shall be commensurate with products type, nature and potential risk to human health. Thus, there are different strategies to expedite the Market Authorization Process such as Risk based approach, Fast track registration and expedited assessment (accelerated procedure). High risk medicines needs rigorous dossier assessment and in-depth evaluation that need expertise and more time compared to low risk medicines that need partial review of the product dossier consuming less time waiving routine dossier assessment. The Authority has been giving prioritized market authorization and port clearance of radionuclide generators such as Mo-99/Tc-99m generators as well as diagnostic radionuclides obtained daily from such generators, for radiopharmaceutical cold kits and for therapeutic radiopharmaceuticals like I-131. In addition, due attention has been given by the Authority during fast-track registration (Market Authorization) of anticancer drugs used at the cancer center for chemotherapy.

Radiopharmaceuticals are a special type of medicinal products that deserve the subject of a specific guideline covering their particular requirements. The particularities of radiopharmaceuticals derive mainly from the fact that, when ready for administration to the patient, they contain one or more radionuclides, that the strength is expressed in terms of the radioactivity (radioactivity concentration for liquid dosage forms or total radioactivity per dosage unit in some cases), the posology is expressed in terms of the amount of radioactivity administered to the patient and not in terms of mass (or amount of substance) and finally, that the amount of radioactivity decreases with time. This has led to the need of defining, along with 'radiopharmaceutical', three additional specific types of medicinal products: radionuclide generator, radionuclide precursor and cold kit (for radiopharmaceutical preparation/labeling/formulation). Thus, this guideline provides additional guidance for Marketing authorization of radiopharmaceuticals.

Relevant provisions of the current European Pharmacopoeia and due account must be taken of relevant EMA guidelines which should be applied with special interpretation, recommendation or completion for radiopharmaceuticals, as discussed in this guideline. Radiopharmaceuticals are exempted from a number of guidelines, but with special interpretation they could still give the necessary guidance on the matter. Radiopharmaceuticals are used for diagnostic and therapeutic purposes. Diagnostic radiopharmaceuticals are usually given only once unless they are required to be repeated.

This is to say that a cold kit or pharmaceutical agent used in a radiopharmaceutical formulation/labeling is employed in its dose range much below its quantity required to induce/cause the pharmacologic effect when it is labeled with its corresponding radionuclide/radioisotope. Hence the finally produced radiopharmaceutical in this manner is administered to patients for diagnostic imaging or therapeutic purposes. Therefore, such a radiopharmaceutical produced in which the radionuclide chemically attached to the very small quantity of pharmaceutical agent/cold kit (which is also termed as radiopharmaceutical formulation or labelling). The properly formulated radiopharmaceutical in this way is employed to allow for organ scintigraphic imaging purpose with diagnostic radiopharmaceuticals & for treatment purposes with therapeutic radiopharmaceuticals. In both cases any radiopharmaceutical

is specifically localized in comparatively higher ration at the target organ intended to be diagnosed or treated due to the specific localization property of the pharmaceutical agent (cold kit) in the prepared radiopharmaceutical. Such radiopharmaceuticals do not often show any measurable pharmacodynamic effect. Radiation is a general property of all radiopharmaceuticals, which when administered gives the patient an inevitable radiation dose. In the case of therapeutic radiopharmaceuticals, the radiation effect is the wanted property. Radiopharmaceuticals have decreasing content of radioactivity with time, as a consequence of the radioactive decay. The physical half-life of the radionuclide is often short for radiopharmaceutical diagnostics. In these cases, the final preparation has to be done shortly before administration to the patient. This is also the case for positron emitting radiopharmaceuticals for Tomography (PET radiopharmaceuticals). It often leads to the use of semi-manufactured products such as radionuclide generators, radioactive precursors and kits. Due to the very short half-lives of many PET Radiopharmaceuticals/radionuclides the hospital or medical cyclotron is usually required to manufacture/produce them daily in hospitals or at such medical/clinical patient service giving centers as it is practically difficult to transport them from long distances for daily uses.

2. BACKGROUND AND CHALLENGES

The risk of marketing of substandard, adulterated, unsafe, non-efficacious and poor-quality radiopharmaceuticals due to weak regulations or low registration coverage is intolerable to the public and unacceptable from regulatory point of view. Therefore, it is deemed necessary to protect the public health by ensuring the safety, efficacy and quality of radiopharmaceuticlas via Market Authorization system through dossier assessment, GMP inspection and quality control testing medicine regulatory authority (EFDA). (In this case there is no much importing of radiopharmaceuticals and market in Ethiopia. We need to encourage investors and professionals in this area who are interested to establish radiopharmaceutical manufacturing firms within the country and/or who are also interested professionally to practice radiopharmacy and nuclear medicine in the country by avoiding process that may take unnecessarily longer time which could be discouraging to the national development in this regard. However, materializing & promoting this national principle without violating the principles of ensuring the safety & security of radiopharmaceuticals. In addition care should be taken also not to treat

radiopharmaceuticals as merely normal medicines as this can complicate the various processes of its diversified handlings & can unnecessarily elongate its normal process.

Although regulation of radiopharmaceuticals is stated in different legislations, challenges in different areas with respect to its implementation to ensure the safety, efficacy and quality of radiopharmaceuticals have been faced.

