World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

International Atomic Energy Agency (IAEA)/ World Health Organization (WHO) guideline on good manufacturing practices for investigational radiopharmaceutical products

Please send your comments to **Dr Sabine Kopp**, Team Lead, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before **30 April 2021**. Please use the "Table of Comments" for this purpose.

Our working documents are sent out electronically and are also placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/current-projects) for comments under the "*Working documents in public consultation*" link. If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.

SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/21.878:

International Atomic Energy Agency (IAEA)/World Health Organization (WHO) guideline on good manufacturing practices for investigational radiopharmaceutical products

Description of Activity	Date
Following a recommendation by the Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), the WHO Secretariat was recommended to revise the existing guideline on good manufacturing practices (GMP) for investigational products.	October 2020
Preparation of first draft working document. The GMP guidelines for Investigational radiopharmaceutical products is prepared in alignment with the revised document on GMP for Investigational products QAS/20.863 by an International Atomic Energy Agency (IAEA) expert working group.	January-February 2021
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	March 2021
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	May 2021
Discussion of the feedback received on the working document in a virtual meeting with an IAEA expert working group.	June-July 2021
Preparation of working document for next round of public consultation.	July 2021
Mailing of revised working document inviting comments, including to the EAP, and posting the working document on the WHO website for a second round of public consultation.	July 2021
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	September 2021
Discussion of the feedback received on the working document in a virtual meeting with an IAEA expert working group.	September-October 2021
Presentation to the Fifty-sixth meeting of the ECSPP.	11-15 October 2021
Any other follow-up action as required.	

International Atomic Energy Agency (IAEA)/World Health Organization (WHO) guideline on good manufacturing practices for investigational radiopharmaceutical products

Background

In view of a rapidly expanding field of molecular imaging and targeted radiopharmaceutical therapy, combined with the absence of a dedicated guidance specific to the manufacture of investigational radiopharmaceuticals used in both early and late clinical trials, the World Health Organization (WHO), in partnership with the International Atomic Energy Agency (IAEA), has raised the urgency for the generation of a new *IAEA/WHO guideline on good manufacturing practices for investigational radiopharmaceutical products* .

The objective of this guideline is to meet current expectations and trends in good manufacturing practices (GMP) specific to investigational radiopharmaceuticals used in clinical trials (i.e. Phase I, Phase II and Phase III trials) and to harmonize the text with the principles from other related international guidelines.

This text was developed in alignment with the *Good manufacturing practices; supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans (1).*

1. Introduction

1.1. Radiopharmaceuticals are rapidly re-emerging as clinically valuable tools used in the diagnosis and treatment of various types of disease. Molecular imaging agents offer unparalleled methodology to not only help elucidate the presence and the extent of disease but also to help characterize the disease, select specific patients for a particular therapy or to evaluate a treatment response. Additionally, novel targeted radioligand therapies offer alternatives to patients for whom no other treatment options exist.

1.2. This rapid expansion is accompanied by a set of challenges due to the complexity and unique nature of these agents. One of the main challenges associated with novel radiopharmaceutical development is how to define the proper balance with respect to the investigational radiopharmaceuticals manufacturing controls required when conducting early clinical studies, and the subsequent implementation of additional controls as the radiopharmaceutical is developed further into pivotal Phase III trials. Having inadequate manufacturing controls during early clinical evaluations either carries the risks of unnecessary patient harm or jeopardizes the validity of the collected study results. On the other hand, redundant manufacturing controls, particularly in the initial stages of development, carry the risk of slowing the pace of clinical development of potentially life-saving therapies. This risk is further intensified by other factors such as the high costs and lengthy time associated with the actual clinical conduction of the study, the completion of the agent pre-clinical evaluation, and the low probability of successful marketing approval. In light of these challenges, a balanced approach with respect to manufacturing process controls is essential as the degree of manufacturing process controls is correlated to the particular stage of radiopharmaceutical development, the nature of the agent itself, and the clinical study goals.

1.3. This guidance provides recommendations on the minimum standards that should be in place when preparing novel radiopharmaceuticals for Phases I-III clinical investigations that do not have a marketing authorization (MA).

1.4. Investigational radiopharmaceuticals are used for testing purposes, as a reference in a clinical trial for an unauthorized indication and to gain further information about the authorized form.

1.5. Depending on the country, these products are sometimes not covered by legal and regulatory provisions in the areas of GMP. The lack of both high-level GMP requirements and prior knowledge of the risk of contamination and cross-contamination of products contribute to the risk of using them in human subjects. In addition, the risk may be further enhanced in cases of incomplete knowledge of the potency, human biodistribution, and toxicity of the investigational radiopharmaceuticals.

1.6. To minimize the risks and to ensure that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture, investigational radiopharmaceuticals should be manufactured and managed in accordance with an effective quality management system (QMS) and the recommendations contained in this guideline.

