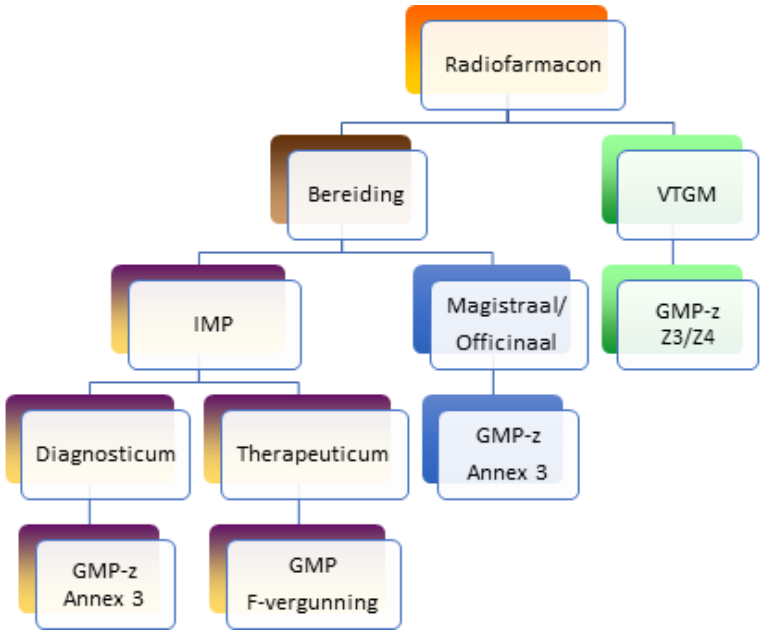
GMP-z Annex 3: Bereiding van radiofarmaca

Inleiding
Annex 3 van de GMP-z beschrijft de principes die van toepassing zijn bij de magistrale bereiding van radiofarmaca voor reguliere klinische zorg en de bereiding van diagnostische radiofarmaca voor klinisch geneesmiddelonderzoek. VTGM voor beide categorieën valt niet onder deze annex maar onder de GMP-z Z3 en Z4. Zie ook onderstaand figuur.



GMP item	Gewijzigd richtsnoer GMP-z	Toelichting
Introduction		
1. The manufacturing and handling of radiopharmaceuticals is potentially hazardous. The level of risk depends in particular upon the types of radiation, the energy of radiation and the half-lives of the radioactive isotopes. Particular attention must be paid to the prevention of cross contamination, to the	GMP	

retention of radionuclide contaminants, and to waste disposal. 2.		
2. Due to short shelf-life of their radionuclides, some radiopharmaceuticals may be released before completion of all quality control tests. In this case, the 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 quality assurance system is essential.	GMP	
3. This guideline is applicable to manufacturing procedures employed by industrial manufacturers, Nuclear Centres/Institutes and PET Centres for the production and quality control of the following types of products: - Radiopharmaceuticals - Positron Emitting (PET) Radiopharmaceuticals - Radioactive Precursors for radiopharmaceutical production - Radionuclide Generators	3 Z. Deze annex is van toepassing op de bereiding en kwaliteitscontrole van (PET) radiofarmaca en diagnostische IMP radiofarmaca.	
4. The manufacturer of the final radio-pharmaceutical should describe and justify the steps for manufacture of the active substance and the final medicinal product and which GMP (part I or II) applies for the specific process/ manufacturing steps.	GMP	
5. Preparation of radiopharmaceuticals involves adherence to regulations on radiation protection.	GMP	
6. Radiopharmaceuticals to be administered parenterally should comply with sterility requirements for parenterals and, where relevant, aseptic working conditions for the manufacture of sterile medicinal products, which are covered in Eudralex Volume 4, Annex 1.	6 Z De steriliteitseisen en de eisen aan de aseptische werkwijze tijdens de bereiding van parenterale (PET) radiofarmaca staan genoemd in de GMP-z Annex 1.	
7. Specifications and quality control testing procedures for the most commonly used radiopharmaceuticals are specified in the European Pharmacopoeia or in the marketing authorisation.	GMP	
8. Radiopharmaceuticals intended for use in clinical trials as investigational medicinal products should in	GMP	