- As radiopharmaceuticals are unique kinds of pharmaceutical products that need special expertise and training, lacking these competency building opportunities for regulators of radiopharmaceuticals poses problems for competent conduction of radiopharmaceutical regulatory activities nationally.
- Inadequate collaboration between medicine regulatory authorities and Ethiopian Technology Authority (ETA) to carry out the complementary and synergistic regulatory activities on radiopharmaceuticals nationally.
- Inadequate regulatory guidelines for radiopharmaceuticals on Dossier assessment, Good Manufacturing Practice (cGMP) Inspection and Quality specifications.
- Inadequate capacity of radiopharmaceutical regulators for cGMP inspection, Dossiers Assessment, Inspections and Audits on radiopharmaceutical preparations.
- Most developing countries in Africa including Ethiopia do not have radiopharmaceuticals manufacturer and products are imported from abroad in a very small amount and lacks motivation of applicants.

3. SCOPE

This guideline covers the following products:

- ready-for-use radiopharmaceuticals, including certain PET radiopharmaceuticals,
- non-radioactive components (kits and chemical precursors including those for positron emission Tomography) for combination with a radioactive component (e.g. eluate from a radionuclide generator or a cyclotron produced radionuclide),
- radionuclide generators such as Mo-99/Tc-99m generators
- Radionuclide precursors used for radiolabelling other substances prior to administration.

This guidance document provides a general overview of the minimum requirements for dossier assessment of radiopharmaceutical products for Market Authorization. The main principles of dossier assessment are described in detail in draft EFDA Guideline for Registration of Medicines (fourth edition; 2023).

4. Major Challenges for Regulation of Radiopharmaceuticals in Ethiopia

The risk of marketing of substandard, adulterated, unsafe, non-efficacious and poor-quality radiopharmaceuticals due to weak regulations or low registration coverage is intolerable to the public and unacceptable from regulatory point of view. Therefore, it is deemed necessary to protect the public health by ensuring the safety, efficacy and quality of radiopharmaceuticlas via Market Authorization system through dossier assessment, GMP inspection and quality control testing medicine regulatory authority (EFDA). (In this case there is no much importing of radiopharmaceuticals and market in Ethiopia. We need to encourage investors and professionals in this area who are interested to establish radiopharmaceutical manufacturing firms within the country and/or who are also interested professionally to practice radiopharmacy and nuclear medicine in the country by avoiding process that may take unnecessarily longer time which could be discouraging to the national development in this regard. However, materializing & promoting this national principle without violating the principles of ensuring the safety & security of radiopharmaceuticals. In addition care should be taken also not to treat radiopharmaceuticals as merely normal medicines as this can complicate the various processes of its diversified handlings & can unnecessarily elongate its normal process.

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5. Registration and Market Authorization requirement Radiopharmaceuticals

Module 1: Administrative and Product Information

The main principles and general formal requirements for documents and the requirements for Module 1 are similar and as specified in EFDA Guideline for Registration of Medicines will be applicable in this guideline as required. Assessor should ensure availability of the following information.

The safety rules and special conditions of storage, transport and utilization are described. They are summarized in the SmPC, packaging slip and labeling plans

- Dated and signed covering letter for submission of the dossier by mentioning the product included in the dossier from the manufacturer and/or local agent or local representative responsible for registration.
- A completed and signed application form should be submitted through eRIS and the date of application should correspond to the date of submission of the registration dossier to the Authority.
- A valid current good manufacturing practice (cGMP) certificate issued by the local authority in the country of origin and an officially signed and dated valid cGMP Waiver letter issued

by EFDA or a valid current good manufacturing practice (cGMP) certificate issued by EFDA should be provided.

- Product information including the package insert, labeling, and summary of product characteristics (SmPC) should be provided. Specific requirements for product information of Radiopharmaceuticals are annexed in this guideline.

MODULE 3: DRUG SUBSTANCE(S)

Radiopharmaceuticals are significantly different from "conventional" medicines, in both their characteristics and the production process, the requirements applicable to the manufacture of "conventional" pharmaceuticals may often be different from those applied to the manufacture and control of radiopharmaceutical products.

Radiopharmaceutical-specific characteristics generally include the following:

- simple distribution chain, with direct delivery of the finished product from the manufacturer to the nuclear medicine department;
- small batch size;
- limited shelf-life/half-life of minutes to several days; and
- Quality control (QC) sample representing the entire batch and release before analysis result is ready.

In addition, diagnostic radiopharmaceuticals often have a low potential to exert pharmacological or toxic effects, owing to the micro-dose levels administered. Furthermore, radiopharmaceuticals are often administered prior to completion of all QC testing. Tests such as sterility and determination of endotoxin content and radionuclidic purity may need to be performed post-release.

In a radionuclide generator, both mother and daughter radionuclides are to be considered as active ingredients. For radiopharmaceutical kits, the active ingredient is considered to be that part of the formulation that is intended to carry or bind the radionuclide or to permit its binding. In addition, the radiolabelled form obtained after radiolabelling with a suitable radionuclide should be described.

The active substance of a radiopharmaceutical kit and the chemical precursor for the synthesis of PET radiopharmaceuticals also refer other relevant guidelines. Information on chemical precursors including those for synthesis of PET radiopharmaceuticals may be presented in a separate section 3.2.S.

Radioactive drug substances are as a rule not isolated; they are usually presented as solutions. This gives advantages when handling and reduces the effect of radiolysis.

For radiopharmaceuticals prepared from kits, documentation on the chemistry of the active substance can in some cases be obtained and presented differently from what is described in the relevant note for guidance (e.g. some technetium complexes). It should however be ensured that all information necessary to evaluate the active substance specifications (e.g. information on related substances and residual solvents) is available.