1.7. Procedures should be flexible to allow for changes whenever necessary, as knowledge of the process increases over time and in accordance with the stages of development of the product.

1.8 Investigational radiopharmaceuticals should be manufactured in a manner that is compliant to GMP requirements that are specific to the particular stage of agent development.

1.9 As the clinical development of radiopharmaceutical progresses from Phases I-II to the pivotal pPhase III and commercial stage, process and analytical method validation should be implemented so as to ensure:

- that subjects of clinical trials will be protected from poor quality products due to unsatisfactory manufacturing;
- that consistency exists between and within batches of the investigational radiopharmaceuticals; and
- that consistency exists between the investigational product and the future commercial product.

1.10 The selection of an appropriate dosage form for clinical trials is important. While it is accepted that the dosage form in early trials may be different from the anticipated final formulation (e.g. different buffers, radiostabilizers and other excipients), in the pivotal Phase III studies, it should be similar to the projected commercial presentation. If there are

significant differences between the investigational and commercial dosage forms, data should be submitted to the registration authorities to demonstrate that the final dosage form is equivalent, in terms of bioavailability and stability, to that used in the clinical trials.

1.11 The quality of investigational radiopharmaceuticals should be appropriate for the particular stage of development. For example, it should be feasible to apply only the critical manufacturing controls for agents in Phase I and Phase II trials, while the manufactured investigational radiopharmaceuticals in Phase III clinical studies should be characterized and assured at the same level as for commercial manufactured products.

1.12 This document should be read in conjunction with other World Health Organization (WHO) GMP guidelines, including good clinical practices (GCP), good documentation practices and International Atomic Energy Agency (IAEA) radiation protection documents related to radiopharmaceuticals *(2-8)*.

2. Scope

2.1 The recommendations in this guideline are applicable to investigational radiopharmaceutical products for human use.

2.2 The recommendations of this guideline do not apply to radiopharmaceuticals in Phase IV (with MA) that already have regulatory authority approval for a certain indication but might be used to conduct a clinical study for a different indication. In those situations, the IAEA/WHO guideline on GMP for radiopharmaceutical products should be used *(2)*.

3. Glossary

The definitions given below apply to the terms used in this guideline. They may have different meanings in other contexts.

"as low as reasonably achievable" (ALARA). Used to define the principle of underlying optimization of radiation protection. This is practised based on the principles of time, distance and shielding, as well as an emphasis on creating adequate awareness among all stakeholders.

active pharmaceutical ingredient (API). With respect to radiopharmaceutical preparations, the API is the radioactive molecule that is responsible for the radiopharmaceutical mechanism of action. This API may be in the form of the radionuclide by itself, if its use by itself is clinically indicated, or in the form of radionuclide coupled to a non-radioactive ligand or vector molecule.

drug substance (DS). Another name for an active pharmaceutical ingredient (API).

drug product (DP) or final drug product (FDP). With respect to radiopharmaceutical preprarations, the drug product is a combination of the drug substance and other components of the formulation such as diluents, radioprotectants and other formulation excipients. In some instances, the drug substance is co-produced concurrently with the drug product in a single seamless process. In other cases, the radioactive drug substance is synthesized first and then is fomulated further as a seprate process to yield the final drug product.

clinical trial. Any systematic study on (radio)pharmaceutical products in human subjects, whether in patients or other volunteers, in order to discover or verify the effects of, and/or identify any adverse reaction to, investigational products and/or to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally divided into Phases I-IV, although Phase IV studies usually do not apply to investigational radiopharmaceuticals and, thus, are not mentioned further. It is not always possible to draw clear distinctions between these phases and different opinions about details and methodology do exist. However, the individual phases, based on their purposes as related to the clinical development of pharmaceutical products, can be briefly defined as follows:

- **Phase I.** These are the first trials for new radiopharmaceuticals (also called "first in human"), often carried out in healthy volunteers. Their purpose is to make a preliminary evaluation of safety, and an initial pharmacokinetic/pharmacodynamic profile, an initial safety assessment of the active ingredient and radiation dosimetry.

- **Phase II**. The purpose of these studies is to determine activity and to assess the short-term safety. The trials are performed in a limited number of subjects, but higher than Phase I, and are also aimed to determine optimal administered dose. In case of therapeutic radiopharmaceuticals, they are also aimed to the clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.
- **Phase III**. This phase involves trials in large (and possibly varied) patient groups for the purpose of determining the short- and long-term safety-efficacy, and assessing its overall and relative diagnostic accuracy and therapeutic value of the intended radiopharmaceutical. Phase III studies are often multicentric. The pattern and profile of any frequent adverse reaction must be investigated and special features of the product must be explored (e.g. clinically relevant drug interactions, factors leading to differences in effect, such as age, etc.). In general, the conditions under which the trials are conducted should be as close as possible to the normal conditions of use.

