Australian Government
Department of Health
Therapeutic Goods Administration

Manufacture of sterile radiopharmaceuticals labelled with fluorine-18

Interpretation of the PIC/S guide to GMP

Version 3.0, February 2019

TGA Health Safety Regulation

Contents

About this guidance

This guidance is for TGA licensed manufacturers of positron emission tomography (PET) sterile radiopharmaceuticals labelled with fluorine-18, and is about the application of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* PE009 (PIC/S Guide to GMP).

While this guidance is intended for **TGA licensed manufacturers** of sterile radiopharmaceuticals labelled with fluorine-18, it may also be of use to manufacturers who:

- are exempt from the requirement to hold a TGA licence to manufacture under Schedule 8 of the *Therapeutic Goods Regulations 1989*
- manufacture sterile radiopharmaceuticals labelled with fluorine-18

The scope of this guidance only applies to radiopharmaceuticals that are:

- labelled with fluorine-18 [^{18}F] (which has a short half-life)
- used as radiotracers for diagnostic imaging
- synthesised using cassette-based methodology, with cassettes and their reagents being supplied intact, as a kit (pre-assembled, low-bioburden, and ready for use) by qualified suppliers
- manufactured in small batches and small volumes, typically <50mL
- produced as a sterile finished good for parenteral use

Purpose

The TGA has adopted the PIC/S Guide to GMP, as the manufacturing principles for the manufacture of medicines, including sterile radiopharmaceuticals.

This guidance explains TGA's interpretation and expectations for compliance by TGA licensed manufacturers of sterile radiopharmaceuticals labelled with fluorine-18 with the PIC/S Guide to GMP. This guidance document provides specific interpretation of PIC/S clauses, and how compliance may be met. Where no specific guidance is provided, full compliance with the requirements of the PIC/S clause(s) is expected.

Comply with the requirements of the marketing authorisation unless the medicine you manufacture is exempt from Part 3-2 of the *Therapeutic Goods Act 1989*.

In all cases, default standards apply to the manufacture of radiopharmaceuticals as defined under the *Therapeutic Goods Act 1989*.

Development of this guidance

This guidance has been developed in collaboration with the radiopharmaceuticals technical working group. Technical Working Groups (TWG) have been established by the TGA to bring together manufacturing technical expertise from industry and the regulator to address the application of the currently adopted version of the PIC/S guide to GMP.

Disclaimer

This guidance is not mandatory or enforceable under law. It is not intended to be restrictive. We recommend following this guidance document to facilitate regulatory obligations being met. The guidance describes a way that a manufacturer may operate to demonstrate compliance with the relevant manufacturing principles (PIC/S Guide to GMP).

Guidance documents are not intended to establish a minimum standard of practice for inspection purposes. Guidance documents are not enforceable.

Related information

- TGA interpretation and expectations for demonstrating compliance PE009-13, the PIC/S guide to GMP for medicinal products
- Implementation of updates to ISO 14644 Parts 1 & 2 (2015)
- Compounded medicines and good manufacturing practice (GMP)
- ARGPM Guidance 20: Radiopharmaceuticals
- ICH guideline Q10 on pharmaceutical quality system
- EMEA/CHMP/QWP/306970/2007 – Guideline on radiopharmaceuticals
- ISO 13408-2:2018 Aseptic Processing of Healthcare Products – Part 2: Sterilising filtration
- Uniform recall procedure for therapeutic goods (URPTG)

Sections of PE009-13 that apply

In general, follow the principles of Part I (for the manufacture of the dosage form) and Part II (for the manufacture of the radiochemical API) of PE009-13, and in addition, all annexes relevant to your operation, such as:

- Annex 1 (manufacture of sterile medicinal products)
- Annex 3 (manufacture of radiopharmaceuticals)
- Annex 8 (sampling)
- Annex 13 (manufacture of investigational medicinal products)
- Annex 11 (computerised systems)
- Annex 15 (qualification and validation)
- Annex 19 (reference and retention samples)

Pharmaceutical quality system (PQS)

The principle of the pharmaceutical quality system (PQS), formerly called Quality Management System (QMS), is to ensure medicinal products are:

- ü fit for their intended use
- ü comply with relevant authorisation requirements
- û do not place patients at risk due to inadequate safety, quality or efficacy

To comply, your PQS should incorporate GMP and Quality Risk Management (QRM) principles and be:

- designed comprehensively
- documented fully
- implemented correctly
- monitored for effectiveness
- adequately resourced and fully supported by senior management

Marketing Authorisation

Where an applicable Marketing Authorisation (MA) is in place, manufacture the goods in full accordance with the conditions of the MA. (Part I, Chapter 1, Principle).