Radioactivity should be expressed in Becquerel or Curie at a given date, and time if appropriate. If a calibration time is stated, the time zone used should be stated (e.g. GMT/CET). Where practicable, specific radioactivity, carrier free, non-carrier added or carrier added should be stated.

3.2.S.1. General Information (3.2.S.1)

3.2.S.1.2. Structure

The structural formula should indicate the position of the radionuclide if applicable. For radiopharmaceutical kits the structure of the radiolabelled compound should be described.

3.2.S.1.3. General Properties (3.2.S.1.3)

For radionuclides, their source must be specified, i.e. whether fission or non-fission, the decay characteristics of the radionuclide e.g. half-life, type, energy and probability of its emission should be stated for the most frequent. Information on whether the radionuclide is carrier-free, carrier-added or not-carrier-added should be provided.

3.2.S.2. Manufacture

3.2.S.2.1. Manufacturer(s)

For radionuclides this should include the source of any irradiation target materials and site(s) at which irradiation occurs.

3.2.S.2.2. Description of Manufacturing Process and Process Controls

Except for non–radioactive components a full description is required of the production process of the radionuclide (isolation or manufacturing of the radioactive starting material).

3.2.S.2.3. Control of Materials

Requirements for the target material (specifications and control methods) should be described here when applicable.

3.2.S.2.6. Manufacturing Process Development

For radionuclides this should include nuclear transformation, including unwanted transformations that may occur under the irradiation conditions used due to isotopic impurities present in the target material; irradiation conditions, including effect of variations on nuclear reactions; description and validation of separation processes; influence of geometry of the target chamber and its material.

3.2.S.3. Characterisation

3.2.S.3.1. **Elucidation** of Structure and other Characteristics

For radiopharmaceutical kits the structure of the radiolabelled compound should be elucidated where possible.

3.2.S.3.2. Impurities

Radionuclidic impurities should be described and their physical characteristics should be stated. Radiochemical impurities should be discussed. The effect of radiolysis on the purity should be addressed.

3.2.S.4. Control of Drug Substance

3.2.S.4.1. Specification

For radioactive substances the specification should include radionuclidic identity and purity, radiochemical identity and purity, specific radioactivity and radioactive concentration. In addition the specification should describe the potential and existing impurities and the respective quantity limits.

3.2.S.4.3. Validation of Analytical Procedures

The ICH guideline provides a definition for each of the mentioned validation characteristics and methodology, with practical hints on how to investigate specificity, linearity, etc.; thus, it represents a general and commonly accepted basis for the validation of analytical methods. However, in the ICH guidelines it is also stated that "approaches other than those set forth in this guideline may be applicable and acceptable. It is the responsibility of the applicant to choose the validation procedure and protocol most suit□able for their product", thus recognizing that the suggested methodology may not be fully applicable in special cases. Although they are not specifically mentioned in ICH text, radiopharmaceuticals are certainly a special case. With the aim to provide guidance on the validation of radioanalytical methods, the ICH parameters has been modified to address the specific tests required for radiopharmaceuticals as indicated below (Table 1)

Table 1. ICH table adapted to Radiopharmaceuticals

Type of analytical procedure	Radioactivity Content (assay)	Radionuclide identity (approx. t½)	Radionuclide identity (spectrometry)	Radiochemical identity (HPLC/TLC)	Radionuclidic purity (limit test)	Radionuclidic purity (spectrometry after decay)	Radiochemical purity[a] (HPLC/TLC)
Characteristics							
Accuracy	+	–	+	–	+	+	+
Precision (Repeatability)	+	+	–	–	–	(+)	(+)
Intermediate Precision	–	–	–	–	–	(+)	(+)
Specificity	+	+	+	+	+	+	+
Detection Limit	–	–	–	–	+	–	–
Quantification Limit	–	–	–	–	–	+	+
Linearity	+	+	–	–	–	+	+
Range	+	+	–	–	–	+	+

(+) not always possible (e.g. short half life, see text)
[a]radioenantiomeric purity measurements should be validated analogously

3.2.S.4.5. Justification of Specification

Information with regard to justification for the specification should be provided.
The specification for the amount of radioactivity and radiochemical impurities may deviate from general principles of assay and related substances due to limitations of the measurement procedures, the special chemistry involved and the small chemical amounts present.

3.2.S.5. Reference Standards or Materials

Information on calibration standards used in radioactivity measurements should be provided.

3.2.S.6. Container Closure System

The lead shielding is secondary packaging and should only be briefly described.

3.2.S.7. Stability

The shelf life and the storage conditions for the active substance should be specified and justified. The general stability guidelines are fully applicable on the non-labelled active ingredient applied in radiopharmaceutical kits and chemical precursors for the production of PET radiopharmaceuticals. They are not fully applicable for drug substances used in ready-for-use radiopharmaceuticals, radionuclide generators and radioactive precursors due to the radioactive nature of these substances. Stress testing of radioactive substances is often not feasible. In some cases simulated stress testing may be performed on the non-radioactive chemical form.

MODULE 3: DRUG PRODUCT (3.2.P)

3.2.P.1. Description and Composition of the Drug Product

Radioactivity should be expressed in Becquerel or Curie at a given date, and time if appropriate. If a calibration time is stated, the time zone used should be stated (e.g. GMT/CET). Where

practicable, specific radioactivity, carrier free, non-carrier added or carrier added should be stated.

For radiopharmaceutical kits, the chemical amount of active substances should be specified.
Only one activity and/or radioactive concentration (volumic activity) may be included in the application of radiopharmaceuticals ready-for-use and this can apply to all activities and radioactive concentrations of the same radiopharmaceutical without the need for separate application. However radiopharmaceuticals having both diagnostic and therapeutic uses can be applied in a single application.