good manufacturing practices for radiopharmaceutical products. Good manufacturing practices (GMP) for radiopharmaceutical products are a set of practices, using a traceable process, that ensure that radiopharmaceutical products are consistently produced and controlled to the quality standards appropriate for their intended use and designed to consistently yield the radiopharmaceutical product. GMP fall under the umbrella of the overall quality management system (QMS).

investigational radiopharmaceutical. Any radiopharmaceutical product (new product or reference product) or placebo being tested or used as a reference in a clinical trial.

investigator. The person responsible for the trial and for protecting the rights, health and welfare of the subjects in the trial. The investigator must be an appropriately qualified person, legally allowed to practice medicine/dentistry.

monitor. A person appointed by, and responsible to, the sponsor for monitoring and reporting the progress of the trial and for the verification of data.

order. An instruction to process, package and/or ship a certain number of doses of an investigational radiopharmaceutical.

radiopharmaceutical product. For the purpose of this document, this term is defined in the same way as in the WHO guidelineon good manufacturing practices (GMP) for radiopharmaceuticals *(3),* such as, any pharmaceutical product that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for medicinal purposes.

product specification file(s). Reference file(s) containing all the information necessary to draft the detailed written instructions on processing, packaging, labelling, quality control testing, batch release, storage conditions and shipping.

protocol. A document which gives the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations and the conditions under which it is to be performed and managed. It should be dated and signed by the investigator/institution involved and the sponsor, and can, in addition, function as a contract.

retention sample. An additioninal sample of the final drug product that is collected and stored for the purposes of being analysed, should the need arise.

sponsor. An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, the investigator also then assumes the role of the sponsor.

4. Quality management

4.1 There should be a comprehensively designed, clearly defined, documented and correctly implemented QMS in place. Senior management should assume the responsibility for this, as well as for the quality of the investigational product.

4.2 All parts of the QMS should be adequately resourced and maintained.

4.3 The QMS should incorporate GMP which would be applied to all the life cycle stages of the products, including the transfer of technology, and the interface between the manufacture and the trial site (e.g. shipment, storage, labelling).

4.4 The QMS should ensure that:

- products are designed and developed in accordance with the requirements of this document and other associated guidelines, such as good laboratory practices (GLP), good clinical practices (GCP) and good storage and distribution practices (GSDP), where appropriate *(3-5)*;
- responsibilities are clearly specified in job descriptions;
- operations are clearly specified in a written form;
- arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- all necessary controls on starting materials, intermediate products, bulk products and other in-process controls are in place;
- calibrations and validations are carried out where necessary;
- the finished product is correctly processed and checked according to the defined procedures;
- deviations and changes are investigated and recorded with an appropriate level of root cause analysis done and appropriate corrective actions and/or preventive actions (CAPA) identified and taken;
- there is an appropriate system for quality risk management; and
- satisfactory arrangements exist to ensure, as far as possible, that the investigational radiopharmaceuticals are stored, distributed and subsequently handled so that their quality is maintained.

5. Quality risk management

5.1 A quality risk management system (QRM) should cover a systematic process for the assessment, control, communication and review of risks to the quality of the product and, ultimately, to the protection of the trial subjects and patients *(6).* Specific areas of quality risk assessment should include:

- sterility assurance;
- expiration time;
- route of injection ;
- method of sterilization;

- mass of the drug substance or ligand;
- physicochemical properties of the radionuclide/radopharmaceutical;
- planned dosing schedule (i.e. single dose or multiple doses into the same study subject);
- route of administration;
- agent specific in-vitro stability; and
- the degree of clinical investigator supervision.

5.2 The QRM should ensure that:

- the evaluation of the risk is based on scientific knowledge and experience with the process and product;
- as the agent development continues, the basis of risk assessment should be the transition from scientific knowledge and experience to process validationl
- procedures and records for QRM are retained; and
- the level of effort, formality and documentation of the QRM process is commensurate with the level of risk.

5.3 QRM should be applied both proactively and retrospectively, when appropriate.

6. Personnel

6.1 There should be a sufficient number of appropriately qualified personnel available to carry out all the tasks for which the manufacturer of investigational products is responsible.

6.2 Individual responsibilities should be clearly defined, recorded as written descriptions and understood by all persons concerned.

6.3 A designated person, with a broad knowledge of product development and clinical trial processes, should ensure that there are systems in place that meet the requirements of this guideline and other relevant GMP guidelines.

6.4 Personnel involved in the development, production and quality control of investigational

products should be appropriately trained in relevant GMP and in the requirements specific to the manufacture of investigational radiopharmaceuticals.

6.5 Production and quality control operations should be carried out under the control of clearly identified responsible persons who are separately designated and independent, one from the other.

6.6 In the manufacture of investigational radiopharmaceuticals, the same operator may be qualified either as a production operator or quality control operator, or both, and the training for a specific function should be documented. However, the same operator should not perform both manufacture and quality control testing of the same batch of investigational radiopharmaceuticals.

