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## GMP in Radiopharmacy

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# GMP in radiopharmacy: The current situation in its context

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## Prologue

Over the last decades, Good Manufacturing Practice (GMP) has evolved from a kind of uncomfortable requirement to an indispensable tool for the production and quality control of state of the art pharmaceuticals. Somewhat later than regular pharmacy, also radiopharmacy was encouraged to comply with GMP. The short version of this story, is that this was not a straightforward process. For example, in the year 2000, it was still a common opinion that GMP for the radiopharmacy could consist of a kind of “light version” compared to the GMP regulations used within the pharmaceutical industry. As the involvement of Inspectorates and Industries in Radiopharmacy increased, GMP was there to stay. And, as we will see in this chapter, not in a kind of “light version.” The aim of this chapter is to give a concise overview on radiopharmaceutical GMP. Furthermore, some future perspectives are provided to point out where it may lead us.

## GMP—A short description

Nowadays, quality management in the production of pharmaceuticals, food and cosmetics is required by the authorities. As the quality aspects of a product cannot be checked for 100% on each batch, quality requirements are needed to cover all potentials flaws optimally. GMP therefore consists of-

- 1) Regulations on the circumstances under which productions should take place.
- 2) A list of quality specifications for starting materials, intermediates, in-process controls and for the final product. Optimal quality controls (QC) are in place to verify whether the quality specifications are met.
- 3) All involved staff is adequately trained for their tasks.
- 4) The production facility is designed to establish and protect the production situation according to the specifications of the product. Monitoring of these circumstances takes place to warrant and prove optimal production situations.
- 5) When a production was suboptimal, a deviation system is place to record the root-cause as well as the potential solution to correct the problem and prevent similar situations in the future.
- 6) For other optimization and further improvement of production and facility circumstances, planned changes in any aspect of production or quality control are documented in a change control system.
- 7) Responsibilities for the release of any aspect of the production process are documented carefully. In the EU and the UK, a Qualified Person is finally responsible for the overall release of a pharmaceutical production. In the US, this task is performed by a Responsible Pharmacist.

- 8) The software used in the production and QC of pharmaceuticals was validated before use.
- 9) The hardware used is qualified.
- 10) The combination of soft- and hardware in one system (this is called an automated system) is validated.
- 11) At last, processes and procedures are validated.

### **The past: It all started in the 1970s**

GMP started to develop in the 1970s. To prevent new pharmaceutical disasters like the use of not so well investigated toxic solvents (1930s), the Thalidomide and DES drama's (1950–1975), GMP was developed as one of the new weapons to avoid these and many other problems. The intention of preventing big mistakes by accurate quality management seemed to work pretty well, although it would and will never be for 100% perfect. Together with GMP, licensing of medication, Good Clinical Practice and the first established clinical trials emerged, being protective in another way (Boersma et al., 2012).

Within an parallel time frame (1950–1980), radiopharmacy was born as well. It made its first steps in helping out medicine as a new diagnostic toolkit. Big advantage of radiopharmaceuticals is that they mostly do not contain high doses of active pharmaceutical ingredients, thereby preventing the risk of adverse events caused by a pharmaceutical/therapeutic dose with potential toxic properties.

Then, over the years 1985–2010, procedures for Good Radiopharmacy Practice started to develop. Basically it started with simple preparation protocols and QC protocols. Then calibration of Dosimeters, pH meters and LAF-hoods were protocolled. And the quality development went on. Of course, not without discussion and delays. Finally, it ended up in complete quality systems, containing all GMP-features required. In Europe, the EU-GMP fueled the implementation of GMP in the pharmaceutical industry and also in the radiopharmaceutical industry from 1995 onwards. Although the "ideal" situation is not reached all over the world, GMP in radiopharmacy has developed as a gold standard in many countries, including guidelines for GMP production of radiopharmaceuticals, in the EU, US, UK and many other countries. This chapter reflects especially the EU-GMP situation as currently implemented in larger university hospital settings (Elsinga et al., 2010; Gillings et al., 2021; PIC/S, 2014).

### **Current GMP in the radiopharmaceutical field**

To get a good picture of GMP nowadays, we need to have a close look on what it actually represents at this moment. Therefore, we need to start with a small tour in a radiopharmaceutical GMP facility in order to be able to see the bigger picture.

#### **Premises**

Premises in compliance with GMP start with a limited accessibility. Only staff can admit the facility directly, mostly using a card reader. For example during audits, visitors will be accompanied by staff to enter the cleanroom complex.