3.2.P.2. Pharmaceutical Development

Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96) and Note for Guidance on Pharmaceutical Development (ICH Q8) (EMEA/CHMP/167068 /2004).

3.2.P.2.1.1. Drug Substance

Data on the influence of radioactivity on the excipients should be provided.

3.2.P.2.2.1. Formulation Development

Data on stability of particles (e.g. of colloidal size), after reconstitution, should be presented.

3.2.P.2.3. Manufacturing Process Development

For radiopharmaceutical kits the suitability of the proposed radiolabelling procedure should be fully demonstrated, using the extremes of volume and radioactivity recommended. The specification of the radioactive material necessary for labelling kits should be established, Specification should include i.e. content of radioactivity, volume, purity and pH. Instructions for final preparation (the reaction time and any manipulation necessary during final preparation, including dilution prior to administration where relevant should be detailed and justified). Any special quality requirement for the diluent should be stated here if appropriate. Quality control

procedures to be applied by the end-user should be justified during the development pharmaceutics. Reproducibility and robustness must be demonstrated. Moreover, the quality control method used by the end-user should be cross-validated against the quality control method applied for batch release by the manufacturer.

For a radionuclide generator a general description of the system must be given, with a detailed description of those components that could have an influence on the composition of the eluate. The materials supplied with the generator to permit elution (e.g. eluent and evacuated vials) should be described. The recommendations for use of the generators should be discussed and documented. Measures to take to avoid problems during transportation should be discussed.

Influence of the purity of any substance (e.g. reagents and materials such as tubes, filters, column materials) used in the production of radiopharmaceuticals in automated units (e.g. PET radiopharmaceuticals) and of the parameters of this process on the quality of the final preparation should be discussed.

Potential and actual impurities should be discussed not only for any direct effect on the patient but also for their possible influence on the radiochemical purity and/or bio-distribution of the product.

3.2.P.2.4. Container Closure System

Compatibility of the radiolabelled product with the container and closure should be considered and validated where appropriate. It should be described if compatibility problems between the product and representative syringe materials or container closures used for patient doses were observed or expected.

3.2.P.3. Manufacture

Information on manufacturer of Radiopharmaceuticals should refer relevant EMA guidelines such as Note for Guidance on Manufacture of the Finished Dosage form (CPMP/QWP/ 486/95).

3.2.P.3.2. Batch Formula

Batch sizes of radiopharmaceuticals containing radionuclides may vary from batch-to-batch. The minimum and maximum batch size that can be applied in commercial manufacturing should however be defined in the dossier and justified by process validation data.

3.2.P.3.3. Description of Manufacturing Process and Process Controls

Apart from the manufacturing process, in addition the following, should be described in the dossier for radiopharmaceuticals:

- For radiopharmaceutical kits a detailed description of the radiolabelling procedure should be given.
- For radionuclide generators a detailed description of the elution procedure should be included. Because of the complexity of the production of radiopharmaceuticals such as generators, special attention should be paid to methods for obtaining and maintaining sterility during manufacture (preparation and assembly).
- For radiopharmaceuticals containing radionuclides of short physical half-life (e.g. PET radiopharmaceuticals), that can be released before all results on finished product testing are available, special attention should be devoted to the purity and control methods for all starting materials, reactants, chemicals, reagents and solvents used in synthesis and purification.
- For radiopharmaceuticals, which are synthesized in automated units, including PET radiopharmaceuticals, the unit and all production steps in this unit should be described in detail, including cleaning and steps to avoid contamination where relevant. Indicators of malfunctioning computer control should be stated.
- In the case of radiopharmaceutical suspension information on particle size distribution should be provided.

3.2.P.3.4. Controls of Critical Steps and Intermediates

For radiopharmaceuticals containing radionuclides of short physical half-life (e.g. PET radiopharmaceuticals), that can be released before all results on finished product testing are available, special attention should be devoted to in-process controls for critical parameters of the production process. The filter used in final filtration should be tested for integrity before release of the product in accordance with Ph.Eur requirements (5.1.1 Methods of Preparation of Sterile Products - Filtration).

3.2.P.3.5. Process Validation and/or Evaluation

When radiopharmaceuticals are manufactured in situ for direct administration to the patient (PET radiopharmaceuticals with physical half-life of the radionuclide ≤ 20 min), the consistency of the production process has a particularly great importance.

For radiopharmaceuticals containing radionuclides of short physical half-life, that can be released before all results on finished product testing are available (e.g. PET radiopharmaceuticals), the manufacturing process should be fully validated.

3.2.P.4. Control of Excipients

Note for Guidance on Excipients in the dossier for application for marketing authorisation of a medicinal product (CHMP/QWP/396951/06).

3.2.P.5. Control of Drug Product

3.2.P.5.1. Specification(s)

The specifications should cover the generally required tests for the specific dosage form (such as dissolution for capsules and sterility and endotoxins for parenteral products).

Specifications for radiopharmaceuticals should also include radiochemical identity and purity, chemical purity and, where relevant specific radioactivity, radionuclidic identity and purity. Special attention should be paid to impurities that influence the radiochemical purity or biodistribution of the product. Acceptance limits for the radioactive concentration for diagnostic radiopharmaceutical should be within 90 to 110% of the label claim. For therapeutic radiopharmaceuticals, acceptance limits should be within 95 to 105% of the label claim. Wider limits must be conclusively justified (e.g. inferior accuracy of radioactivity measurement).