6.7 In the manufacture of investigational radiopharmaceuticals, it may be possible for the expertly qualified person responsible for batch release to also participate in either the batch production or quality control of a particular batch of investigational radiopharmaceuticals.

7. Documentation

7.1 Good documentation is an essential part of a QMS. The documents should be appropriately designed, prepared, reviewed and distributed. They should also be appropriate for their intended use.

7.2 The documents should be approved, signed and dated by the appropriate responsible person(s). No authorized document should be changed without the prior authorization and approval of the responsible person(s).

7.3 The documentation requirements applied during the manufacture of Phases I-II investigational radiopharmaceuticals may be less vigorous than the documentation requirements applied during the manufacture of Phase III investigational radiopharmaceuticals, but they would still need to be adequate in order to allow for traceability of the manufacturing process.

Specifications

7.4 Specifications (for starting materials, primary packaging materials, intermediate, bulk and finished products), batch formulae and preparation instructions should be as precisely detailed as possible and should take into account the latest state of the art.

7.5 In developing specifications, attention should be paid to the characteristics which may affect the efficacy and safety of products, namely:

- sterility and bacterial endotoxins;
- radioactive strength;
- radiochemical purity;
- specific activity, if applicable;
- the batch size that is intended for the trial, where applicable;
- the in-use stability;
- the preliminary storage conditions; and
- the shelf life of the product.

7.6 As a result of the development of an investigational radiopharmaceutical, specifications may be changed by following a documented procedure. Changes should be authorized by a responsible person. Each new version should take into account the latest data and information, current technology, and regulatory and pharmacopoeia requirements. There should be traceability of the previous version(s). The reasons for any change should be recorded. The impact of the change on any on-going clinical trial, product quality, stability, bio-availability and bio equivalence (where applicable) should be considered.

Product specification file(s)

7.7 A product specification file (or files) should contain the information necessary to prepare the investigational radiopharmaceutical using a controlled process. The product specification file may be in the form of a single document or multiple assembled documents that contain detailed written instructions on processing, packaging, quality control testing, batch release, labelling, storage conditions and/or shipping of the final product.

7.8 The product specification file should indicate who has been designated or trained as the designated responsible person(s) for the release of batches.

7.9 The product specification file(s) should be continuously updated whilst, at the same time, ensuring the appropriate traceability to the previous version(s).

7.10 The information contained in the product specification file should form the basis for the assessment of the suitability and release of the batch by the designated responsible person(s). It should include or refer to the following documents:

- specifications for starting materials, packaging materials, intermediate, bulk and finished product;
- analytical methods for starting materials, intermediate and finished product;
- manufacturing methods;
- in-process testing and methods;
- approved label;
- relevant clinical trial protocols;
- relevant technical agreements, as appropriate;
- stability data; and
- storage and shipment conditions.

Note: The contents and level of details will vary depending on the product and stage of development.

Manufacturing formulae and processing instructions

7.11 Detailed manufacturing formulae, processing and packaging instructions and records should be available. Where this is not possible, other clear, written instructions and written records should be available for every manufacturing operation or supply.

7.12 These records should be used when preparing the final version of the documents to be used in routine manufacture.

7.13 Batch records should be retained for at least five years after the termination or discontinuance of the clinical trial or after the approval of the investigational radiopharmaceutical.

7.14 Where the data are intended for inclusion in an application for MA purposes, the records should be maintained until the end of the life cycle of the product.

Batch manufacturing records

7.15 Processing, packaging and testing records should be kept in sufficient detail for the sequence of operations to be accurately traced. They should contain any relevant remarks which increase the existing knowledge of the product, allow and reflect changes and improvements in the manufacturing operations, and justify the procedures used.

8. Premises

8.1 The premises, where investigational radiopharmaceutical products are manufactured, should be located, designed, constructed and maintained to suit the operations to be carried out. The design of the laboratories used for the handling of radioactive materials should always consider the need for radiation protection, ALARA compliance, and exhibit a high level of cleanliness and controls to minimize possible microbial contamination *(7-9)*.

8.2 Because of the potentially high radiotoxicity of some long-lived, high potency products (e.g. alpha-emitters), cleaning and active monitoring are of particular importance. Effective cleaning procedures should be followed in order to prevent contamination of the operators. The visual inspection after cleaning, sampling and test procedures should be appropriate and the acceptance limits used after cleaning should be justifiable. Where cleaning agents are used, their selection should be justifiable.

8.3 In case the same facility and equipment are used to prepare different radiopharmaceuticals, including investigational radiopharmaceuticals, the layout and design of premises should aim to minimize the risk of errors and mix-ups and permit effective cleaning and maintenance in order to avoid contamination, cross-contamination and, in general, any adverse effect on the quality of the products.