#### **Incoming goods area**

When entering our radiopharmacy facility, you find first some offices. Passing the offices, you will enter finally in the room where all incoming goods arrive. This room has a refrigerator and a freezer to store goods at appropriate temperatures and several shelves to store materials at room temperature. To ensure the right temperatures, the fridges and freezers in the facility are qualified. Furthermore, a system that monitors temperature, humidity, air pressure, air speed and particles is installed and qualified. This system sends alarms by email in case of out of specification situations.

Logically, all incoming goods locations have a quarantine part and a part that is dedicated to already released materials, which are to be picked up for the production areas.

#### **Organization of manufacturing in the premises**

Actually, the start of a production session for a radiopharmaceutical is dependent on the availability of the isotope. The physical half-life of the isotope plays an important role in the location of the production site. All isotopes with a very short half-life should be available on site, whereas those with a half-life of roughly  $>2$  h could be produced on a certain distance of the hospital. Furthermore, availability on site can take place in various ways. Mostly, the availability is covered by a cyclotron or a generator.

Furthermore, incoming starting materials and reagents need to be approved and released before they can be used in GMP-production. See Figs. 1 and 2.

From left to right, gowning area with door interlocks, weighing room, safety hood for storage of released hazardous materials.

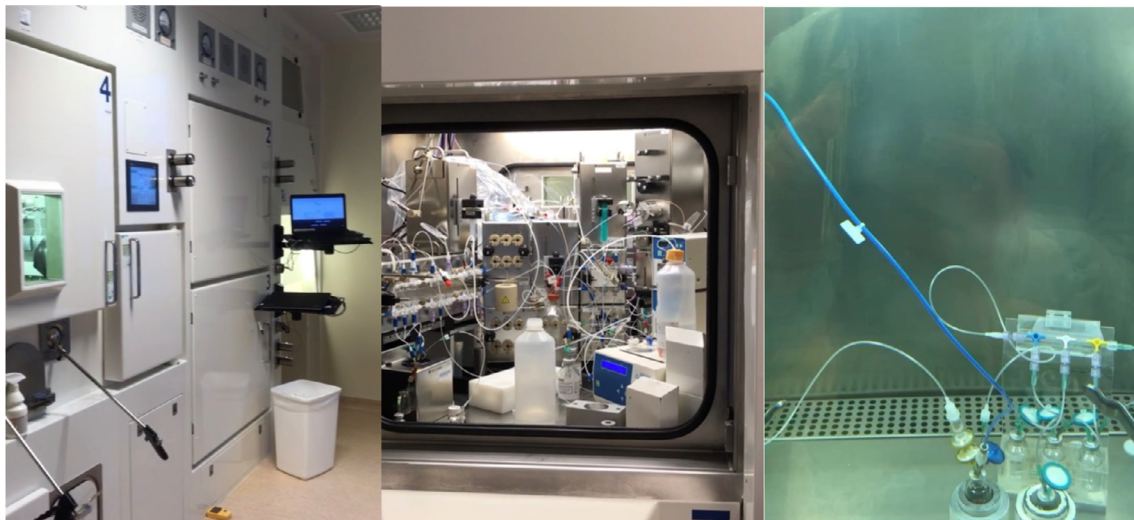
The air quality of a cleanroom is usually maintained by a HVAC, a Heat Ventilation Air Conditioning system. Having a basis in good air quality provided by the HVAC system, the radiopharmacy/GMP facility needs an up and running cleanroom facility with continuous monitoring of temperature, pressure, humidity and particles in all relevant areas. A cleanroom is shown in Fig. 3 on the left side of the figure. Class A areas are the cleanest air class under GMP circumstances and are dedicated to aseptic filling of the final product (Fig. 3, image on the right side). See EU-GMP Annex 1 for a complete oversight of air quality area definition (Eudralex, EU-GMP, website visited December 2021, 2021). Moreover, a microbiology monitoring system need to be in place. On average this



**Fig. 1** Incoming goods. On the upper shelf, the quarantined goods are stored. As soon they are released by the Qualified Person (QP), they are moved to the lower shelf. Similar processes take place in freezer and refrigerator.



**Fig. 2** Before the production can start, one needs to pass through the areas shown here.



**Fig. 3** Production areas. On the left side, closed hotcells ready for the production of FDG. In the middle an opened grade C hotcell with module in preparation for a new production is depicted. The right picture shows a typical aseptic filling situation in an grade A hotcell with grade B background definition (Eudrax, EU-GMP, website visited December 2021, 2021).