addition be produced in accordance with the principles in Eudralex Volume 4, annex 13.		
Quality assurance		
9. Quality assurance is of even greater importance in the manufacture of radiopharmaceuticals because of their particular characteristics, low volumes and in some circumstances the need to administer the product before testing is complete.	GMP	
10. As with all pharmaceuticals, the products must be well protected against contamination and cross contamination. However, the environment and the operators must also be protected against radiation. This means that the role of an effective quality assurance system is of the utmost importance.	GMP	
11. It is important that the data generated by the monitoring of premises and processes are rigorously recorded and evaluated as part of the release process.	GMP	
12. The principles of qualification and validation should be applied to the manufacturing of radiopharmaceuticals and a risk management approach should be used to determine the extent of qualification/validation, focusing on a combination of Good Manufacturing Practice and Radiation Protection.	GMP	
Personnel		
13. All manufacturing operations should be carried out under the responsibility of personnel with additional competence in radiation protection. Personnel involved in production, analytical control and release of radiopharmaceuticals should be appropriately trained in radiopharmaceutical specific aspects of the quality management system. The QP should have the overall responsibility for release of the products.	13 Z Alle bereidingshandelingen worden uitgevoerd door personeel met voldoende training in stralingsveiligheid. Alle betrokkenen bij bereiding, kwaliteitscontrole en vrijgifte zijn getraind in de specifieke aspecten van het kwaliteitssysteem rond radiofarmaca. Training, taken en verantwoordelijkheden van betrokkenen bij en toezichthouders van stralingshygienische aspecten voldoen aan de vigerende regelgeving en richtlijnen. Dit is vastgelegd in het kwaliteitssysteem.Vrijgifte vindt plaats onder verantwoordelijkheid van een bevoegd apotheker.	
14. All personnel (including those concerned with	GMP	

cleaning and maintenance) employed in areas where radioactive products are manufactured should receive appropriate additional training specific to these types of procedures and products.		
15. Where production facilities are shared with research institutions, the research personnel must be adequately trained in GMP regulations and the QA function must review and approve the research activities to ensure that they do not pose any hazard to the manufacturing of radiopharmaceuticals.	GMP	
Premises and equipment		
16. Radioactive products should be manufactured in controlled (environmental and radioactive) areas. All manufacturing steps should take place in self-contained facilities dedicated to radiopharmaceuticals	GMP	
17. Measures should be established and implemented to prevent cross-contamination from personnel, materials, radionuclides etc. Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, precautions should be taken to minimize the risk of contamination. The risk assessment should demonstrate that the environmental cleanliness level proposed is suitable for the type of product being manufactured.	GMP	
18. Access to the manufacturing areas should be via a gowning area and should be restricted to authorised personnel.	GMP	
19. Workstations and their environment should be monitored with respect to radioactivity, particulate and microbiological quality as established during performance qualification (PQ).	GMP	
20. Preventive maintenance, calibration and qualification programmes should be operated to ensure that all facilities and equipment used in the manufacture of radiopharmaceutical are suitable and qualified. These activities should be carried out by competent personnel and records and logs should be maintained.	GMP	
21. Precautions should be taken to avoid radioactive	GMP	

contamination within the facility. Appropriate controls should be in place to detect any radioactive contamination, either directly through the use of radiation detectors or indirectly through a swabbing routine.		
22. Equipment should be constructed so that surfaces that come into contact with the product are not reactive, additive or absorptive so as to alter the quality of the radiopharmaceutical.	GMP	
23. Re-circulation of air extracted from area where radioactive products are handled should be avoided unless justified. Air outlets should be designed to minimize environmental contamination by radioactive particles and gases and appropriate measures should be taken to protect the controlled areas from particulate and microbial contamination.	GMP	
24. In order to contain radioactive particles, it may be necessary for the air pressure to be lower where products are exposed, compared with the surrounding areas. However, it is still necessary to protect the product from environmental contamination. This may be achieved by, for example, using barrier technology or airlocks, acting as pressure sinks.	GMP	
25. Sterile radiopharmaceuticals may be divided into those, which are manufactured aseptically, and those, which are terminally sterilised. The facility should maintain the appropriate level of environmental cleanliness for the type of operation being performed. For manufacture of sterile products the working zone where products or containers may be exposed to the environment, the cleanliness requirements should comply with the requirements described in the Eudralex Volume 4, Annex 1.	25 Z Bij bereidingen voor reguliere klinische zorg en diagnostische IMP radiofarmaca geldt GMP-z Annex 1.	
26. For manufacture of radiopharmaceuticals a risk assessment may be applied to determine the appropriate pressure differences, air flow direction and air quality.	GMP	
27. In case of use of closed and automated systems (chemical synthesis, purification, on-line sterile filtration) a grade C environment (usually “Hot-cell”) will	27 Z Het benodigde regime bij bereidingen waarbij gebruikgemaakt wordt van gesloten en geautomatiseerde systemen, zoals in	