8.4 General technical requirements for the premises involved in the routine preparation of radiopharmaceuticals also apply in case of investigational radiopharmaceuticals. For instance,

drains should be avoided wherever possible and should not be present in clean rooms. Where drains are required, these should be appropriately designed; sinks should be excluded from clean areas; technical area (e.g. rooms to access the rear of hot cells) access points should be configured in a way to minimize the entrance of the maintenance and technical personnel to the production (clean) areas.

8.5 The heating, ventilation and air-conditioning (HVAC) system and pressure cascade design for the different areas should be appropriately designed and maintained to minimize the risk of product contamination, and to protect the personnel from risks of radiation exposure. The pressure differentials should be controlled, monitored and recorded *(11).*

8.6 The appropriate controls should be in place to promote containment of radioactive gases and vapours.

8.7 Radioactive gases should be removed through separate air handling units fitted with the appropriate filters before being exhausted. These should be regularly checked for performance. The recirculation of radioactive contaminated air should not be allowed.

8.8 A dedicated area and dedicated equipment should be used for the manufacture of any investigational radiopharmaceutical product involving human blood or plasma.

8.9 Quality control laboratories should be separated from production areas.

9. Equipment and utilities

9.1 Equipment and utilities should be selected, located, constructed and maintained to suit the operations to be carried out.

9.2 Equipment and utilities should be qualified for their intended use. This may include user requirement specifications, design qualification (if applicable), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). Equipment and devices, as appropriate, should be calibrated and maintained.

9.3 Equipment maintenance, qualification and calibration operations should be recorded and records maintained.

9.4 Computerized systems, such as those controlling equipment, should be verified to ensure they are reliable and fit for the intended purpose *(10)*.

9.5 The dose calibrator (also known as the activity meter) should be qualified using suitable reference standards. If such a reference standard recognized by a national authority is not available, dose calibrator manufacturer recommendations or published literature may be used when deciding upon the appropriate dial setting.

10. Materials

Starting materials

10.1 The consistency of the production of investigational radiopharmaceutical products may be influenced by the quality of the starting materials. Their physical, chemical and, when appropriate, microbiological properties should therefore be defined, documented in their specifications, and controlled.

10.2 Specifications for precursors for radiolabelling should be as comprehensive as possible, given the current state of knowledge. They should include, for example, identity, purity or certification of origin (if applicable) and any other parameter or characteristic required to make the material suitable for its intended use.

10.3 Detailed information on the quality of precursors for radiolabelling and excipients (as well as of packaging materials) should be available.

10.4 Starting materials should be accepted by performing in-house testing. During the manufacture of investigational radiopharmaceuticals for Phase I-II clinical trials, the in-house testing may also be in the form of a review of the Certificate of Analysis (CoA) supplied by the reliable material supplier, to confirm compliance with the specification set by the investigational agent manufacturer. For positron emission tomography (PET) radiopharmaceuticals, the materials

acceptance based on CoA review may also apply to the Phase III stage, as long as the final product release testing adequately confirms that materials of correct quality were used. For the manufacture of cold kit products, generators and therapeutic radiopharmaceuticals in Phase III stages, additional physical tests (e.g. material identity confirmation) may need to be performed by the radiopharmaceutical manufacturer as part of material acceptance process, in addition to CoA review.

Reference standards for analytical purposes

10.5 Reference standards from reputable sources (e.g. qualified vendors) should be used, if available.

10.6 If not available from any source, the reference substance(s) for the precursor for radiolabelling should be prepared, tested and released as reference material(s) by the producer of the investigational pharmaceutical product.

11. Production

11.1 Investigational radiopharmaceuticals intended for use in clinical trials should, as far as possible, be manufactured at a facility that is described in the clinical trial regulatory application.

11.2 The batch size for investigational radiopharmaceutical products manufactured in a small-scale facility (sometimes, especially in hospital/academic settings, called a "radiopharmacy"), as opposed to the commercial batch size, may vary widely.

11.3 Where activities are outsourced to contract facilities, the contract must then clearly state, inter alia, the responsibilities of each party, compliance with GMP or of this guideline, and that the product(s) to be manufactured or controlled are intended for use in clinical trials. Close cooperation between the contracting parties is essential.

11.4 Access to restricted areas should be by authorized and trained personnel only.

11.5 Processes should be designed to minimize the risk of contamination, cross-contaminations and mix-ups. The following measures may be adopted to minimize these risks:

(a) procedures for clearing the room of previous product materials;

(b) processing and filling in segregated areas;

(c) avoiding the manufacture of different products at the same time, either in the same dedicated space or by the same personnel;

(d) performing manufacturing area decontamination and visual pre-checks;

(e) using manufacturing "closed systems" (e.g. automated systems), whenever possible; and

(f) using pre-assembled kit (cassettes), whenever possible.

11.6 The stability and shelf life of the finished product should be defined following the execution of a suitable written protocol.