Where there is no Marketing Authorisation, e.g. where the product is exempt from the requirement to be included in the Australian Register of Therapeutic Goods (ARTG), the product formulation should be in line with the formally received clinician order and any default standards relevant to the production of the medicine.

Order management

Orders can be received in any format (phone/fax/email), but normally in written form (including a prescription), with the order then used as part of the final release check. Any changes made to the order should follow an established process to ensure appropriate documentation and approval of any change to avoid any mix-up.

If the order is not clear enough, then it should be clarified with the customer.

- For products supplied under Schedule 5A, Item 5 of the Therapeutic Goods Regulations 1990, the manufacturer should be aware of the specific conditions of supply, and is required to ensure that the product is not substantially similar to a product that is available commercially.
- For orders for products supplied under Schedule 5, Item 6 of the Therapeutic Goods Regulations 1990, the manufacturer should ensure that a specific patient(s) is identified within the order.

Personnel

The clauses in Chapter 2 of PE009-13 (including clause 2.1) place particular emphasis on the roles and responsibilities of senior management who have ultimate control over manufacturing facilities and activities. Senior management are accountable for ensuring appropriate resources are available to support the relevant manufacturing activities. Senior management are to define roles, responsibilities, and authorities for key management personnel (part I, clause 2.5).

Personnel involved in the manufacture of sterile radiopharmaceuticals labelled with fluorine-18 should have the appropriate education, training, experience and skills, or any combination of these elements that will ensure that staff can perform assigned duties and functions at an acceptable level. (Part I, clause 2.1)

Adequate microbiology expertise, either on or off site, is needed to support the provision of acceptable quality (including sterility assurance and environmental monitoring programs).

Documentation

Manufacturing formula and processing instructions

Approved manufacturing formula and processing instructions in writing are required for each product to be manufactured. The basic requirements of Chapter 4 of the PIC/S Guide to GMP still apply, although it is common for these to be included in one concise document.

Include all items used in the manufacture of the product in the Bill of Materials (BOM) with their uniquely identifiable batch number. Where a separate BOM is not used, list these items on the batch record.

A statement of the expected final yield with the acceptable limits, and yields for relevant intermediates, where applicable, should be included in the manufacturing formula (part I, clause 4.17d).

Retention of documentation

Retain all records associated with the manufacture of sterile radiopharmaceuticals labelled with fluorine-18 for at least 3 years (Annex 3.33).

Production

Sampling and management of starting materials

Radioactive starting material

Reference samples of radioactive starting materials, are not required (part I, clause 1.9viii).

The radioactive starting material fluorine-18 (^{18}F), does not need to be sampled or tested by the dosage form manufacturer before use where the quality, radioactive properties and identity are examined during the testing of the finished product (part I clauses 1.9ii and 5.30).

Where fluorine-18 (^{18}F) is supplied as an API to third parties, the material does not need to be sampled and tested by the API manufacturer for compliance with *Default Standards* before use where the quality, radioactive properties and identity are examined during the testing of the finished product (part I clauses 1.9ii and 5.30).

You are not expected to perform sampling or testing of radioactive materials where there is a radiological hazard to operators(s) that cannot be effectively controlled to acceptable levels.

Non-radioactive starting materials

Retain reference samples of non-radioactive starting materials and packaging materials in accordance with Annex 19 - *Reference and retention samples*, to permit future examination of the material if necessary.

Reference samples of gases, solvents or water used during production are not expected (Annex 3.49).

Sample every container of non-radioactive starting materials on receipt. Reduced sampling is only permitted in cases where the supplier has undergone a detailed qualification and evaluation, and the sampling procedure validated (refer Annex 8.2-8.3).

Non-radioactive starting materials should meet the requirements of relevant monographs in the default standards e.g. British Pharmacopoeia, European Pharmacopeia or United States Pharmacopoeia, and testing on each delivery of each lot received for compliance with the pharmacopoeia is required. Perform identity testing on each container sampled. Other tests may be performed on composite samples where scientifically justified.