be suitable. Hot-cells should meet a high degree of air cleanliness, with filtered feed air, when closed. Aseptic activities must be carried out in a grade A area.	hot-cells, is afhankelijk van de situatie. Bij bereidingen voor reguliere klinische zorg en diagnostische IMP radiofarmaca geldt GMP-z Annex 1.	
28. Prior to the start of manufacturing, assembly of sterilised equipment and consumables (tubing, sterilised filters and sterile closed and sealed vials to a sealed fluid path) must be performed under aseptic conditions.	28 Z Assembleren van benodigde steriele apparatuur en steriele hulpmiddelen moet aseptisch plaatsvinden. Bij bereidingen voor reguliere klinische zorg en diagnostische IMP radiofarmaca geldt GMP-z Annex 1.	
Documentation		
29. All documents related to the manufacture of radiopharmaceuticals should be prepared, reviewed, approved and distributed according to written procedures.	GMP	
30. Specifications should be established and documented for raw materials, labelling and packaging materials, critical intermediates and the finished radiopharmaceutical. Specifications should also be in place for any other critical items used in the manufacturing process, such as process aids, gaskets, sterile filtering kits, that could critically impact on quality.	GMP	
31. Acceptance criteria should be established for the radiopharmaceutical including criteria for release and shelf life specifications (examples: chemical identity of the isotope, radioactive concentration, purity, and specific activity).	GMP	
32. Records of major equipment use, cleaning, sanitisation or sterilisation and maintenance should show the product name and batch number, where appropriate, in addition to the date and time and signature for the persons involved in these activities.	GMP	
33. Records should be retained for at least 3 years unless another timeframe is specified in national requirements.	GMP	
Production		
34. Production of different radioactive products in the same working area (i.e. hot-cell, LAF unit), at the same time should be avoided in order to minimise the risk of radioactive cross-contamination or mix-up.	GMP	

35. Special attention should be paid to validation including validation of computerised systems which should be carried out in accordance in compliance with Eudralex Volume 4, annex 11. New manufacturing processes should be validated prospectively.	GMP	
36. The critical parameters should normally be identified before or during validation and the ranges necessary for reproducible operation should be defined.	GMP	
37. Integrity testing of the membrane filter should be performed for aseptically filled products, taking into account the need for radiation protection and maintenance of filter sterility.	37 Z Indien membraanfilters worden gebruikt voor aseptisch bereide of uitgevulde radiofarmaca moet een integriteitstest op het filter worden uitgevoerd. Op basis van een risico-evaluatie kan de filterintegriteitstest ook na de conditionele vrijgifte uitgevoerd worden.	De filters kunnen nog een grote hoeveelheid radioactiviteit bevatten. Het gaat om individuele bereidingen waarbij toediening aan de patiënt binnen enkele uren plaatsvindt. Als de bereiding met steriele uitgangsmaterialen met behulp van een gesloten systeem plaatsvindt, kan de integriteitstest worden uitgesteld tot na de conditionele vrijgifte.
38. Due to radiation exposure it is accepted that most of the labelling of the direct container, is done prior to manufacturing. Sterile empty closed vials may be labelled with partial information prior to filling providing that this procedure does not compromise sterility or prevent visual control of the filled vial.	GMP	
Quality control		
39. Some radiopharmaceuticals may have to be distributed and used on the basis of an assessment of batch documentation and before all chemical and microbiology tests have been completed. Radiopharmaceutical product release may be carried out in two or more stages, before and after full analytical testing: a) Assessment by a designated person of batch processing records, which should cover production conditions and analytical testing performed thus far, before allowing transportation of the radiopharmaceutical under quarantine status to the clinical department. b) Assessment of the final analytical data, ensuring all deviations from normal procedures are documented, justified and appropriately released prior to	39 Z In sommige situaties is conditionele vrijgifte van radiofarmaca nodig voordat de volledige kwaliteitscontrole is afgerond. Hierbij worden productie condities en vastgestelde, reeds uitgevoerde analyses beoordeeld voordat het radiofarmacon naar de klinische afdeling kan worden getransporteerd en toegediend. Dit mag gedelegeerd worden aan een gekwalificeerd medewerker, onder verantwoordelijkheid van de apotheker. Als de volledige chemische en microbiologische kwaliteitscontrole is afgerond, vindt definitieve vrijgifte plaats door een bevoegd apotheker .	