For kits, the specifications of the finished product shall include tests on the performance of products after radiolabelling. Appropriate controls on the identification, radiochemical purity,

radionuclidic purity, content of radioactivity and (where relevant) specific radioactivity of the radiolabelled compound shall be included. Radionuclidic purity testing of the radiolabelled product may be omitted if this test is performed on the eluate or the radioactive precursor applied for the labelling and this is justified. Any material essential for radiolabelling shall be identified and assayed (e.g. stannous chloride).

For radionuclide generators, details on testing for mother and daughter radionuclides are required. For generator-eluates, tests for specific activity, mother radionuclides, daughter radionuclides and for other radionuclidic and chemical impurities from the generator shall be provided. Specifications shall also be presented for materials delivered with the generator to permit elution (e.g. eluent and vacuous vials).

For radiopharmaceuticals described in a Ph. Eur. monograph, the suitability of the monograph should in all cases be demonstrated. If certain impurities (e.g. from new routes of production) are not covered by the monograph, methods are to be provided which control these impurities.

For some radiopharmaceuticals it may not be possible to obtain the results of certain tests, e.g. sterility test, before the product is released. However, these tests are important in the validation of the manufacturing process. It should be stated which tests are normally undertaken before the release of the product for use; and which are undertaken after release.

3.2.P.5.2. Analytical Procedures

Quality control tests carried out after labelling of kits to be performed by the end-user, should be described where relevant. These methods should be validated versus the methods applied by the manufacturer (cross validation).

3.2.P.5.6. Justification of Specification(s)

Radionuclidic impurities likely to be present and the changes in the levels of those impurities during the in-use lifetime of the product should be discussed.

For generators the potential of mother radionuclide breakthrough as well as other potential impurities from the generator systems should be discussed.

Release of drug products before all test results are obtained should be justified in each case.

3.2.P.6. Reference Standards or Materials

Information should be provided on radioactive standards used in the calibration of radioactivity measurement equipment.

3.2.P.7. Container Closure System

The lead shielding is secondary packaging and should only be mentioned briefly.

3.2.P.8. Stability

The general stability guidelines are not fully applicable for ready-for-use radiopharmaceuticals, radionuclide generators and radioactive precursors.

However, when applying the stability guidelines to radiopharmaceuticals the following aspects should be taken into consideration.

- In stability testing of ready-to-use radiopharmaceuticals, including PET radiopharmaceuticals, the minimum and maximum amount or concentration of radioactivity at the time of manufacture should be taken into account.
- In the selection of batches for radiopharmaceuticals containing radionuclides, one should not refer to pilot scale or production scale because it is generally not possible to define a fixed production scale size. Due to the short shelf-lives, batch sizes are determined by the market request. Stability results should be presented on three batches for which the applied manufacturing process meaningfully simulates that which will be applied for marketing, taking into account the upper limits for the batch size.
- The specifications and test procedures to apply should take into account the specific characteristics for radiopharmaceuticals (see also section 3.2.P.5.1).

- The minimum time periods covered at submission defined in the stability guidelines (12 months long term testing, 6 months accelerated testing, etc.) cannot be applied for radiopharmaceuticals with a proposed shelf life of less than one year. In these situations, the testing frequency should be adapted, so that data on at least 5 test points (including the initial one) are presented at submission.
- The guideline on Evaluation of Stability Data is generally not applicable to radiopharmaceuticals containing radionuclides.
- For radiopharmaceutical kits, the shelf life and recommended storage conditions of the prepared product should additionally be defined and justified. Data should be provided on the stability (including radiolabelling and biodistribution performance) of the kit (for shelf-life estimation) and of the reconstituted radiolabelled product using maxima and minima of radionuclide content and volume of reconstituting medium (to establish the maximum radiolabelled shelf-life).
- For radionuclide generators, the shelf life and recommended storage conditions of the eluate and of the different materials to permit elution (e.g. eluent and vacuous vials) should additionally be defined and justified. The influence of ageing and elution frequency on eluate quality should be discussed.
- For ready-for-use radiopharmaceuticals, the shelf life after the time of manufacture should be established. Establishing the shelf life after the time of calibration can also be accepted, provided that the time period between manufacture and calibration is strictly defined. The relationship between the production date, the calibration date and the use date should be stated. Moreover, the influence on product specification (e.g. radionuclidic purity) and performance should be discussed.
- Stress testing as generally described is not applicable for radiopharmaceuticals except for radiopharmaceutical kits.
- The storage conditions should be declared using the storage statements given in the relevant Note for Guidance.

- For radiopharmaceuticals prepared in multiple-dose vials, the stability following removal of successive doses, simulating the real use of the product, should be investigated over the proposed in-use shelf life. Sterile radiopharmaceutical products are often unpreserved, maximum shelf life should be one working day after first use or following reconstitution.
- In-use stability in syringes may be included here if available but is usually the responsibility of the end user.

MOUDLE 4: NON-CLINICAL DATA REQUIREMENTS

The application of this module will depend on the molecule under consideration. For new molecule (Innovator), full data on non-clinical study reports will be required while for those molecules which are not innovator (new) molecule but new to the Ethiopian market literature review on non-clinical study will be required. This section of the Guideline is not required for products that have been in Ethiopia.

This guideline describes the non-clinical data that need to be submitted in relation to the non-radioactive part of radiopharmaceuticals, in the context of applications for marketing authorizations. The need for a guidance paper focusing specifically on the non-clinical testing requirements for radiopharmaceuticals has emerged since currently there is no detailed guidance available. Therefore, in addition to the general non-clinical requirements described in e.g. ICH M3 (R2), ICH S9 and ICH S6 (R1), the principles for non-clinical data generation in support of the specific clinical uses of radiopharmaceuticals are laid down in this guideline.