Any reduction in testing must be fully justified in accordance with QRM principles and considering the results of the assessment and qualification of the supplier, and supply history, (Annex 8.3)

The sampling of gases purchased from commercial sources and used during production is not expected, and the approval for use of these gases may be performed based on supplier approval and certificates of analysis.

Stabilising solutions or additives

Manufacture any stabilisers used in the production of sterile products in accordance with GMP requirements, e.g. sodium thiosulphate.

$H_2{}^{18}O$ starting materials

Source the $H_2{}^{18}O$ used in the production of ^{18}F from a suitably qualified supplier. Assess each lot received for compliance with a defined specification; certificates of analysis should be available for each lot used.

Synthesis kits

Reference samples are not required for commercial synthesis kits and their accompanying reagents manufactured in accordance with GMP, e.g. peptide precursors and solvents (part I, clause 1.9viii).

Synthesis kits and reagents supplied directly from a supplier in the supplier's sealed containers and supplied with a certificate of analysis are exempt from sampling and identification testing, where the supplier is an approved supplier under the quality system of the finished product manufacturer (Annex 8.3).

Sampling areas for starting materials

A separate sampling area is not usually required for radiopharmaceutical starting materials. However, where sampling is performed and materials are exposed to the environment, conduct sampling in such a way as to prevent contamination or cross-contamination of the material and environment (part I, clause 3.22).

Qualification of suppliers

All suppliers of starting materials (including packaging materials) should be qualified under the manufacturer's Pharmaceutical Quality System (PQS) and in accordance with Quality Risk Management Principles. Take account of the following when validating starting materials (Annex 8.3):

- manufacturer and supplier understanding of GMP requirements of the pharmaceutical industry
- Quality Assurance system of the manufacturer
- manufacturing conditions
- nature of the starting material and the medicinal products in which it will be used

Clean areas

Clean room and clean air device design

Carry out the manufacture of sterile products in clean areas. There are four grades of clean area, A, B, C and D, classified according to required environmental characteristics of the area (Annex 1.3, 1.4 & 1.19). Air supplied to clean rooms or clean air devices should be passed through filters of an appropriate efficiency.

Hot-cells

'Hot-cells' used for the production of sterile radiopharmaceuticals labelled with fluorine-18 should be carefully designed and located so that:

- the required air quality for the respective zones can be achieved in accordance with Annex 1.3 & 1.17
- the risk of contamination from the environment of aseptically manufactured products is effectively minimised

For hot-cell systems that are built or upgraded after 1 January 2019, the following grade requirements should be met.

Grade	Examples of operations for manufacture of sterile radiopharmaceuticals labelled with fluorine-18
A	Aseptic preparation and filling
B	Background or adjacent environment for the grade A zone, e.g. transfer hatch between grade C and grade A environments
C	Preparation of solutions prior to sterile filtration, e.g. synthesis Fully closed and automated operations

A hot-cell with a Grade C internal environment will be suitable when closed and automated systems (for example chemical synthesis, purification, on-line sterile filtration) are used. Hot-cells are required to meet a high degree of air cleanliness, with filtered feed air when closed. Carry out aseptic activities in a Grade A area (Annex 3.27).

Hot-cells used for aseptic processing should normally be equipped with integrated transfer systems that allow multiple decontamination steps via areas of increasing cleanliness in accordance with Annex 1.1, 1.31 & 1.33, requirements, e.g. materials are transferred from grade D → grade C → grade B → grade A.

Facilities seeking TGA licensing or licenced manufacturers upgrading their facilities after 1 January 2019 would be expected to design and implement equipment meeting the full requirements of Annex 1. i.e. Grade A/D interfaces would not be permitted.

Existing manufacturing facilities licensed by the TGA before 1 Jan 2019

For existing manufacturing facilities licensed by the TGA before 1 January 2019, the use of a laminar flow hot-cell that provides Grade A conditions located in a Grade D room for aseptic processing steps is acceptable (Annex 1.21). However, additional controls regarding the management of the grade D/A interface should be implemented and their effectiveness monitored, such as (but not limited to):