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
85	21190802931-1	11-mei-21	0	07:15	09:15	RH		0,08	2,0	10									
86	21191198131-1	12-mei-21	0	07:30	09:30	BP		0,08	2,0	10									
87	21191720831-1	14-mei-21	0	07:15	09:15	RH		0,08	2,0	10									
88	21201475031-1	19-mei-21	0	07:15	09:15	DG		0,08	2,0	20									
89	2130209631-1	21-mei-21	0	07:30	09:30	DG		0,08	2,0	20									
90	21210493431-1	25-mei-21	0	09:00	11:00	RH		0,08	2,0	20									
91	?	26-mei-21	?	?	?	?				20			DEV-2021-122		FDG-21-07				
92	21211431031-1	27-mei-21	0	07:00	08:00	RB		0,04	1,0	20									
93	21211863231-1	28-mei-21	0	07:30	09:30	ZC		0,08	2,0	21									
94	21220343931-1	31-mei-21		08:00	10:00	BP		0,08	2,0	22			DEV-2021-138		FDG-21-100				
95	21220103331-1	1-jun-21	0	07:30	09:30	BP		0,08	2,0	22									
96	21221192331-1	2-jun-21	0	07:30	09:30	ZC		0,08	2,0	22									
97	21221539731-1	3-jun-21	0	07:15	09:15	AN		0,08	2,0	22									
98	21221921731-1	4-jun-21	0	07:30	09:30	AN		0,08	2,0	22									
99	21230302831-1	7-jun-21	0	09:00	11:00	HD		0,08	2,0	23									
100	21230600631-1	8-jun-21	0	07:30	09:30	RH		0,08	2,0	23									
101	21231062431-1	9-jun-21	0	07:30	09:30	BP		0,08	2,0	23									
102	21231521631-1	10-jun-21	0	07:30	09:30	BP		0,08	2,0	25									
103	21231896931-1	11-jun-21		09:00	11:00	RH		0,08	2,0	25			DEV-2021-139		FDG-21-109				
104	21240585131-1	15-jun-21	0	07:00	09:00	RH		0,08	2,0	24									
105	21241438531-1	17-jun-21	0	07:30	09:30	BP		0,08	2,0	24									
106	21241452731-1	16-jun-21	0	08:00	10:00	HD		0,08	2,0	24									
107	21241685331-1	18-jun-21	0	07:00	09:00	RH		0,08	2,0	24									
108	21241944331-1	19-jun-21		08:30	08:30	RB		0,04	1,0	26									
109	21250320031-1	21-jun-21	0	09:15	11:15	HD	Micrococcus luteus	0,08	2,0	25			DEV-2021-140		FDG-21-114				
110	21250584531-1	22-jun-21	0	07:00	09:00	RH		0,08	2,0	25									
111	21251036731-1	23-jun-21	0	07:30	09:30	HD		0,08	2,0	25									
112	21251303531-1	24-jun-21	0	07:00	09:00	RH		0,08	2,0	25									
113	21251880531-1	25-jun-21	0	07:30	08:30	AN		0,04	1,0	25									
114	21260117231-1	28-jun-21	0	08:30	09:30	RB		0,04	1,0	26									
115	21260542031-1	29-jun-21		07:00	09:00	RH		0,08	2,0	26									
116	21261030331-1	30-jun-21	0	07:30	09:30	HD	Janibacter species	0,08	2,0	26			DEV-2021-142		FDG-21-121				
117	21261309731-1	1-jul-21	0	07:00	09:00	RH		0,08	2,0	26									
118	21261706131-1	2-jul-21	0	07:30	09:30	BP		0,08	2,0	26									
119	21261874531-1	3-jul-21	0	07:30	09:30	BP		0,08	2,0	26									
120	21270210631-1	5-jul-21	0	08:00	10:00	RH		0,08	2,0	27									
121	21270741131-1	6-jul-21	0	07:30	09:30	HD		0,08	2,0	27									
122	21271070931-1	7-jul-21	0	07:00	08:00	BP		0,04	1,0	27									
123	21271327631-1	8-jul-21	0	07:00	08:00	RB		0,04	1,0	27									
124	21271982131-1	9-jul-21	0	07:00	09:00	RH		0,08	2,0	27									
125	21280273931-1	12-jul-21		08:00	09:00	SB		0,04	1,0	28									
				09:30	09:30	RP	Staphylococcus												

**Fig. 4** Typical example of monitoring results for a Class A area. Please note that in real life, a hard copy will be signed and dated by a designated person.

means that for the Class A and B areas daily monitoring is required, whereas for the less critical C and D background areas a weekly or monthly frequency of monitoring can be sufficient enough, dependent on the overall air quality and correlated microbial growth results in the cleanrooms. All outcome of the microbial monitoring needs to be aggregated and reported on a frequent basis. As soon as excursions of e.g. microbiological measurements are available, there is a need to write deviations in order to mitigate the risk of re-occurrence in the future. A typical example of monitoring results is shown in Fig. 4. Apart from environmental monitoring, a maintenance and cleaning schedule is required to maintain the overall facility specifications.