documented certification by the Qualified Person. Where certain test results are not available before use of the product, the Qualified Person should conditionally certify the product before it is used and should finally certify the product after all the test results are obtained.		
40. Most radiopharmaceuticals are intended for use within a short time and the period of validity with regard to the radioactive shelf-life, must be clearly stated.	GMP	
41. Radiopharmaceuticals having radionuclides with long half-lives should be tested to show, that they meet all relevant acceptance criteria before release and certification by the QP.	41 Z Radiofarmaca met langlevende radionucliden worden pas vrijgegeven nadat de volledige kwaliteitscontrole is afgerond.	
42. Before testing is performed samples can be stored to allow sufficient radioactivity decay. All tests including the sterility test should be performed as soon as possible.	GMP	
43. A written procedure detailing the assessment of production and analytical data, which should be considered before the batch is dispatched, should be established.	GMP	
44. Products that fail to meet acceptance criteria should be rejected. If the material is reprocessed, preestablished procedures should be followed and the finished product should meet acceptance criteria before release. Returned products may not be reprocessed and must be stored as radioactive waste.	GMP	
45. A procedure should also describe the measures to be taken by the Qualified Person if unsatisfactory test results (Out-of-Specification) are obtained after dispatch and before expiry. Such events should be investigated to include the relevant corrective and preventative actions taken to prevent future events. This process must be documented.	45 Z De benodigde maatregelen bij afwijkende testresultaten liggen vast in een Out of specification (OOS)-procedure. Dit geldt ook in het geval een OOS ontdekt wordt ná vrijgifte en vóór het vervallen van het product. De correctieve en preventieve maatregelen worden gedocumenteerd.	
46. Information should be given to the clinical responsible persons, if necessary. To facilitate this, a traceability system should be implemented for radiopharmaceuticals.	GMP	
47. A system to verify the quality of starting materials	GMP	

should be in place. Supplier approval should include an evaluation that provides adequate assurance that the material consistently meets specifications. The starting materials, packaging materials and critical process aids should be purchased from approved suppliers.		
Reference and Retention samples		
48. For radiopharmaceuticals sufficient samples of each batch of bulk formulated product shall be retained for at least six months after expiry of the finished medicinal product unless otherwise justified through risk management.	48 Z Bij bereidingen voor reguliere klinische zorg en diagnostische IMP radiofarmaca geldt GMP-z annex 19.	
49. Samples of starting materials, other than solvents gases or water used in the manufacturing process shall be retained for at least two years after the release of the product. That period may be shortened if the period of stability of the material as indicated in the relevant specification is shorter.	49 Z Z Bij bereidingen voor reguliere klinische zorg en diagnostische IMP radiofarmaca geldt GMP-z annex 19.	
50. Other conditions may be defined by agreement with the competent authority, for the sampling and retaining of starting materials and products manufactured individually or in small quantities or when their storage could raise special problems.	Z Bij bereidingen voor reguliere klinische zorg en diagnostische IMP radiofarmaca geldt GMP-z annex 19.	
Distribution		
51. Distribution of the finished product under controlled conditions, before all appropriate test results are available, is acceptable for radiopharmaceuticals, providing the product is not administered by the receiving institute until satisfactory test results has been received and assessed by a designated person.	GMP	

Literatuur:

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3. Guide to good practices for the preparation of medicinal products in healthcare establishments (PE 010-3), 2008. www.picscheme.org.
4. Guidelines on current good radiopharmacy practice (cGRPP) in the preparation of radiopharmaceuticals. EANM Radiopharmacy Committee, version 2, march 2007. www.eanm.org
5. Elsinga P, Todde S, Penuelas I et al. Radiopharmacy Committee of the EANM. Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals. Eur J Nucl Med Mol Imaging 2010;37(5):1049-62.
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7. Lange R, ter Heine R, Decristoforo C, Penuelas I, Elsinga PH, van der Westerlaken MML, et al. Untangling the web of European regulations for the preparation of unlicensed radiopharmaceuticals: a concise overview and practical guidance for a risk-based approach. Nucl Med Commun 2015;36:414–422.