- Detailed *in-operation* and *at-rest* classification data demonstrating the appropriateness of the operations and manipulations at the A/D interface.
- *Comprehensive In-operation* and *at-rest* air-flow visualisation studies to clearly indicate and demonstrate the impact of the grade D air on the critical operation and cleanliness of the grade A zone is negated.
- *In-operation* and *at-rest* recovery studies to assess the required recovery time for the cleanliness of the grade A zone.
- Validated decontamination processes for the transfer of all materials from the grade D zone into the grade A zone. Ongoing routine environmental monitoring of the effectiveness of the decontamination processes employed both viable and non viable.
- Validated cleaning processes using a cleaning agent(s) with broad-spectrum activity. Consider the possibility of spore-forming isolates being present that may contaminate the grade A zone during set-up.
- Comprehensive environmental and personnel monitoring of the grade A, B, C and D environments where applicable during critical operations, e.g. equipment transfer and set-up, based on a risk assessment of the operations and qualification data (Annex 1.8). Reviewing any organisms isolated from the grade A environment and identifying to species level and maintaining a database of organisms to verify existing disinfectant regimes are effective in rendering the organisms(s) non-viable. On-going trend analysis to be performed on all operators to verify consistency with strict environmental monitoring limits, and appropriate procedures in place regarding exclusion where demonstrated non-compliance is observed.
- Ensuring operators wear gowns, facemasks, goggles and gloves that provide protection to the grade A environment and decontaminated equipment during critical operations, e.g. equipment transfer and set-up.
- Initial and on-going process simulations (media fills) including worst case manufacturing operations for all operators performing sterile manufacture.

Classification

Classify clean areas under both **in-operation** and **at-rest** conditions in accordance with EN ISO 14644-1. Detailed environmental characteristics can be found in Annex 1.4–1.5 of PIC/S Guide to GMP.

Monitoring of clean air device and clean rooms

Monitor clean areas under both **in-operation** and **at-rest** conditions in accordance with EN ISO 14644-2. Detailed environmental characteristics can be found in Annex 1.8–1.20 of PIC/S Guide to GMP. Follow Quality Risk Management principles when determining the ongoing environment monitoring programme; justify the selection of sampling locations, frequencies and methods based on risk to product quality (Annex 1.8).

Commence monitoring of the Grade A zone for both non-viables and viables at the start of each work session (during set-up) and where possible continue for the full duration of the session. Monitor and trend viable results.

During release of products manufactured in that session, consider:

- non-viable results for the session,
- the impact of any historical out of specifications or out of trends for viable results in determining whether the manufacturing environment is in control, any subsequent impact on product quality and if any corrective action needs to be taken.

Perform the environmental monitoring of lower grade areas in accordance with Annex 1 requirements.

If continuous monitoring cannot be achieved, e.g. due to the presence of radiological hazards, provide a full and comprehensive risk based justification of the processes employed in relation to environmental monitoring (Annex 1.9).

You need to set appropriate alert and action limits for the environmental results of particulate and microbiological monitoring, in alignment with Annex 1. If these limits are exceeded, operating procedures should prescribe corrective action.

Perform environmental monitoring whenever possible.

You are not expected to perform environmental monitoring where there is a radiological hazard to operator(s) that cannot be effectively controlled to acceptable levels.

Entry to clean areas

Access to clean manufacturing areas should be via a separate gowning area and restricted to authorised personnel (Annex 3.18). High standards of personal hygiene and cleanliness are essential.

Personnel, equipment and materials should enter clean areas through appropriately designed, controlled and operated airlocks. All items transferred into clean areas should be suitably cleaned, decontaminated and sanitised in order to prevent contamination of the grade into which the item is transferred. Decontamination and sanitisation processes should include the use of a sporicidal agent and should be validated for effectiveness, (Annex 1.61, 1.62, 1.64, 1.76, & 1.81).

Further guidance relating to the transfer of items into aseptic areas may be found in the TGA's guidelines for compounded medicines and good manufacturing practice (GMP).

Clothing

Clothing and its quality should be appropriate for the process and the grade of the working area. Wear clothing in a way to protect the product from contamination (Annex 1.42). A description of clothing required for each grade can be found in Annex 1.43.

Choose clothing to match the grade in which it is used, e.g. low-linting sterilised gowns and gloves are required for personnel entering the grade A/B areas of the facility.

Provide and record training in appropriate gowning processes. For aseptic areas, operators should undergo an initial qualification, and the operator's ability to correctly gown should be assessed periodically. Monitoring of the gown surfaces and gloves worn in grade A and B areas should be performed frequently, e.g. each session, in accordance with risk management principles, (Annex 1.8). Operator gowning qualifications should include all set up processes related to the manufacturing operations for grade A. Operators who do not demonstrate compliance with the environmental monitoring limits should be excluded from aseptic operations until such time they have demonstrated consistent reproducible consistency.

