U.K. Radiopharmacy Group

Guidance for Introduction of a $^{68}Ge/^{68}Ga$ Generator and Labelling Service into Routine Clinical Practice

UK Radiopharmacy Group

1. Introduction

Further to recent updates on the status of ^{68}Ga in the UK, a visit by an MHRA Inspector (with responsibility for PET inspections) took place in a radiopharmacy currently using a ^{68}Ga generator in a routine clinical setting. This enabled clarification around many issues relating to the GMP preparation of ^{68}Ga labelled peptides in the UK. This document looks at the issues surrounding the setting up and running of a service. It does not provide advice on choice of generator or synthesis unit

2. Facilities required

As the process of preparing ^{68}Ga labelled peptides uses unlicensed non-sterile starting materials, the facility necessarily must be an MHRA inspected site rather than a (radio) pharmacy operated under a section 10 exemption of the Medicines Act 1968.

It was confirmed that as some of the starting materials and components used for synthesis are non-sterile, then the product must be terminally sterilised. Realistically this can only be achieved by aseptic filtration.

Synthesis of ^{68}Ga labelled peptides can be regarded in a similar fashion to the synthesis of ^{18}F FDG. This process is well described and in this case:

- sterile components and cassettes are assembled in a grade A environment prior to loading into the synthesis module
- the initial (radioactive) bulk preparation and aseptic filtration by closed systems into a sterile container is undertaken in a GMP grade C environment or better
- bulk (sterile) stock is transferred to a grade A environment for dose dispensing

The actual siting of the generator and synthesis module within a GMP grade C environment or better will depend on the radiation shielding requirements for these pieces of equipment. Thus it could be in a hot cell, isolator, VLFC or indeed on a work surface in a GMP compliant Grade B environment where a VLFC is sited. It is likely that radiation protection requirements may mandate that ^{68}Ga synthesis has to be undertaken in dedicated areas within a radiopharmacy and may need to be separate from routine SPECT based production areas, unless appropriate risk assessments have been undertaken and approved.

3. Quality of starting materials

It is not intended in this document to fully describe the requirements for starting materials. Indeed, general monographs of the EP *Substances for pharmaceutical use (2034)* and *Radiopharmaceutical preparations (0125)* are available for this purpose [1]. However where starting materials have a monograph in a pharmacopoeia this may not be specific enough for the synthesis of ^{68}Ga peptides. For example the limits for Iron content of both water for injection and hydrochloric acid are not strict enough in the respective European Pharmacopeia monographs to allow successful ^{68}Ga radiolabelling.

Thus it is incumbent on the user to pre-define the specification of all starting materials and this may necessarily mean purchasing the starting material sets (cassettes and solutions of buffers, eluents) from the manufacturer of the synthesis module, as these are often specific to that particular system. These suppliers must be audited to determine their ability to provide materials suitable for the preparation of medicinal products. Where possible it is recommended that NHS "Specials" manufacturers are used as they will have been inspected by MHRA, so their GMP status is known.

Because the finished product is unlicensed - as it has been prepared from a range of unlicensed starting materials, there is no requirement to use licensed starting materials should they be available, as they may not be directly equivalent. For example the choice of generator may determine the choice of eluent, starting materials, solid phase extraction cartridge and final product diluent. Thus a change of generator manufacturer will completely alter the range of starting materials needed.

4. Quality Assurance and Quality Control

There are now monographs in the current EP for both ^{68}Ga Gallium Chloride for radiolabelling and ^{68}Ga Edotreotride Injection. Prior to commencing work, users are recommended to create in house product specifications which mirror these monographs.

Appendix I shows examples of product specifications and Appendix II describes the acceptance testing that should be put in place before using a new unlicensed generator for clinical use.

Once the generator has been accepted, then a programme of weekly testing is undertaken in addition to any radio-peptide synthesis (Table 1).