11.7 The expiration dates and times for radiopharmaceuticals should be based on the results of an adequate number of stability tests.

Manufacturing operations

11.8 As process knowledge of an investigational radiopharmaceutical is often not comparable with that of a radiopharmaceutical used for standard clinical care, process validation may not always be complete during the development phase of products; thus, critical quality attributes, process parameters and in-process controls should be identified, based on risk management principles and experience with analogous products, if available.

11.9 The necessary instructions for preparation should be defined and may be adapted based on the experience gained during radiopharmaceutical development itself.

11.10 For sterile investigational products, the controls to assure sterility of the final drug product should be no less than for licensed products *(9)*. However, sterility verification studies (i.e. bacteristasis/fungistasis) may not need to be conducted prior to pivotal Phase III studies.

Packaging and labelling

11.11 At least the following information should be listed on the primary packaging container label:

(a) name of the product and batch number;

(b) name of the manufacturer;

(c) route of administration;

(d) amount of activity in appropriate units;

(e) radioactive concentration per millilitre at calibration date and time;

(f) volume;

(g) where relevant, the international symbol for radioactivity;

(h) end-of-synthesis date and time;

(i) expiration date and time;

(j) specific activity or mass, if appropriate; and

(k) cautionary statements (e.g. "Caution: radioactive material" or "For clinical investigational use only").

Note: reporting information about activity ("strength") on the primary label may not always be possible due to radiation protection reasons. In this case, the information may be reported on the secondary packaging label.

11.12 In the absence of regulatory authority requirements, the following minimum information may be listed on the secondary packaging container label, in addition to any information listed on the primary packaging:

(a) the qualitative composition;

(b) excipient information;

(d) storage instructions; and

(e) the address of the manufacturer.

11.13 The packaging must ensure that the investigational product remains in good condition during transport and storage. Any opening of, or tampering with, the outer packaging during transport should be readily discernible.

12. Quality control

12.1 Quality control should cover the sampling and testing of both the starting materials and the radiopharmaceutical final drug products, ensuring that materials are not released for use until their quality has been determined to conform to the predefined acceptance specifications.

12.2 As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets the approved specification at the time of testing.

12.3 The release of a batch of an investigational radiopharmaceutical product should only occur after the designated responsible person has certified that the product meets the relevant batch release requirements. At a minimum, these requirements should include the following:

- a review and approval of batch records, including control reports, in-process test reports, changes, deviations and release reports demonstrating compliance with the product specification file, the order and protocol;
- verification of appropriate production conditions;
- verification of the quality of starting materials (status of approval, CoA, etc.) ;
- verification of the validation status of facilities, equipment, processes and methods, as appropriate; and
- verification of conditions of storage and shipment.

12.4 Due to the inherent rapid radioactive decay of radiopharmaceuticals containing radionuclides with relatively short half-lives, these products may be released and administered prior to completion of all quality control testing. Under these circumstances, the required pre-release and post-release testing should be clearly defined and documented.

12.5 Sampling procedures should consider the nature and the characteristics of the material being sampled (e.g. a small batch size and/or its radioactive content) to make sure that the samples are representative of the entire batch of radiopharmaceutical.

12.6 Quality control samples should be prepared, handled and stored in a way to ensure the adequate identification and segregation of the test samples to avoid mix-ups and cross-

contamination.

12.7 Radiopharmaceutical final products failing to meet the acceptance criteria should be rejected and segregated. Such events should be investigated and the investigation outcome and proposed actions should be documented. Should the out-of-specification be detected after delivery/shipping of the finished product, information should be quickly given to the user, so as to prevent its administration.

12.8 Retention samples from every batch of a particular investigational radiopharmaceutical product should only be collected if they can be used to obtain meaningful testing data in the future. However, the collection of the retention samples is not required. The duration of storage of retention samples should be based on the ability to collect valid test data from using the sample.

13. Qualification and validation

13.1 The extent of qualification and validation activities should be in accordance with a risk-based approach, considering the complexity and critical aspects of the intended radiopharmaceutical production.

13.2 The extent of qualification and validation required for the manufacture of investigational radiopharmaceuticals in Phases I-II trials may be less than for the manufacture of investigational radiopharmaceuticals in pivotal Phase III trials. Nevertheless, the critical characteristics of the investigational radiopharmaceutical should always be addressed. For example, critical manufacturing step in-process control parameters such as reaction temperatures and/or transfer of the activities, may need to be defined and monitored at any stage of development; on the other hand, the validation of less critical controls such as bioburden sample collection or determination of maximum in-process holding times, may not be required during the Phases I-II.

13.3 The facilities and equipment need to be properly maintained and calibrated at any stage of development.

13.4 Equipment should be qualified for its intended use. At a minimum, the equipment should be verified to have conformance to the equipment manufacturer preventative maintenance (PM) and OQ requirements, as well as investigational radiopharmaceutical manufacturer PQ requirements.