Aseptic processing

Process simulation should cover all parts of the aseptic process, including all aseptic manipulations and should be supported by valid process simulation studies. This is normally achieved by substituting the aseptically produced product with a sterile nutrient medium (media fill) (Annex 1.66).

Perform process simulation tests for aseptically produced sterile products as part of initial validation and repeated at 6 monthly intervals. They should be representative of the batch sizes manufactured.

Perform operator process simulation test twice per year for every operator involved in aseptic manipulations. A risk assessment reviewing the potential impact of operators on product sterility can be used to determine the number of operator process simulation tests performed by each operator; however, operators must participate in at least one operator process simulation test annually.

Process simulation tests using a nutrient medium (media fills) are required unless media in the appropriate container size are not available. In that case process simulation tests using sterile water for injection BP or saline for injection BP are an acceptable alternative to media fills, provided the entire contents of each filled vial are tested for sterility by a validated membrane filtration method (Annex 1.66).

Bioburden monitoring

Where synthesis kits are used and filter sterilisation is in line, the requirement to monitor the pre-sterilisation bioburden of the radioactive solution during routine production is waived due to the radiological hazard of collecting and analysing active samples, (Annex 1.80).

However, manufacturers should implement procedures to control the pre-sterilisation bioburden and this should be monitored by alternative means. For example:

- monitoring of the bioburden and endotoxin levels in a flush sample from the transfer lines between the cyclotron and synthesis units
- monitoring of the bioburden and endotoxin levels in a flush sample from the transfer lines between the synthesis units and grade A dispensing units
- monitoring the bioburden of any non-sterile additives, e.g. stabilising solutions.

The results of bioburden monitoring should be reviewed against working levels on contamination immediately before sterilisation. These levels should be defined and related to the efficiency of the method to be used. Organisms isolated should be identified to species level and data collected verified against the current disinfectant regimes to ensure the currently employed and validated disinfectant processes remain valid.

You are not expected to sample radioactive products for pre-sterilisation bioburden where there is a radiological hazard to operators(s) that cannot be effectively controlled to acceptable levels.

Sterilising filtration

Sterilisation processes should be validated (Annex 1.83) and in particular, data to demonstrate the ability of the sterilising filter to sterilise the specific product formulation should be available prior to product release.

Sterilising filter validation should include data to meet the requirements of Annex 1.110 – 115, and include:

- Data to demonstrate the bacterial retention capabilities of the filter assembly;
- Data to demonstrate the compatibility of the product-contact parts of the filter to ensure that the filter does not affect the solution and *vice-versa*;
- Data to establish the integrity testing values used to demonstrate filter integrity.

Additional guidance regarding the validation of sterilising filters may be found in ISO 13408 2:2018 Aseptic Processing of Healthcare Products – Part 2: Sterilising filtration.

Filter integrity testing

Confirm the post-use integrity of the sterilising filter using a validated filter integrity test, as soon as practicable. Typically this is performed the next working day, when radiation levels have decayed sufficiently to render the filter safe to handle (Annex 1.113). However, advancements in radiopharmaceutical manufacturing equipment technology can now provide filter integrity test results prior to administration into patient(s), and should be performed if the capability exists within the manufacturers organisational infrastructure.

- Accumulating used sterilising filters over a period of several working days to test for filter integrity in one session is not acceptable.

Filter integrity test data should be recorded and retained with the batch record.

Finished product

Crimping vial caps

It is not recommended to crimp outside of the dispensing hot-cell where filling has taken place, due to the radiation risk involved (Annex 1.119). If vial crimping is required, the equipment used to crimp vial caps should be designed to avoid the generation of non-viable particulates.

Visual inspection

Visually inspect, to a practical level, filled containers of parenteral products individually for extraneous contamination or other defects (Annex 1.124), for example focusing on external contamination and gross defects which may be supported by post decay examination.

Validate the inspection process through operator training and check the performance of the inspection equipment and operators at defined intervals. Record results of the validation and routine inspection results.

Operators performing visual inspection of filled containers should pass regular eye-sight examinations, and wear corrective lenses where required, (Annex 1.124). Retain records of eye-sight examinations.

You are not expected to perform visual inspection of filled containers where there is a radiological hazard to operator(s) that cannot be effectively controlled to acceptable levels.