This guideline covers radiodiagnostics as well as radiotherapeutics, and provides guidance for a targeted approach to assess pharmacology and safety of the non-radioactive part of a radiopharmaceutical. The principles explained in this document address the non-clinical evaluation as prerequisite for marketing authorization application. However, some of the principles outlined in this guideline might also apply to the non-radioactive component of so called “kits” and non-radioactive chemical precursors.

4.1.General principles

Scientific innovation and the ability to generate highly-targeted ligands led to the development of many different types of radiopharmaceuticals which show a large variety of clinical uses. They may be used as radiodiagnostics for scintigraphy imaging, for measurement of biodistribution or as radiotherapeutics administered to humans only once or with a low frequency of repeated administrations at doses lacking a measureable pharmacological effect. One common feature is that many of these radiopharmaceuticals are prepared in small-scale quantities for the use in exploratory trials and will not undergo a full development programme aiming to marketing authorization. However, like for other medicinal products, the same principles of safety evaluation should apply prior to the use of radiopharmaceuticals in humans in clinical trials as well as for marketing authorization purposes.

In the case of radiopharmaceuticals it has to be considered that they represent a special class of pharmaceuticals due to their conjugated design and radiolabel. They are composed of a non-radioactive, "cold", part with a radionuclide attached. The radionuclide may be linked to the non-radioactive ligand by a linker and/or chelators also called "carrier". Hence, all possible forms of the non-radioactive moiety are being named "non-radioactive part" throughout the paper.

General guidance, especially for the timing and duration of nonclinical safety studies, can be received from ICH M3 (R2) EMA/CPMP/ICH/286/1995. However, in many cases knowledge of the non-clinical characteristics and a clinical experience already exists for the non-radioactive part. In common with any other submission the presence of published or clinical data may obviate the need to conduct the complete non-clinical programme in line with ICH M3 (R2). This would also contribute to a reduction of animal use in line with the principles of 3Rs. Factors that are important to consider are the level of evidence on the pharmacological properties and toxicological characteristics of the non-radioactive part, the anticipated mass dose of the radiopharmaceutical in the clinical trial or for marketing authorization and the duration of treatment.

4.2."Targeted" non-clinical evaluation of radiopharmaceuticals:

4.2.1. Basic considerations

Toxicity of radiopharmaceuticals may be driven by the non-radioactive as well as the radioactive components of the radiopharmaceutical. The radiation emitted by the radionuclide is a wanted property of radiotherapeutics. In the case of radiodiagnostics, however, radionuclides with much lower emission of radiation and with usually a very short physical half-life are used.

For different scenarios as outlined below, where evidence needs to be only partly generated, a targeted non-clinical programme for the non-radioactive part of the radiopharmaceutical can be considered:

- Radionuclide changed in a known radiopharmaceutical: only the radionuclide is changed and the non-radioactive part was already used in numerous clinical trials or even authorized with other radionuclides. In this case, evidence should be provided by the applicant on the availability and results of the non-clinical testing already performed for the non-radioactive unchanged part of the formerly used radiopharmaceutical(s). Reference in the dossier to previous applications with the investigational radiopharmaceutical may be possible in cases the applicant is the same or has obtained permission to use non-clinical data of other applications. The use of literature or other publicly available data is possible but should be of good scientific quality and justified by the applicant.
- Radionuclide added to a known non-radioactive pharmaceutical: information is needed that the radiolabelling does not significantly alter the pharmacology of the whole molecule when the radionuclide is replacing an existing non-radioactive atom.
- Minimal change of the non-radioactive part of a radiopharmaceutical: this could be a small change in the amino acid sequence of a peptide or another small change in the molecular structure of the non-radioactive part of a known radiopharmaceutical, intended for example to improve stability. For this new but structurally closely related entity, the applicant should bridge from existing non-clinical data of the known radiopharmaceutical

and address possible changes in its pharmacology and safety in order to allow for a possible reduced non-clinical programme.

The micro-dose approach described in ICH M3(R2) is reflecting single as well as multiple administrations up to five including a wash out period and implies a reduced non-clinical testing in which safety 152 assessment in a single (rodent) species can suffice.

Due to possible peculiarities as outlined above a reduced non-clinical testing could be anticipated for additional scenarios. For example at dosages outside microdose toxicities related to the non-radioactive part are usually still minor compared to radiation-induced toxicities of a radiotherapeutic in oncology treatment. The amount of non-clinical data needed for the non-radioactive part is therefore dependent on risk–benefit considerations and exposure levels to the non-radioactive part. Hence, also in these cases a study in one species could be considered to be sufficient.

The aspects outlined above give rise to specific considerations regarding the extent and type of the non-clinical data package to support clinical trial and marketing authorization of radiopharmaceuticals. Specific approaches will avoid the unnecessary use of animals, allowing an optimal use of resources and, ultimately, facilitate the progression of these medicinal products into clinical use. In this regard, such a targeted non-clinical programme represents an opportunity for limiting animal testing in accordance with the 3Rs principles and is strongly encouraged. However, the spectrum of possible combinations of molecules to construct a radiopharmaceutical in addition to the possible therapeutic targets of radiopharmaceuticals is very broad.

Therefore, a flexible approach on a case by case basis might still be needed despite this guideline.