In designing a cleanroom, attention must be made to prevention of cross contamination. This is for example done by the prevention of crossing of logistical lines. Other specifications of importance are the smoothness of all surfaces in order to prevent accumulation of dirt and dust as well as their suitability for cleaning.

## Production

### Starting materials

As shown in the section about the Incoming Goods Area, all GMP-impacted incoming goods need to be released by the QP before use in GMP production. And before this, the supplier of each GMP-critical starting material or GMP critical device needs to be evaluated, eventually audited and finally approved. Furthermore, the release criteria need to be specified and documented in a kind of inspection and release document, which is to be checked and signed by the QP. After release of the starting materials, they need to be transferred from the quarantine room to their storage location in the cleanroom. To comply with GMP, and prevent crossing lines, the way the starting material follows should be different from the route of the staff members.

### Gowning

Before entering the cleanroom, the accessing persons need to redress in the changing corridor and redress in a cleanroom outfit, wear a disposable hair net, and if needed a disposable mouth mask or beard mask. In most cases, disposable gloves are required as well. Before gloves are put on, or before entrance of the cleanroom hands need to be cleaned and disinfected.

### Cleaning

To fulfill GMP requirements, efficient hygiene measures and cleaning schedules are very important.

In fact, the effectiveness of cleaning should always be combined with an evaluation of microbiological house flora. Regular cleaning schedules are once per week a cleaning of the cleanroom floor and non-involved areas. All surfaces used directly for the production of radiopharmaceuticals should be hygienically cleaned at least once per week and disinfected before each production session (Todde et al., 2017).

### Production processes

Each production process of e.g. a PET-radiopharmaceutical takes place in a dedicated hotcell or LAF-hood. The minimum requirement for an area is grade C, and when aseptic filling is in the same area, like for  $^{15}\text{O}$ -water, the area should be grade A, ideally with a grade B background, although some healthcare inspectorates may be willing to allow a grade C background because of the very short half-life of the radiopharmaceutical which can be regarded as a risk reducing factor because of the very short shelf life of the final product.

Ideally, any production of a radiopharmaceutical using either a high amount of activity or using highly energetic isotopes will be done in a hotcell. Furthermore most hotcell-based radiopharmaceutical productions will be automated by using a synthesis module. All synthesis modules should be GMP-compliant including the used software for the synthesis module. The software should have an audit trail and does comply with Good Automated Manufacturing Practice, GAMP (Todde et al., 2017).

Typical tasks for the modules to perform are heating of the radioactive reaction mixture, shaking or swirling the reaction mixture, cooling the reaction mixture and performing purification of the final product. Aseptic filling should be done in a separate grade A hotcell with grade B.

Typically preparations done without a hotcell or module are most SPECT radiopharmaceuticals and PET-radiopharmaceuticals using smaller amounts of activity or with a very short half-life, like  $^{15}\text{O}$ -water and  $^{13}\text{N}$ -ammonia.

### Quality control (QC)

Generally, a variety of chromatography methods are used for determination of the radiochemical purity. For SPECT, mostly thin layer chromatography is used, whereas for PET, mostly liquid chromatography, such as HPLC and UPLC are used. Furthermore, tests on endotoxins, residual solvents, pH, osmolarity and sterility are usually performed. Before the start of a implementation of a radiopharmaceutical, the applicable methods need to be validated when the method was not described in a pharmacopeia. This means generally spoken a thorough test on aspects like justness, lowest limit of quantitation, accuracy, specificity, reproducibility (Aerts et al., 2014; Gerrits et al., 2017; Elsinga et al., 2010; Gillings et al., 2020). Furthermore, all laboratory equipment and devices should be maintained and calibrated as frequent as needed (Gerrits et al., 2017). In Fig. 5, an example is shown a QC laboratory. An exception made for radiopharmaceuticals, is that given the fact that all used methods have been validated, not all results of the QC can be obtained before the radiopharmaceutical is administered to the patient, due to the short half-life of the product. This exception is also a statement within e.g. the EU-Pharmacopeia.