Product yield

There are various measurements of product yield, and some variation in the product yield in terms of radioactivity is acknowledged.

It is important that manufacturers define which yield calculations are an indicator of product quality; normally the monitoring of synthesis yield is expected as a minimum. Synthesis yield may be calculated as follows:

$$\%\ Synthesis\ yield = \frac{Activity\ of\ product\ at\ end\ of\ synthesis}{Activity\ delivered\ to\ synthesis\ unit}$$

Document and trend yield results and investigate any significant deviation from the expected yield, as this may be indicative of a process issue that may impact product quality. (Part I, clause 5.39).

A variation in yield need not necessarily affect a decision to release the product if the finished product complies with specifications.

Rejected and waste materials

Clearly mark and store rejected materials, rejected product and waste from the manufacturing process in a safe manner until the radioactivity has decayed to a safe level (part I clause 5.61). A hot-cell used specifically for storing decaying rejected materials, product rejected prior to release and waste materials should be clearly labelled as such.

Finished product retention samples

Retain retention samples from each batch of product in accordance with Annex 19 requirements. The volume of the retained sample should be sufficient to permit repeat testing of samples in case of complaint or quality incident.

Container integrity

Due to the radiological hazard associated with sterile radiopharmaceuticals labelled with fluorine-18, batch specific testing for container-closure integrity is not expected. However, validation to support the integrity of the container-closure system should be performed to verify its ability to maintain the quality of the finished drug product and sterility over the expiry period. (Annex 1.117).

Quality control

Testing

Perform the testing of starting materials and each batch of product manufactured in accordance with any conditions of a Marketing Authorisation (where relevant) and default standards relevant to the material or product. Validate all test methods used in the analysis of starting materials and finished products before use, (Part I, clause 6.15).

All tests for finished products including the test for sterility should be performed as soon as possible (Annex 3.42)

Material specifications

A specification for the testing requirements for each starting material and finished good should be available and documented in the PQS. The specifications for finished products should include a clear justification for the test regime, particularly where the testing of specified related substances is omitted.

Fluorine-18 based radiopharmaceuticals are allowed to be dispatched before formal completion of all tests; however, the specification should outline the mandatory tests that should be conducted before the product is released for shipment or released for supply (i.e. administration into patients) respectively, (Annex 3.39).

Chemical testing

Perform chemical testing of sterile radiopharmaceuticals labelled with fluorine-18 for each batch manufactured. Testing protocols should normally include:

- appearance of solution
- half-life of fluorine-18
- radioactivity
- pH
- radiochemical purity
- radionuclidic purity
- stabilising agents
- residual solvents
- impurity testing

Sterility testing

Due to the relatively small batch size, of sterile radiopharmaceuticals labelled with fluorine-18, full compliance with the sample number and volume requirements specified in the default standards is not expected. Justify sampling plans and test volumes in accordance with quality risk management principles.

Commence sterility testing of filled containers as soon as practicable after radiation levels have decayed sufficiently to render the product safe to handle, preferably the next working day, unless otherwise justified and documented (Annex 1.125-1.127).

Utilising quality risk management and validation principles, it may be possible to justify the accumulation of sterility samples over a period of several working days (up to a week) before shipment for sterility testing. However, sterility testing should be performed as soon as practicable when:

- any quality issues are identified that indicate any possible impact to product sterility for batches awaiting testing
- changes to the manufacturing process, materials or environment indicate the need for expedited testing
- a newly qualified operator has commenced production of product for commercial supply and clinical use

Any delay in sterility testing (following decay of radioactivity) should be supported by appropriate validation to demonstrate that contamination in the product would be detected, i.e. there is no risk of false-negative sterility results following accumulation of samples.

The pooling of sterility samples across multiple batches is not encouraged, but may be permissible where justified by risk assessment. If pooling is conducted, you must fully investigate all batches (and input materials) implicated by a sterility failure.

Endotoxin testing

Perform endotoxin testing on each batch as soon as practicable, unless otherwise justified in accordance with the principles outlined in the sterility testing section and appropriately documented (Annex 1.125–1.127).

Test endotoxin samples from each batch as discrete samples (i.e. not pooled).

Endotoxin samples should be representative of the whole of the batch. Justify sampling plans and test volumes in accordance with quality risk management principles.