Following synthesis of the ^{68}Ga peptide, release can only occur when the prospective validated tests as described in the specification have been undertaken (highlighted in yellow). It is thus essential that the pieces of equipment listed in Table 2 are accessible and regularly maintained, calibrated and validated**.**

Release documentation should clearly indicate that all prospective testing has been completed before final release of the product.

Background monitoring of the environment for viable organisms should be undertaken on a sessional basis in line with GMP Annex 1 requirements. Sterility testing of ^{68}Ga samples by an external department (e.g. pharmacy microbiological unit) must be risk assessed under EPR 2010 as the samples will contain ^{68}Ge (effectively not decaying to any great extent) which will necessitate transport and handling issues.

All of these initial and on-going QC/QA regimens should be described in a master validation plan produced before any work commences. Process validation and Operational Qualification (OQ) should be established to ensure that synthesis can be reliably conducted. Performance Qualification (PQ) should also be monitored to ensure on-going yields throughout the shelf life of each generator.

Table 1. Routine Generator QC tests

QC Procedure	Frequency
Elution	Daily (Mon. – Fri.)
pH	Weekly
Yield	Each sample not used for synthesis
^{68}Ge Breakthrough	Each sample not used for synthesis
Sterility	Weekly
Appearance	Each sample not used for synthesis

Table 2. QC equipment required

Equipment	Purpose
Radio HPLC	Identity and radiochemical purity
Gamma spectrometry system	Radionuclidic purity
Radio TLC system	Radiochemical purity
Filter Integrity tester e.g. bubble point or pressure hold	Filter integrity
Endosafe PTS system	Endotoxin
Dose Calibrator	Radioactive concentration

5. Practical Considerations

5.1 Planning

To introduce a ^{68}Ga labelling service necessitates the development of a comprehensive business plan which takes into account cost, additional staff, facilities required, QA/QC requirements, existing capacity, future ^{68}Ga based radiopharmaceuticals, PET camera time allocation (i.e. batch size).

A Master Validation Plan (MVP) following the guidance in Annex 15 of EudraLex Volume 4 [2] should be drawn up in conjunction with QC and QA staff.

5.2 Staffing

Whatever system for peptide synthesis is chosen, the time involved is considerable. Additional staffing must be considered as part of the business case to implement a routine service. In a recent case it was estimated that after an introductory phase, the unit's capacity would be three production runs per week. For that level an additional 0.5wte of a band 6 qualified radiopharmaceutical technologist was employed. It has now been estimated that to set up the starting materials, perform the synthesis, undertake QC, and independent release and on-going QA around this alone takes a minimum of 6 hours. To perform this process, it involves a minimum of three members of staff.

5.3 Training

It is likely that no member of staff in a routine radiopharmacy setting has prior experience of gallium synthesis. Thus it is essential to nominate a (senior) member of staff to coordinate the introduction and subsequent routine management of this project.

Pitfalls are commonly encountered, thus this person must have experienced problems at first hand, in order to be able to devise a training programme for staff such that it encompasses trouble shooting. It is advisable to develop a Frequently Asked Questions FAQ section of the relevant section of the training manual. It may be desirable to send staff to other centres already undertaking such work.

Production of SOPs will involve a protracted period of intense work and many iterations will be needed before even the first version can be put into clinical use.

5.4 Routine Production

It is recommended that a clinical service should only be introduced after a considerable time has been spent performing validation runs to confirm PQ. From experience this requires at least 10 consecutive runs producing test products. Additionally, the performance of the generator with unlicensed starting materials may change during its shelf life, and cannot be predicted from a few trial elutions. Issues relating to column performance will only become apparent towards its expiry. Yields may also vary if there are changes in batches of starting materials (e.g. eluents) during the shelf life of the generator.

6. Conclusion

Implementation of a Ga68 labelling service cannot be undertaken lightly and will involve the cooperation of many staff groups, some whom may not have been involved before with radiopharmaceutical production. Clear communication is key to establishing and maintaining a high quality reliable service.