13.5 The validation of aseptic investigational radiopharmaceutical preparation procedures presents special problems, as the batch size is often very small and the number of units filled may be not adequate for a full validation protocol. Thus, the validation of aseptic procedures needs to be supported by an operator and process validation via media fill test, which consists of conducting a process simulation using broad spectrum bacterial growth media to demonstrate that the aseptic processing/controls and production environment are capable of producing a sterile product. The successful completion of media fill testing is a prerequisite for the manufacture of investigational radiopharmaceuticals at any stage of development.

13.6 Manufacturing process validation should only be carried out after all of the critical requirements (e.g. media fill testing, relevant standard operating procedures {SOP} for operator training, and equipment PM OQ) have been completed. The validation batches campaign should include an adequate number of batches of the intended radiopharmaceutical(s). The number of batches and the batch size range should be predetermined as part of a risk assessment performed prior to process validation. In general, the completion of a minimum of three consecutive batches aimed for validation and stability studies is sufficient for the purposes of completing manufacturing process validation in Phase I trials. However, the number of batches produced may need to be increased in certain situations. For example, more validation and stability runs may be required when the manufacturer is trying to qualify multiple suppliers of a particular critical component (e.g. radionuclide provided by multiple suppliers).

13.7 Defined, documented and reproducible analytical methods aimed to establish chemical, radiochemical and radionuclidic purity, as well as identity, specific activity (if applicable) and impurities content, should be established before any manufacture for human subjects begins. However, analytical method validation protocols fully compliant with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards *(12)* for validation may be generated and implemented as part of transition into

pivotal Phase III trials.

13.8 Compendial analytical methods applied by the investigational radiopharmaceutical manufacturer that are described in relevant pharmacopeia do not require validation but may require verification prior to the initiation of manufacture for pivotal Phase III trials. For example, the compendial endotoxin testing method may not require full analytical method validation as described in relevant ICH guidances but may require the verification via conduction of drug product specific inhibition/enhancement studies.

13.9 General principles on validation of analytical procedures may be followed *(12)*, however, the unique nature of radioactivity should be considered and specific adaptations should be made, where required.

14. Complaints

14.1 There should be a written procedure describing the management of complaints. The procedure should provide a clear and concise description of responsibilities, actions that may need to be undertaken, communication pathways and structure, traceability and reporting requirements in the event a complaint is received.

14.2 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated.

14.3 Where necessary, the appropriate follow-up action, possibly including product recall, should be taken after the investigation and evaluation of the complaint.

14.4 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

14.5 The competent authorities should be informed if a radiopharmaceutical manufacturer is considering any action following the identification of serious quality problems with a product that may be impacting trial subjects or patients.

14.6 Any potential impact on the trial and/or on the product development should be investigated in order to determine the cause and to take any necessary corrective action.

15. Recalls

15.1 There should be a written procedure describing the managing of a recall of an investigational radiopharmaceutical. The procedure should provide a clear and concise description of responsibilities, actions that may need to be undertaken, communication pathways and structure, traceability and reporting requirements in the event a product recall is initiated.

15.2 The recall of a product should be documented and inventory records should be kept.

15.3 Multiple project-specific and product recall procedures may need to be implemented for various radiopharmaceuticals in order to reflect the requirements for a specific project. For example, the product recall requirements for a manufacturer that supplies investigational agents to the clinic within the same institution or hospital may differ significantly from the manufacturer that works with a pharmaceutical company sponsor and distributes the manufactured product to multiple external clinics. In all cases, the exact requirements need to be clearly defined and the staff need to be trained on those specific requirements.

16. Returns

16.1 Investigational radiopharmaceuticals should be returned under the agreed conditions defined by the sponsor, specified in written procedures and approved by authorized staff members.

16.2 Return processes should be in accordance with the handling of radioactivity and radiation protection rules.

16.3 Inventory records of returned products should be kept.

16.4 Returned radiopharmaceuticals should not be reused.

16.5 Since the return of radioactive products is often not practical, the main purpose of recall procedures for radiopharmaceutical products should be to prevent their use rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with national, and where applicable, international transport regulations *(13)*.

17. Shipping

17.1 The shipping of investigational radiopharmaceuticals should be carried out in accordance with written procedures laid down in the protocol or shipping order given by the sponsor.

17.2 Shipping processes should also be in accordance with international and local rules *(13)*.

17.3 The shipment should be accompanied by a printed form, including the relevant information related to the investigational radiopharmaceutical (e.g. the same information included in the secondary packaging label).

18. Destruction

18.1 The activity of the active principle of investigational radiopharmaceuticals decreases following the decay law and half-life of the radionuclide; thus, usually there is no need for product destruction.