Stability testing

Perform stability testing for sterile radiopharmaceuticals labelled with fluorine-18 in accordance with the principles of Part I Clauses 6.26-6.36. Stability data addressing each product, formulation and activity level should be available for each product supplied. Stability testing should represent worst-case conditions, for example, include batches manufactured at the upper activity concentration.

Additional stability is required to support the shelf-life and storage conditions for any additives or stabilisers added to the formulated preparation to assure the chemical and microbiological quality of the finished product.

Environmental monitoring (EM)

Controls in place for microbiological media should include supplier evaluation and the availability of a certificate of analysis (C of A). Verify the suitability of each lot of prepared media before use, either by performing growth promotion testing of each delivery of each lot of media received, or alternatively, by validating the transport system used by qualified pre-prepared media suppliers to ensure that media deliveries are routinely transported under appropriately controlled conditions. Media and their containers (such as agar plates) used in grade A/B areas must be sterile before use.

The identification of all microorganisms in grade A areas should routinely be to species level. Staff performing identification tests should be adequately trained and experienced.

Isolates from Grade B should be identified to at least genus level except when:

- high individual counts are recovered
- negative trends indicating a deterioration in environmental control emerge
- recovery of potentially objectionable organisms

In these cases, additional identification of organisms (at least to species level) should be performed to aid in investigation and rectification of the event.

Typical local isolates should also form part of the validation for cleaning and EM programs. Isolates from the grade A areas upon identification should be verified against the EM validation database to ensure that the currently employed validated decontamination programme remains valid.

Perform reading and incubation of any microbiological plates in a location and in a manner that does not present a risk to manufacturing operations.

Release for supply

Annex 3.2, 3.39 & 3.51 permit sterile radiopharmaceuticals labelled with fluorine-18 to be dispatched to the clinical institute (under quarantine status) before formally recording the conformity of the batch with all QC tests and conditions. These provisions of Annex 3 prevail over Part I, clauses 1.4xv &1.9vii.

The finished product must not be administered to patients until the batch has been conditionally certified (released) for patient administration by the Authorised Person. The Authorised Person performing release for supply can conditionally certify the product for patient use, and then finally certify the product after all the relevant test results are obtained (Annex 3.39).

Procedure for release for supply

Establish a written procedure detailing the assessment of production and analytical data and include an exact and detailed description of the whole release procedure including the responsibilities of the involved personnel and the continuous assessment of the effectiveness of the PQS (Annex 3.2 and 3.51). The written procedure should be followed and compliance demonstrated before the batch is dispatched (Annex 3.43).

The release procedures should clearly outline the production and quality control data that should be reviewed before the product is dispatched (Annex 3.43).

Product distribution to the clinical institute may commence while the product is under quarantine providing:

- The receiving site has been fully briefed in the shipment and release process and has signed a contract agreeing that they will not administer the product before notification from the manufacturer.
- Appropriate sampling of the batch has been performed.
- All checks that are required prior to dispatch have been completed and any results assessed.
- The product is shipped with documents clearly indicating that the product must not be administered prior to conditional certification by the Authorised Person.

The order for the product (in written format) should be available at the time of performing the final check for product release. It can be an authorised true-copy of the original order. The final product release should include an independent check against the original order and this check should be recorded on the batch record. Any discrepancies should be investigated and appropriate corrective action taken before the product is released for administration to the patient.

This procedure should also describe the measures to be taken if unsatisfactory test results (out-of-specification) are obtained after dispatch and before expiry (Annex 3.45), and the process effectiveness verified. Out-of-specification events should be investigated and documented, including the relevant corrective actions taken and preventative actions put in place to prevent future events.

Procedures should clearly indicate the formalised communication mechanisms for ensuring the customer receives the release for administration for recording in the patient's documentation, and in the case of defective in-expiry product, the formalised notification processes and customer confirmation.

Separate testing and release person

The testing of a batch of radiopharmaceutical should be by a separate individual from the person who manufactured the batch. Likewise, the release for supply should be performed by an Authorised Person who was not involved in the manufacture or testing of the product, (part I, clause 2.5).

However, under exceptional circumstances, this may not always be possible and therefore release procedures should address these situations. When a single person is responsible for testing, release and manufacturing of a batch of a radiopharmaceutical, a review of the testing results and release of that batch by an independent person should be performed at the earliest opportunity, ideally within 24 hours.