- Non-clinical safety programme for a known or minimally changed non-radioactive part of a new radiopharmaceutical
- Non-clinical safety programme of a new radiopharmaceutical using microdose
- Non-clinical safety programme of a new radiopharmaceutical using single sub-pharmacological or pharmacologically active doses
- Non-clinical safety programme for radiopharmaceuticals using multiple dosing

4.3.Non-clinical safety programme for a known or minimally changed non-radioactive part of a new radiopharmaceutical

In case no reference is possible to previous applications or other public data using the identical non-radioactive part of the investigational radiopharmaceutical, the reduced non-clinical programme outlined below for a known or minimally changed non-radioactive part should be considered.

In case no reference is possible to previous applications or other public data using the identical non-radioactive part of the investigational radiopharmaceutical, the reduced non-clinical programme outlined below for a known or minimally changed non-radioactive part should be considered.

4.3.1. Pharmacology

The appropriate characterization of pharmacology of the non-radioactive part alone is also expected in he case where the non-radioactive part of an already known radiopharmaceutical is claimed to be minimally changed. Emphasis should be laid on in vitro target/ receptor profiling. The selectivity and specificity of the non-radioactive part as well as secondary pharmacodynamics, defined as effects on other than the desired therapeutic targets, should be critically evaluated and documented. Measureable pharmacodynamic effects are normally not expected to be seen from the non-radioactive part of most radiopharmaceuticals for diagnostic or therapeutic purposes. However, evidence for the absence of pharmacodynamic effects is expected, and should be supported by appropriate data.

If no data are provided, the applicant has to justify the absence of in vitro/in vivo pharmacology data even in the case of a minimal change to the molecule.

4.3.2. Pharmacokinetics

For such minimally changed radiopharmaceuticals information on in vivo stability should be available. In addition, the biodistribution study performed in healthy animals of a relevant species including dosimetry should be thoroughly evaluated to detect any change in biodistribution and target organs related to the non-radioactive part compared to the former, known molecule. For radiotherapeutics, the study may be performed in an animal model of disease, if appropriate, to support that the targeted area/organ will still be reached adequately.

4.3.3. Toxicology

Main focus should be laid on the evaluation of the target organs of biodistribution and possible persistence of the modified non-radioactive part possibly leading to so far unknown toxic effects even if the change is claimed to be minimal. A biodistribution study in one species with single application and integrated measurement of toxicity endpoints can be generally considered sufficient. If off target binding is likely to be minimal from the results of the dosimetry study, histo-pathological examination may be limited to target organs.

In the case of an exploratory trial with intended clinical dose of the radiopharmaceutical being a microdose according to approach 1 or approach 2 as outlined in ICH M3(R2) (see also 5.3) and if, in addition, the absence of pharmacological activity of the non-radioactive part could be demonstrated, such a biodistribution study could be waived.

4.4. Non-clinical data for new radiopharmaceutical using microdose, single sub-pharmacological or pharmacologically active doses; using multiple dosing

In case no reference is possible to previous applications or other public data using the identical non-radioactive part of the investigational radiopharmaceutical, the reduced non-clinical programme outlined below for a known or minimally changed non-radioactive part should be considered.

The minimal requirements for the non-clinical development of a radiopharmaceutical carrying a new non-radioactive part using single sub-pharmacological (but above microdose) or pharmacologically active doses are outlined below. This non-clinical package is usually also considered sufficient for marketing authorization applications using the same dosing regimen.
In absence of complete clearance between administration of multiple doses in the therapeutic range standard ICH M3(R2) requirements should be followed for the non-radioactive part. There are no general differences in this respect between the expected non-clinical data package for radiodiagnostics and radiotherapeutics. In the case of a radiotherapeutic used in oncology, ICH S9 should be considered if applicable.

4.4.1. Recommendations for Radiodiagnostics

In most cases microdose approach 1 of ICH M3 (R2) will be used for radiodiagnostics since no pharmacological effect is intended and only a very small mass dose is administered after single administration.

4.4.1.1. Pharmacology

Radiodiagnostics are not intended to exert pharmacological activity, but evidence for the absence of pharmacological activity of the non-radioactive part should be provided. In this context, in vitro target/receptor profiling is usually sufficient.
Pharmacological activity of the non-radioactive part or its absence has to be shown by the applicant. In this context, in vitro target/ receptor profiling is usually sufficient.

4.4.1.2. Pharmacokinetics

A biodistribution study including dosimetry should be performed with a single dose of the radiodiagnostic. Information on in vivo stability, distribution and elimination should be available to allow estimation of tissue and whole-body radiation doses in the clinic and to identify target

organs for distribution and persistence of the radiodiagnostic. If relevant, information should be provided on absorption and biotransformation.

4.4.1.3. Toxicology

According to microdose approach 1 outlined in ICH M3(R2), the results of an extended single dose toxicity study using the intended route of administration (usually i.v. route for radiodiagnostics), with toxicokinetic data should be available for the non-radioactive part.
When using the microdose approach 2, a repeat dose study for at least 7 days would be expected. A study of shorter duration may be considered on a case by case basis.
For both approaches a study in one species, usually rodent, can be generally considered sufficient. In the extended single dose, as well as in repeat dose studies, haematology, clinical chemistry, necropsy data and histopathology will be fully evaluated. Investigation of local tolerance, where applicable, should be done as an integral part of the extended single dose study.
For radiopharmaceutical using single sub-pharmacological or pharmacologically active doses, generally, extended single dose toxicity studies in both a rodent and non-rodent should be available using the intended clinical route of administration with toxicokinetics, haematology, clinical chemistry, necropsy data and histopathology as evaluated endpoints.
If the non-radioactive part of the radiopharmaceutical does not show pharmacological activity at the intended clinical dose only one relevant species, usually rodent, is sufficient.
Investigation of local tolerance, where applicable, should be done as integral part of the extended single dose study. In addition, the standard core battery for safety pharmacology may be included as integral part of the extended single dose toxicity study.