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References

1. European Pharmacopoeia 8th Edition. EDQM. Council of Europe.

2. Annex 15 of EudraLex Volume 4. http://ec.europa.eu/health/files/gmp/2014-02_pc_draft_gmp_annex.pdf

APPENDIX I

1. Example of a Specification for ^{68}Ga Gallium Chloride solution for radiolabelling

Test or Parameter	Specific	Equipment or Method	Specification
Identity of radionuclide	^{68}Ga	Dose calibrator (half-life) Capintec CR-15	62 -74 mins
Radionuclidic Purity	^{68}Ga > 99.9%	Sodium Iodide well counter. CapRac	^{68}Ge < 0.001%
Chemical Purity	Iron content Zinc content	Atomic Absorption Spectrometry or ICP-MS*	Fe and Zn <10µg/GBq
Pharmaceutical or physiological parameters	pH	pH paper (two strip- narrow range) Camlab	1.0 – 2.0
Microbiological parameters	Sterility	EP method.	No growth
Endotoxin content	<175 EU/V	Endosafe PTS	< 100EU / eluate
Activity content	MBq. As measured	Dose calibrator.	500MBq to 1500MBq

*This may be contracted out to an academic institute or private sector

2. Example of a Specification for ^{68}Ga Gallium DOTANOC injection (based on ^{68}Ga edotreotide monograph)

Test or Parameter	Specific	Equipment or Method	Specification	Retrospective / Prospective release
Identity of radionuclide	^{68}Ga	Dose calibrator (Half-life) Capintec CR-15	62 -74 mins	Retrospective
Identity of Radiopharmaceutical	^{68}Ga DOTANOC	Liquid radio chromatography Dionex	Retention time of 11.7 mins	Prospective
Identity of drug substance	DOTANOC	Liquid radio chromatography Dionex	Retention time of 11.7 mins	Prospective
Radiochemical Purity	Impurity of ^{68}Ga colloid	Liquid radio chromatography TLC system	95% of which 3% ^{68}Ga colloid	Prospective
	Impurity of ^{68}Ga chloride	Liquid chromatography (TLC) & (HPLC) (as above)	max 2% ^{68}Ga chloride	
Chemical Purity	DOTANOC content	Mass determined by calculation from SOP	Max 50µg per patient	Prospective
Excipient content	Ethanol	Volumetric- determined from SOP	Max 10%	Prospective
Pharmaceutical or physiological parameters	pH	pH paper (eg two strip-narrow range)	5.0 – 6.0	Prospective
Microbiological parameters	Sterility	EP method.	No growth	Retrospective
Filter integrity	>50psi	Bubble point test –	≥50psi	Prospective
Endotoxin content	<175EU per dose	Endosafe PTS	<17.5EU /ml	Prospective
Activity content	MBq. As measured per batch	Dose calibrator.	100MBq to 800MBq	Prospective

APPENDIX II - Example of Acceptance Tests for new ^{68}Ga Generator

GENERATOR Batch Number	
Date and time	

ACCEPTANCE CRITERION	**TEST METHOD**	**PASS/FAIL**	**DATE(S)**	**SIGNATURE**
Eluate passes at least 5 consecutive sterility tests in accordance with EP	EP method			
Eluted activity is in accordance with manufacturer's reference data and achieves >90% yield for first 5 consecutive elutions	Recorded activity in MBq			
Identity of radionuclide by half-life measurement 62 -74 mins	Record activity of a sample over suitable time frame			
At least 5 consecutive negative endosafe endotoxin tests with positive controls	Endosafe PTS <100EU / eluate			
Equal to or less that 0.001% breakthrough of ^{68}Ge from elutions 2 onwards for the first 5 consecutive elutions	Well counting or spectrometry counts >48 hrs after elution			
Appearance of eluate – clear colourless solution	Visual			
CofA and TSE statement from company	Not manufactured in presence of TSE material			

Accepted for clinical use in the radiopharmacy

Signature Authorised Person:……..

Date:……