**Fig. 5** QC area with typical UPLC equipment (left), and combined HPLC, GC for residual solvents, endotoxin and osmolarity equipment (right). The latter equipment is feasible to perform the QC before and after release for administration in humans.

### **Batch record review and product certification/QP release**

In many cases, there is not much time between the finalization of the QC and release of the radiopharmaceutical for human administration. Therefore, in many cases a designated person, such as a qualified technician, is performing the conditional release of the radiopharmaceutical before the Qualified Person or responsible pharmacist will do the definitive release of the product. If there is any reason to doubt any quality issues, the Qualified Person should be contacted before the radiopharmaceutical is released and administrated. Generally, the QP or Head of Production take more time to do a thorough batch record review in order to check batch records on all kinds of inconsistencies. If any irregularities have occurred, a deviation should be raised according to GMP regulations (Boersma et al., 2012). To avoid any mix-up, each radiopharmaceutical should be labeled immediately after finalization of the product (Gerrits et al., 2017).

It should be stressed that the final release of the radiopharmaceutical takes place when the sterility tests as well as all other post release testing is performed/evaluated in the weeks after production of the radiopharmaceutical. This means also that potentially, deviations will be known just after administration of the radiopharmaceutical.

### **Documentation**

Because of the rather fast nature of the radiopharmaceutical production, many documents are needed to cover all events that may occur during this process to prevent as much risks as possible.

GMP production of regular pharmaceuticals will prevent many more irregularities before release of a product and hence appears to be safer. However, as the shelf life of a radiopharmaceutical is much shorter than any other type of injection, the injected volume is mostly only a few ml, and the administered dose is usually <200 µg, the risk for radiopharmaceuticals is, given the strict procedures and restrictions, justifiable.

### **Quality system**

Most quality systems have a Quality Manual and a Site Master File as a kind of foundation to give insight into all features of the quality system, the production area's as well as the important highlights of the aspects of radiopharmaceutical production on which emphasize is placed. Of course, the quality system is firstly taking care of all quality essentials for radiopharmaceutical production and quality control. Furthermore, attention to Quality Risk Management, Validation and Qualification, Deviation and CAPA management, Out of Specification management, Change Control management, Environmental monitoring, Supplier Qualification and internal audits should at least be present (Boersma et al., 2012; Eudralex, EU-GMP, website visited December, 2021; Gerrits et al., 2017; PIC/S, 2014).

### **Document management**

To ensure an accurate performance of the Quality System, documentation should be managed in a proper way. Moreover, this a cornerstone to meet GMP and regulatory requirements. All documents should be drafted, written, authorized and maintained according to a specific document SOP (Gerrits et al., 2017). Most GMP manufacturers of radiopharmaceuticals use a specific computerized document management system to store all documents digitally. Apart from this, there are also requirements on handwritten paperwork. Over the last years, Good Document Practice has gained much more importance. This way of dealing with documents uses the ALCOA principle, which was introduced by the FDA. The acronym stands for Attributable, Legible, Contemporaneous, Original and Accurate. Generally, this principle really helps in keeping all handwritten documentation aspects neat in a structured way.

### **Personnel**

All staff members need to be adequately trained for their jobs. This includes on the job training as well as frequent training of GMP-knowledge, on the job task performance training and as well a frequent media-fill training to assess and evaluate the microbiological quality of the performed preparation related activities. All training needs to be documented and should be available for audits and inspection visits (de Roo et al., 2015).

### **Future perspectives**

Given its ubiquitous nature, GMP will remain in principle for ever, because as humans are fallible, there will be always room for improvement. Interesting topics to expect in the near future are:

- GMP in combination with lab on a chip for both production and QC of radiopharmaceuticals (Ha et al., 2017; Wang and Van Dam, 2020).
- GMP outside the cleanroom where production will take place in specialized validated modules, able to perform production as well as accurate QC in a continuous process (Ovdiichuk et al., 2021).
- Introduction of novel total body PET camera systems may lead to lower doses needed for PET imaging, which will cause less nuclear energy law issues as well as smaller amounts needed per patient (Abgral et al., 2021).

## Conclusion

Especially for short lived products like radiopharmaceuticals, GMP remains an essential additional requirement to ensure accurate as well as safe production of diagnostic medication in order to ensure a warranted diagnostic outcome for a patient or a relevant contribution to scientific research. In the end, GMP is a cornerstone to assure self-reflection in order to prevent mistakes during production as well as to assure that the chances of reoccurrence of deviations/mistakes from the past, will become smaller.

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