For radiopharmaceuticals using multiple dosing, in the case of complete washout between dosing an extended single dose toxicity study in both a rodent and non-rodent should be available using the intended clinical route of administration with toxicokinetics, haematology, clinical chemistry, necropsy data and histopathology as evaluated endpoints. If the non-radioactive part of the radiopharmaceutical does not show pharmacological activity at the intended clinical dose only one relevant species, usually rodent, is sufficient. Investigation of local tolerance, where

applicable, should be done as an integral part of the extended single dose study. In addition, the standard core battery for safety pharmacology may be included as integral part of the extended single dose toxicity study.

4.4.1.4. Genotoxicity

Genotoxicity studies are not recommended. However, if e.g. data on structure-activity relationship (SAR) assessment are available they should be submitted.

For new radiopharmaceutical using single sub-pharmacological or pharmacologically active doses, the genotoxicity testing of the non-radioactive part of the radiodiagnostic, if not a biotechnology derived product, e.g. an Ames test, would be expected.

4.4.1.5. Reproductive toxicity and Carcinogenicity

For radiopharmaceuticals using multiple dosing, radiopharmaceuticals carrying a radionuclide with a high emission of radiation and a long half-life such as anticancer drugs, carcinogenicity and reproductive toxicity studies could be waived since the radiation emission of these medicinal products is causing well known DNA damage with consequences for carcinogenicity and reproductive toxicity. However, the respective risk should be outlined in the product labeling. Reproductive toxicity and a carcinogenicity studies for the non-radioactive part alone are usually not required unless there is concern due to the duration of the treatment while the radiation emission of the attached radionuclide is low.

4.4.2. Recommendations for Radiotherapeutics

The same testing strategy as outlined above for radiodiagnostics will also apply for new radiotherapeutics when using the microdose approach. The only additional aspect to consider in these cases is that the dosimetry study might be performed in an animal model of disease, if appropriate, to support that the targeted area will be reached adequately.

For new radiopharmaceutical using single sub-pharmacological or pharmacologically active doses, the minimal requirements for the non-clinical development of a radiopharmaceutical carrying a new non-radioactive part using single sub-pharmacological (but above microdose) or pharmacologically active doses are outlined below. This non-clinical package is usually also considered sufficient for marketing authorization applications using the same dosing regimen.

4.5. Good Laboratory Practice (GLP)

It is generally expected that non-clinical safety studies are carried out in conformity with the principles of GLP (Dir 2004/10/EC), but also principles of animal welfare should be applied. However, it is recognized that, due to the specific characteristics of radiopharmaceuticals, it might not be possible to conduct every study in conformity with GLP, in particular when the radiation emission is high. Frequently, such non-GLP results come from biodistribution and dosimetry studies. Therefore, in practice the relevant safety aspects are usually sufficiently addressed by conducting the non-clinical studies with the non-radioactive part of the radiopharmaceutical according to GLP.

If a pivotal non-clinical safety study has not been conducted in conformity with the GLP principles, a scientific justification should be submitted. This justification should also address the potential impact of the non-compliance on the reliability of the safety data. In any case the study should run according to the principles of GLP as close as possible. Detailed documentation of the study conduct, results and archiving of data should be ensured. In addition, the study should be performed in accordance with a prospectively designed study protocol.

5. Post approval Changes and Re-registration Applications

5.1.Variation

For post approval variations, applicants are advised to refer to and provide all relevant documents required by the guideline for submission of post-approval variation medicine

application. Whenever a product has been withdrawn from the market and/or its marketing authorization has been rejected, deferred, or withdrawn from market for any reason (such as deficiencies in GMP, product quality defect or ADE reports) in other countries, the local agent or the manufacturer should notify EFDA as per the article 67(17) of proclamation No 1112/2019.

5.2.Re- registration

Applications for re-registration of these category of medicines shall follow requirements specified in Appendix 4 (Requirements for Re-registration) of the Authority`s guideline for registration of medicines, 4th Edition, 2020.

6. REFERENCES

1) Note for Guidance on Summary of Requirements for Active Substances in Part II of the Dossier (CHMP/QWP/297/97 Rev. 1).
2) Guideline on Radiopharmaceuticals. EMEA/CHMP/QWP/306970/2007.
3) Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)
4) Note for Guidance on Pharmaceutical Development (EMEA/CHMP/167068 /2004)
5) Note for Guidance on Manufacture of the Finished Dosage form (CPMP/QWP/ 486/95).
6) Note for Guidance on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (CHMP/QWP/396951/06).
7) Guideline on manufacture of the finished dosage form, EMA/CHMP/QWP/245074/2015.
8) Eudralex Vol 4: Good Manufacturing Practice, Annex 3 - Radiopharmaceuticals.
9) COUNCIL DIRECTIVE 2013/59/EURATOM: laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing

Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom.

10) Guideline on the non-clinical requirements for 4 radiopharmaceuticals, EMA/CHMP/SWP/686140/2018.

11) Guidance for Pre-Clinical Studies with Radiopharmaceuticals, IAEA.

12) Gillings et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:7; EANM guideline on the validation of analytical methods for radiopharmaceuticals, EJNMMI Radiopharmacy and Chemistry, accessed on 06/09/2023.