Outsourced activities

Full compliance with chapter 7 requirements is expected. All outsourced GMP-related activities that may impact on product quality should be assessed, defined and covered by a written contract.

Examples of outsourced activities include, but are not limited to:

- contract manufacturing and analysis
- maintenance and calibration services
- providers of critical consumables, e.g. gowns, sterilised componentry
- suppliers and manufacturers of raw materials, packaging materials and printed artwork
- provision of training and consulting services
- validation services associated with facilities, equipment, utilities, process and product design, qualification and validation
- provision of transport and logistical services for products
- contract cleaning and waste management services
- contract pest control services
- agencies that provide temporary or contract personnel

Contracts should be in place between the site of manufacture and the entity receiving the goods, e.g. private hospital, public hospital, public institution, clinician, medical imaging centre, etc.

Complaints & recalls

It is expected that all suspected or serious adverse reactions related to sterile radiopharmaceuticals labelled with fluorine-18 will be reported to the TGA.

In addition, in circumstances where the manufacturer is made aware of any quality issue that would have resulted in recall of products these events are reported to the TGA recalls coordinator, irrespective of whether any units are recoverable, e.g. following identification of retrospective sterility testing failures or significant environmental monitoring excursions that indicate an unacceptable risk to process integrity or product quality.

Recall actions should follow the guidance given in the Uniform Recall Procedure for Therapeutic Goods (URPTG). Related guidance is also provided in Compounded medicines and good manufacturing practice (GMP).

Investigational medicinal product manufacture

Annex 13 - *Manufacture of investigational medicinal products*, is applicable to manufacture of sterile radiopharmaceuticals labelled with fluorine-18 where the product is intended for use as an investigational medicinal product, (IMP).

Manufacture investigational medicinal products in accordance with the PIC/S Guide to GMP, but note that there is an exception for the manufacture of IMPs when used in initial experimental studies in human volunteers. Take into account other guidelines where relevant and as appropriate to the stage of development of the product.

Interpretation of the basic GMP requirements

The tables below reference the section in this guidance that refers to a particular clause or Annex. Only the clauses and annexes with a specific interpretation for manufacture of sterile radiopharmaceuticals labelled with fluorine-18 are listed in the tables.

Interpretation of PE009-13 Part I

Clause(s)	Page*	Interpretation
Chapter 1 - Principle	1	Comply with marketing authorisation requirements
1.4xv, 1.9vii	3, 5	Release for supply Procedure for release for supply
1.9ii	5	Radioactive starting material Non-radioactive starting material
1.9viii	5	Reference samples
2.5, 2.9	9 – 10	Separate testing and release person
3.22	15	Sampling areas for starting materials
4.17(d), 5.39	21, 29	Product yield
5.30	29	Starting material collection and testing
5.58	31	Release for supply
5.61	32	Rejected and waste materials

*: Page in Part 1 of the PIC/S guide to GMP

Interpretation of PE009-13 annexes

Clause(s)	Page*	Interpretation
Annex 1 - Principle	1	Sterility
Annex 1.9	3	Monitoring of clean air device and clean rooms
Annex 1.21	5	Isolator technology
Annex 1.66	11	Media fills

Clause(s)	Page*	Interpretation
Annex 1.80	12	Bioburden monitoring
Annex 1.113	16	Filter integrity tests
Annex 1.119	17	Crimping vial caps
Annex 1.124	17	Visual inspection
Annex 1.125-1.127	17	Sterility testing
Annex 1.125-1.127	17, 18	Endotoxin testing
Annex 3.18	48	Entry to clean areas
Annex 3.27	49	Isolator technology
Annex 3.33	50	Retention of documentation
Annex 8.3	82	Synthesis kits Validation of starting materials
Annex 13	99	Investigational medicinal product manufacture
Annex 19	149	Reference samples

*: Page in the Annexes of the PIC/S guide to GMP

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Office of Manufacturing Quality	1 December 2009
V2.0	Alignment with new Code of GMP: PIC/S Guide to GMP for Medicinal Products PE009-8 - 15 January 2009 General revision of interpretations	Office of Manufacturing Quality	1 June 2011
V2.1	Template update	Office of Manufacturing Quality	1 July 2013
V3.0	Alignment with updated PIC/S Guide for GMP: PIC/S Guide to GMP for Medicinal Products PE009-13 - 1 January 2017 Restructured information	Manufacturing Quality Branch	February 2019

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