18.2 Should the product be destroyed, however, international and local rules on handling radioactivity and radiation protection should be followed. A dated certificate of, or receipt for, destruction should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

Abbreviations

CAPA	corrective actions and/or preventive actions
GCP	good clinical practices
GLP	good laboratory practices
GMP	good manufacturing practices
GSDP	good storage and distribution practices
HVAC	heating, ventilation and air conditioning
MA	marketing authorization
IQ	installation qualification
OQ	operational qualification
PQ	performance qualification
PM	preventative maintenance
QMS	quality management system
QRM	quality risk management (system)
SOP	standard operating procedures

References

1. WHO good manufacturing practices for investigational pharmaceutical products for clinical trials in humans. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fourth report. Geneva: World Health Organization; 1996: Annex 7 (WHO Technical Report Series, No. 863; (https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs863-annex7-who-gmp-investigational-pharmaceutical-products-clinical-trials-humans.pdf?sfvrsn=2432f236_0, accessed 4 November 2020).
Update in process: WHO Working Document QAS/20.863 (https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/qas20-863-gmp-for-investigational-products.pdf?sfvrsn=3993da76_2, accessed 26 February 2021).
2. IAEA/WHO guideline on good manufacturing practices for radiopharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth

report. Geneva: World Health Organization; 2020: Annex 2 (WHO Technical Report Series, No. 1025 (https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/trs1025/trs1025-annex2.pdf?sfvrsn=7aceb0c1_6, accessed 28 January 2021).

3. WHO handbook for good clinical research practices, 2002; (https://www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf, accessed 4 November 2020).

4. WHO Handbook: Good laboratory practice, Quality practices for regulated non-clinical research and development, TDR/PRD/GLP/01.2, 2001; (https://www.who.int/tdr/publications/training-guideline-publications/good-laboratory-practice-handbook-ver1/en/, accessed 4 November 2020).

5. WHO good storage and distribution practices (GSDP). In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2020: Annex 7 (WHO Technical Report Series, No. 1025; https://www.who.int/publications/m/item/trs-1025-annex-7-gdp-medical-products, accessed 4 November 2020).

6. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs981-annex2-who-quality-risk-management.pdf?sfvrsn=2fa44bc4_2, accessed 4 November 2020).

7. IAEA safety standards for protecting people and the environment. Radiation protection and safety of radiation sources: international basic safety standards. Jointly sponsored by EC, FAO, IAEA, ILO, OECD/NEA, PAHO, UNEP, WHO. Vienna: International Atomic Energy Agency; 2014 (General Safety Requirements Part 3 No. GSR Part 3; https://www-pub.iaea.org/MTCD/publications/PDF/Pub1578_web-57265295.pdf, accessed 4 December 2019).

8. IAEA safety standards for protecting people and the environment. Radiation protection and safety in medicinal uses of ionizing radiation. Jointly sponsored by IAEA, ILO, PAHO, WHO. Vienna: International Atomic Energy Agency; 2018 (Specific Safety Guide No.SSG-46; https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1775_web.pdf, accessed 4 December 2019).

9. WHO good manufacturing practices for pharmaceutical product for sterile products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report.

Geneva: World Health Organization; 2011: Annex 6 (WHO Technical Report Series, No. 961; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs961-annex6-gmp-sterile-pharmaceutical-products.pdf?sfvrsn=61682f0c_0, accessed 4 November 2020).

10. WHO good manufacturing practices: guidelines on validation. Appendix 5. Validation of computerized systems. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 12 August 2020).

11. ISO 14644:2019(en). Cleanrooms and associated controlled environments – Part 3: Test methods (https://www.iso.org/obp/ui/#iso:std:iso:14644:-3:ed-2:v1:en, accessed 4 December 2019).

12. ICH Topic Q2(R1) "*Validation of Analytical Procedures: Text and Methodology*", June 2005; (https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-2-r1-validation-analytical-procedures-text-methodology-step-5_en.pdf, accessed 28/1/2021).

13. IAEA safety standards for protecting people and the environment. Regulations for the safe transport of radioactive material, 2018 edition. Vienna: International Atomic Energy Agency; 2018 (Specific Safety Requirements No. SSR-6(Rev. 1); (https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1798_web.pdf, accessed 8 January 2020).

Further reading

- International Ethical Guidelines for Health-related Research Involving Humans Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Geneva, 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 4 November 2020).
- The International Pharmacopoeia. Geneva, World Health Organization; updated regularly (https://www.who.int/medicines/publications/pharmacopoeia/en/ and https://apps.who.int/phint/2019/index.html#p/home, accessed 1 May 2020).

948 • EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, EU Commission
949 Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC
950 (https://ec.europa.eu/health/documents/eudralex/vol-4_fr, accessed 4 November 2020).
951 • WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO
952 Expert Committee on Specifications for Pharmaceutical Preparations: forty-eight report.
953 Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986
954 https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex2.
955 pdf?ua=1 accessed 4 November 2020).
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